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Eye-Tracking Measures Of Attentional Bias In Cocaine Dependent Subjects

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EYE-TRACKING MEASURES OF ATTENTIONAL BIAS IN COCAINE

DEPENDENT SUBJECTS

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EYE-TRACKING MEASURES OF ATTENTIONAL BIAS IN COCAINE DEPENDENT SUBJECTS

Nadeeka Rukshani Dias, B.S.

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Cocaine-dependent (CD) subjects show evidence of attentional bias toward cocaine-related cues, and this measure of cue-reactivity is predictive of craving and relapse. In previous work, cue-reactivity and attentional bias have been assessed by models that present drug-relevant stimuli (e.g., cocaine-specific Stroop task) and measure physiological and behavioral reactivity (e.g., heart rate, reaction times). Studies have indicated competition between the higher-order cortical processes (frontal eye-fields, DLPFC) in voluntary eye control (i.e., anti-saccades) and more reflexive saccades driven by involuntary midbrain (superior colliculus) perceptual input (i.e., pro-saccades). In addition, neuroimaging studies in patients with cocaine dependence have shown activation in frontal regions during craving and intoxication, in which reaction time (RT) was used as a key index of cognitive and motivational processing. In the present project, we developed a novel attentional-bias task using eye-tracking based measurement of saccadic eye movements towards cocaine and neutral cues. We sought to further understand processes involved in attentional bias in CD users and voluntary/involuntary processes that modulate attention toward and away from drug cues. CD subjects and healthy controls were tested using eye-tracking technology to measure performance on

counterbalanced blocks of pro- and anti-saccade trials featuring cocaine and neutral stimuli (pictures). Dependent measures include error rates during pro-/anti-saccade trials as well as saccadic latencies. Analysis of the eye-tracking data in 81 completed subjects (46 CD, 35 control) indicate higher attentional bias in CD subjects as measured by anti-saccade errors (i.e., looking toward the stimulus), both across all stimuli (35% vs. 19% anti-saccade errors), and specifically in the presence of cocaine-related stimuli (41% vs. 20% anti-saccade errors). During pro-saccade trials, in the presence of cocaine cues the CD subjects displayed significantly faster reaction times (μ=347.07ms) than controls (μ=387.19ms), but no between-group differences were observed in the presence of neutral cues. The data demonstrate increased saliency and differential attentional to cocaine cues, providing a sensitive index of cue-reactivity – a strong predictor of relapse in addiction. This novel saccade-based measure of attentional bias is expected to provide a productive method by which to assess reactivity to drug cues, and eventually to screen for potential relapse prevention interventions.

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CHAPTER 1: INTRODUCTION

A. Clinical challenge: Cocaine Dependence

Cocaine abuse is a widespread problem throughout the world. Within the United States alone, more than 1.4million people over the age of 12 are current users (National Household survey on Drug Abuse, 2011). Currently there are no FDA approved medications to treat cocaine dependence, however, due to the increased rates of dependence, efforts are being made to develop and implement effective treatment programs for these individuals. As with any drug addiction, there are many steps to achieving abstinence, and equally as imperative, maintaining abstinence and avoiding relapse, which presents a complicated challenge to treatment and research. The integration of behavioral interventions such as cognitive behavioral therapy (CBT), which has proven to be effective in outpatient studies, alongside pharmacological approaches may be one of the most effective methods to increase abstinence and reduce relapse rates in cocaine-dependent individuals.

B. Neural circuitry of cocaine addiction

The pathological state of drug addiction is a chronic cyclic disorder, which has been characterized by three defining elements (1) a compulsion to obtain the drug (2) inability to control the amount of intake, and (3) negative emotional state or withdrawal when the drug is no longer accessible (Koob & Volkow, 2009). The acute reinforcing effects of cocaine depend on activation of the mesolimbic dopamine system (Koob, 1992). Evidence from early preclinical animal studies have eludiciated key components of the brain's

reward system, such as the medial forebrain bundle that connects the ventral tegmental area (VTA) to the basal forebrain (Olds and Milner, 1954). Furthermore, cocaine activates the release of dopamine in the nucleus accumbans (NA), a key substrate for drug reward, which has been thought to cause the initial action of drug reward, due to circuitry involving the limbic system, frontal cortex, amygdala, and hippocampus (Figure 1.1) (Koob & Volkow, 2009).

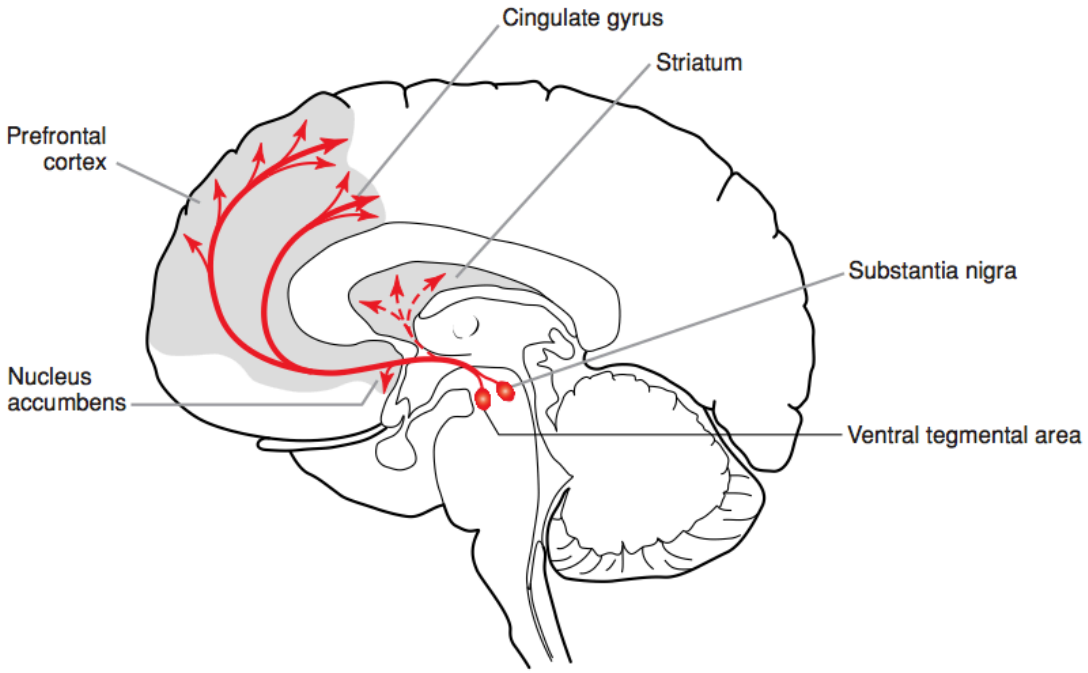

Figure 1.1: Projections of dopamine from the VTA to the NA, and projections from the substantia nigra to the dorsal striatum (Hyman SE, Malenka RC, Nestler EJ (2006) Neural Mechanisms of Addiction: The role of reward-related learning and memory. Annu Rev Neurosci 29:565-98; material may be used in thesis without addition permission as stated by Annual Reviews)

Drug seeking behavior is enhanced by natural rewards and/or drug-associated stimuli, a process termed incentive salience. Disruption of the underlying neural structures involved in this incentive salience contributes to escalating compulsion and leaves cocaine–dependent individuals more susceptible to relapse (Everitt et al., 2008, Koob & Volkow, 2009).

Through the use of multiple neuroimaging techniques, advances have been made in deciphering how cocaine use modifies brain function. Many subcortical and cortical structures are altered by cocaine abuse, leading to emotional responses to drug cues and neurobiological regulation of craving, a strong desire to consume a substance. The ventral striatum, including the VTA and NA, are the primary target sites of cocaine. These regions are rich with the monoamine neurotransmitter dopamine, and are key regions in reward motivated behavior and learning. Cocaine acts at the dopamine transporter by blocking the reuptake of dopamine into the presynaptic membrane, thereby flooding the synapse with dopamine and causing a state of acute euphoria (Figure 1.2) (Volkow et al., 1997).

The VTA is a small structure located in the midbrain where dopaminergic projections to cortical and limbic areas originate, making this structure a key component in addiction reward circuitry. Elevated activity in the VTA has been associated with the 'rush' after acute cocaine administration (Kufahl et al., 2005). The VTA sends afferent projections to the NA. After cocaine use, there is an increase in levels of synaptic dopamine in the NA, which facilitates the reinforcing effects and positive affect of cocaine seeking behavior (Hanlon &

Canterberry, 2012). The NA can be histologically divided into two regions: the shell and core. It is dopamine within the shell regions that appears to influence responses to rewarding stimuli (Ito et al., 2004).

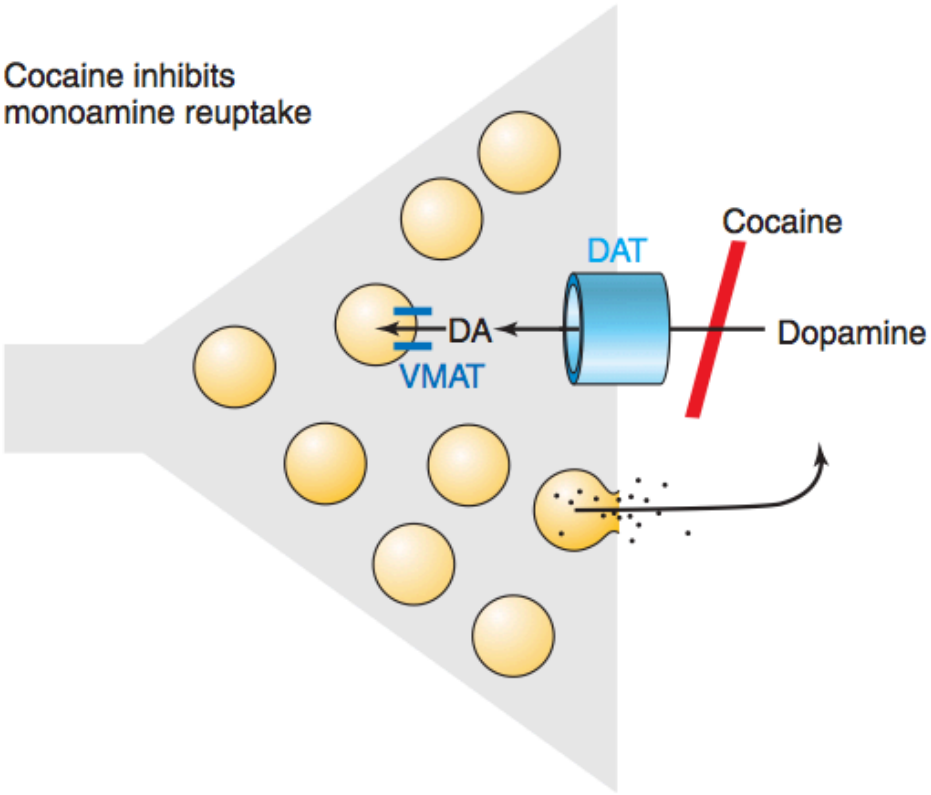

Figure 1.2: Action of Cocaine: The dopamine reuptake transporter (DAT) on the presynaptic membrane is blocked by cocaine, thereby increase the amount of dopamine in the synapse (Hyman SE, Malenka RC, Nestler EJ (2006) Neural Mechanisms of Addiction: The role of reward-related learning and memory. Annu Rev Neurosci 29:565-98; material may be used in thesis without addition permission as stated by Annual Reviews)

The habitual drug-taking behavior of cocaine dependent individuals is associated with dorsal striatum activity, a major input of the basal ganglia, while the ventral striatum has been linked to motivation for drug seeking and reward (Hanlon and Canterberry, 2012). Studies have shown that initial motivation for acute cocaine use is mediated by the ventral striatum, and after 12 or more years of chronic use, this habituation to the drug is evident by the dysfunction seen in the dorsal striatum (Risinger et al., 2005; Hanlon et al., 2009).

Imaging studies have found that the caudate nucleus is active during cued craving for cocaine (Kilts et al 2004). Increased activation in the caudate has been correlated with subjects who report a high rush rating (i.e. feeling the cocaine-induced euphoria after acute use) (Breiter et al, 1997). When cocaine users completed a stress test, which instructed them to imagine stressful scenarios while lying inside the scanner, the activation or Bold Oxygen Level Dependent (BOLD) signal was greater in the caudate for cocaine users than controls. Caudal activation during the stress test was also associated with increased craving for cocaine (Sinha et al., 2005).

Afferent and efferent connections through the thalamus are vital projections for many cortical and subcortical functions. Lower grey matter volume in the left thalamus has been reported for cocaine dependent individuals compared to controls (Sim et al., 2007). During acute administration of cocaine, neuroimaging data showed increased thalamic activity during the presentation of cocaine cues, which was also associated with the drug ‘high’ (Garavan et al, 2000), and a decreased BOLD signal during visual attention and

working memory tasks compared to non-drug using controls (Moeller et al, 2010).

In the interpretation of drug images and word cues that evoke cue-salience and reinforcement for cocaine-dependent individuals, the amygdala is a key region. This structure mediates attention and emotional responses to drug stimuli (Davis and Whalen, 2001). Studies have shown that cocaine-dependent individuals have a smaller amygdala volume relative to controls, as well as increased activation in this region during cue-elicited craving (Kufahl et al, 2005; Bonson 2002; Kilts et al., 2001). These findings complement earlier associations of drug craving with amygdala activity, and the possibility that this decreased volume makes the cocaine user more vulnerable to addiction.

Many structural and functional dysfunctions in cortical areas that project to the aforementioned subcortical regions are also disrupted after exposure to cocaine. Most notably, the prefrontal cortex (involved in top-down cognitive processes and emotion regulation) contains many segments such as the medial prefrontal cortex (mPFC), the dorsolateral prefrontal cortex (DLPFC), as well as the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC), which may all contribute to the development and maintenance of cocaine addiction (Miller and Cohen, 2001).

The mPFC plays a significant role in cognitive deficits seen in cocaine dependent individuals. Gray matter volume of the mPFC of cocaine users is smaller relative to controls (Matochik et al, 2003). Increased activation in this region has been found during completion of a cocaine Stroop task, which also

predicted relapse (Brewer et al, 2008). In addition, cue-induced craving, which is often a strong predictor of drug relapse, also elicits cortical activation of the mPFC (Garavan et al, 2000). Therefore, cocaine-induced impairment in the mPFC is likely to lead to higher instances of drug-cue salience and bias toward drug-related stimuli in the natural world.

The DLPFC plays a role in higher order cortical processes such as decision-making, reasoning, and inhibition. Cocaine use is related to decreased cortical thickness in the DLPFC relative to controls, which provides a mechanism by which these major processes are most often impaired in the cocaine using population (Bolla et al., 2003). Many studies have shown increased activation in this area when cocaine users are viewing cocaine stimuli, and during craving (Bonson, 2002; Maas, 1998; Kufhal, 2005). Cocaine use is related to higher attentional bias toward cocaine-related words, poor inhibitory control, and increased impulsivity, measures all correlated with impaired DLPFC function (Liu et al., 2011, Bolla, 2003)

The OFC is another key part of the mesolimbic dopamine system that plays a role in cocaine reinforcement and response inhibition. Dysfunction of the OFC has been associated with risky decision making (Krawczyk, 2002). Similar to the other regions in the frontal cortex, OFC gray matter volume is smaller in cocaine users compared to controls, and this decreased volume has been associated with longer use and higher compulsion to use cocaine (Matochik et al., 2003; Franklin, 2002; Ersche et al., 2011). Increased activation in the OFC has been shown in cocaine users in the presence of cocaine-related

cues, and individuals who are able to reduce their craving while viewing these cues have a corresponding decrease in OFC activity (Wilson, 2004, Volkow et al., 2010).

Finally, the anterior cingulate cortex (ACC) plays a primary role in inhibitory control, motivation, and the regulation of attention and emotion, such that dysfunction in this area due to cocaine abuse contributes to the cocaine user's inability to control their craving for the drug (Bush, 2000). Gray matter density in the ACC is smaller in cocaine dependent individuals compared to controls (Matochik, 2003). Imaging studies have also found correlations with the cocaine high and the elevation in BOLD signal in the ACC (Risinger et al., 2005).

Collectively, this cortical and subcortical network plays a key role in the abnormal neural adaptations present in cocaine dependence. Dysfunctions in these regions provide insights into the mechanism of action of cocaine that may promote innovation and development of novel assays to establish reliable and sensitive evaluation of these deficits.

C. Attentional bias in substance dependence

The high rate of relapse following abstinence remains a major hurdle in addiction treatment efforts (O'Brien and Gardner, 2005). Presently, there are few effective methods of predicting treatment outcomes or preventing relapse in individuals addicted to cocaine. The majority of cocaine users who seek treatment inevitably relapse, and understanding the cognitive and physiological

factors underlying this failure in treatment remains a challenge (Vadhan et al, 2007). Individual differences in cognitive functions caused by cocaine use, such as decision-making and attentional processes provide important information. However, a full understanding of the biological and psychological mechanisms and their interaction remains incomplete. The literature indicates the influence of attentional bias in substance use relapse, which is defined as the tendency to orient gaze toward a salient stimulus (Franken et al., 2003, Kacanagh et al., 2004; Marlatt and Gordon, 1985; Robinson and Berridge, 1993). Studies also show attentional biases towards drug-related cues among substance users (Bauer and Cox, 1998; Ehrman et al., 2002; Franken et al., 2003; Rosse et al., 1997, Liu et al, 2011). However, there is little research examining attentional bias to drug-related cues with cocaine–dependent subjects. Drug users presented with drug-related stimuli typically produce classically conditioned responses that are both physiological and psychological in nature (O'Brien et al., 1998; Powell et al., 1990). Current literature regards craving as a key phenomenon contributing to the continuation of drug use in active users as well increases the chances of relapse in detoxified abusers (Everitt, 1997). An established method of assessing craving and cocaine abusers response to cocaine stimuli is with a cue-reactivity paradigm (Carter and Tiffany, 1999). This reactivity to and biased attention to salient stimuli is poorly inhibited/controlled and serves as a trigger for drug seeking. It is typically understood to be an automatic (involuntary) process following the association of drug use with conditioned cues (Posner and DiGirolamo, 1998). However,

selective attention experienced during attention bias paradigms can also be voluntary (top-down, controlled). A measure of attention may provide insight into cognitive processing of cocaine cues, and can include both reflexive (involuntary) and volitional processes (Franken, 2003). An approach to measuring cocaine attentional bias to investigate both involuntary and voluntary attentional processes contributing to cocaine attentional bias will be useful in advancing scientific knowledge and help to understand relapse.

High relapse rates during abstinence are often associated with stress, which is known to trigger a state of drug craving (Sinha et al, 2011), and many clinical studies suggest stress is a key factor contributing to relapse (Sinha, 2001). Recent studies examining stress and drug craving have shown that physiological stress responses induced in the laboratory may predict drug relapse (Back et al, 2010, Sinha et al, 2006). The relationship between stress exposure in the drug user's environment and stress-related negative affect is also an indicator of relapse (Cooney et al, 2007; Epstein et al, 2009; Shiffman and Waters, 2004).

Clinical data have shown that obsessive behavior (e.g., obsessive cognitions and drug seeking behaviors related to cocaine) is a contributing factor to the development and maintenance of cocaine dependence (Jardin et al, 2011). Studies of obsessive foraging behavior among cocaine addicts found over 80% engaged in this obsessive behavior for over an hour while under the influence of cocaine (Rosse et al, 1993). We posit this behavior is also a contributing factor to relapse, and its relationship to cue-reactivity and

attentional bias merits further study. Stress and obsessive behavior serve as risk factors for both the initiation of substance use and relapse (Sinha, 2008), and therefore we expect to find positive correlations between these variables and cocaine attentional bias. These relationships will help validate the relationships among these known risk factors.

D. Attentional bias: Current measures and limitations

Several paradigms have been designed to measure attentional bias. Two of the most common in cocaine research are the Stroop and Visual Probe task. The Stroop task requires the participant to ignore the meaning of the presented word and name the ink color of the observed text, typically with a computerized button press (Wuhr and Waszak, 2003). The Visual Probe task is similar in that it requires a button press when a dot appears in the same location as a previously shown stimulus (Amin et al, 2004). These measures, however, have key limitations. Neither task lends well to repeated measures of data collection due to effects of habituation, reliance on reaction time differences, and performance improvements with repeated exposures to the task. In cocaine pharmacotherapies, the observation of pharmacological effects of treatment medications on cocaine cue-reactivity and attentional bias is valuable, however neither of the aforementioned tasks have shown sensitivity to drug effects. A saccade-based measure of attentional bias will allow for repeated measured with decreased likelihood of habitation or expectancy, and may serve as a sensitive measure of drug effects, due to the constrained CNS

circuitry that regulates saccadic processes, e.g., frontal eye fields, DLPFC and ACC, parietal cortex, basal ganglia, thalamus, superior colliculus, and cerebellum (Leigh, 1983).

E. Eye movements: Saccades

Due to the complex cognitive processes that attentional bias paradigms invoke, and their reliance on reaction differences as the primary dependent measure, a measure of reactivity to drug-cues that is less sensitive to disruptions from nuisance variables is warranted. The analysis of eye-movements, in particular saccadic eye movements, hold promise in this regard.

A saccade is a rapid motion of the pupil from one fixation point to another. Saccades are the fastest movement the body is able to produce, and are generated on the order of milliseconds, typically taking about 30-80ms to complete (Holmqvist et al. 2011). There are two main types of saccades: pro-saccades (reflexive) and anti-saccades (goal-directed or voluntary). Saccadic reaction times toward a visual stimulus presented in the visual field may range from 90-400ms, and typically the average is ~200ms (Westheimer, 1954). The most common reflexive response is to look toward a new or salient stimulus (pro-saccade). However, humans can be instructed to look in the opposite direction of a stimulus, which is known as an anti-saccade (Everling and Fischer, 1998). Correct execution of an anti-saccade requires two steps. First, the individual must suppress the reflexive response to attend to the stimulus (pro-saccade), and second make a voluntary visually guided saccade to the

opposite hemifield of the stimulus (anti-saccade) (Munoz and Everling, 2004). A fixation system without deficit will allow individuals to suppress a reflexive pro-saccade toward the stimulus, and give them enough time to generate a voluntary anti-saccade (Guitton et al 1985).

A typical anti-saccade gap paradigm begins with the presentation of a fixation point, which the subject is instructed to fixate on (Figure 1.3). The fixation point then disappears for a constant or jittered time period, which creates a temporal gap between fixation removal and stimulus presentation (gap paradigm). Then, a visual stimulus appears either to the left or the right in the periphery, and the subject has to suppress the pro-saccade, and generate the voluntary anti-saccade away from the stimulus. The pro-saccade task is presented exactly in the same manner, however, the instructions indicate to the subject to look at the stimulus. Typically the metric of most interest is the number of anti-saccade errors (incorrectly made pro-saccade toward the stimulus) as well as the latencies of both types of saccades (Hutton 2008). In the gap paradigm, many studies have found that pro-saccade latencies are reduced on gap trials, and removal of the fixation point in this paradigm allows for attention to be disengaged before the new stimulus appears (Fischer and Weber, 1992; Reuter-Lorenz et al., 1991; Fishcer and Breitmeyer, 1987). A gap paradigm was selected in the proposed study because it generates more anti-saccade errors than procedures that do not use a gap.

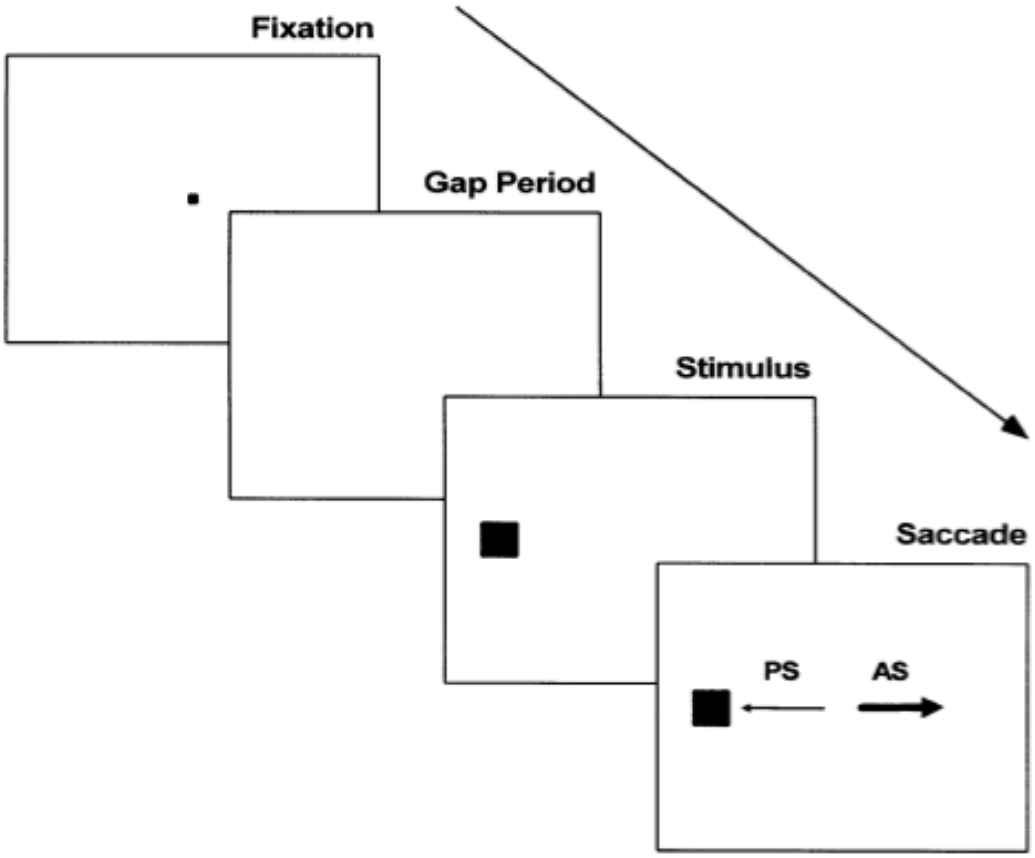

Figure 1.3: Schematic of gap anti-saccade task. PS = Pro-saccade. AS=Anti-saccade (Everling S, Fischer B (1998) The anti-saccade: a review of basic research and clinical studies. Neuropsychologia 36:885-99; permission 3371430490662, 4.17.14, Elsevier)

The cognitive basis for saccades and reasoning as to why saccadic eye movements have long latencies (~200ms) is due to proposed mechanistic time lag needed by the brain to determine not just where to look, but given all of the stimulating options a typical environment, determine if it is even worth looking in that direction at all (Carpenter, 1981; Carpenter, 2001). Another important component in eye movement studies is the state in which the eye remains still over a certain period of time, commonly known as *fixation*. This word is a slight misnomer, in that the eye is never completely still. While stationary, the eye has three distinct micro-movements that are typically studied in human neurology: tremor, micro-saccades, and drifts (Holmqvist et al, 2011). As the number of saccades made to evaluate the current visual field increase, less time is spent on fixations, or stable points needed to process the visual field. Therefore, these saccadic latencies serve as an index of decision time. This decision process involves many neuroanatomical and behavioral influences, including processing of which stimuli have the greatest salience (Hutton, 2008).

Saccadic eye movements are an excellent model to study the components of executive function, including attentional processing and response inhibition (Ploner et al., 2005). The brains' ability to control behavior in a flexible manner, by either responding automatically to a stimulus or suppressing an automatic response in favor of further processing a stimulus are two notable features that are sensitively measured through eye-tracking. The most reliable method to record saccades is through automated eye-tracking,

where an infrared beam illuminates the eye and the resulting pupil and corneal reflection are used to estimate the point of gaze as well as reaction times of each generated saccade. Although it is possible to use pupil-only tracking, the information from the corneal reflection offers an additional point of reference to compensate for small head movements (Holmqvist et al, 2011).

F. Circuitry of saccadic eye-movements

An extensive list of studies utilizing behavioral tests, neuroimaging, animal neurophysiology, and lesion studies have identified several key brain areas that are involved in controlling saccadic eye movements and visual attention/fixation. The main structures involved in anti-saccade generation are the anterior cingulate cortex (ACC), prefrontal cortex (PFC), basal ganglia (BG), frontal eye field (FEF), supplementary eye field (SEF), posterior parietal cortex (PPC), and superior colliculus (SC) (Figure1.4) (Pierrot-Deseilligny et al., 2003).

When a visual stimulus is presented, the information is first processed through the retino-geniculo-cortical pathway leading to the primary visual cortex (V1) (Figure 1.5) (Munoz and Everling, 2004). Likewise, there are concurrent projections from the retinotectal pathway to the superficial layers of the SC. Visual information is then relayed through several other visual/sensory areas before reaching structures that control motor movements, such as the lateral intraparietal area (LIP) in monkeys or the equivalent area in humans, the medial intraparietal sulcus of the PPC (Anderson, 1997; Grefkes and Fink 2005).

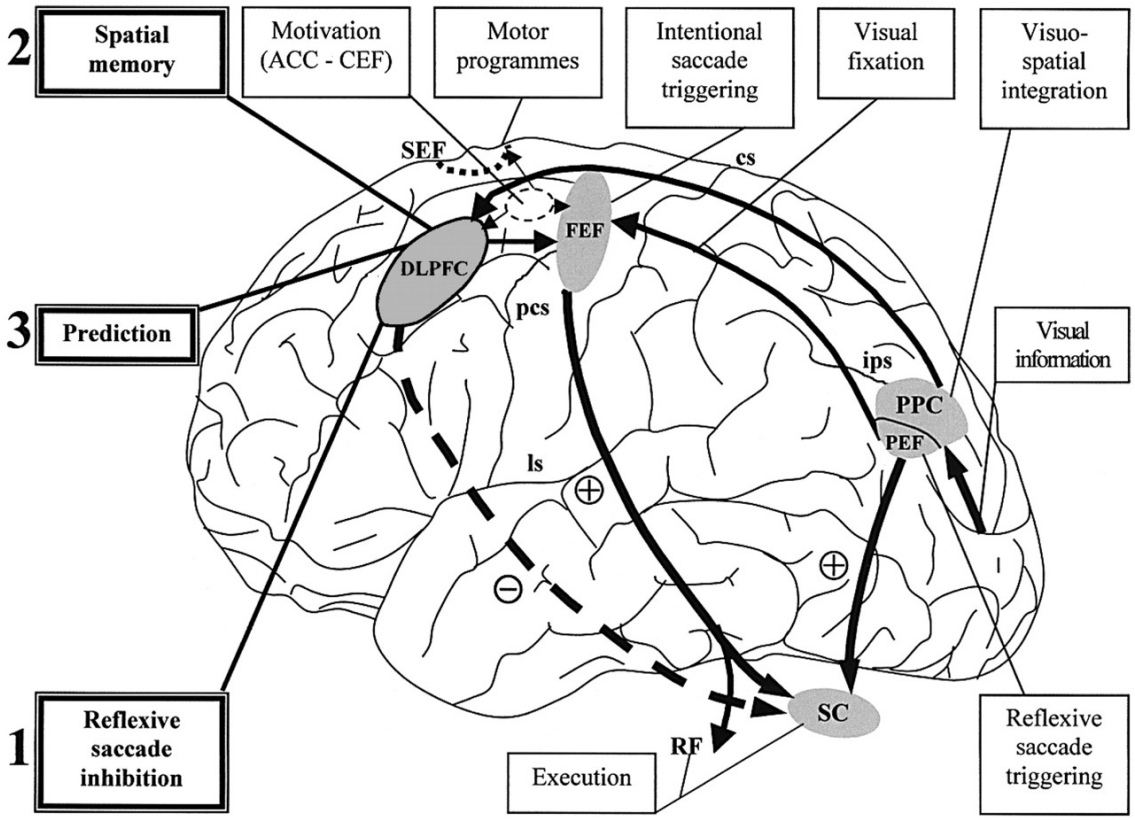

Figure 1.4: Structures involved in execution of a correct anti-saccade task. Dorsolateral prefrontal cortex (DLPFC), frontal eye field (FEF), supplementary field (SEF), posterior parietal cortex (PPC), posterior eye filed (PEF), and superior colliculus (SC) (Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S (2003) Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. Brain 126: 1460–1473; permission 3371430655113, 4.17.14, Oxford University Press)

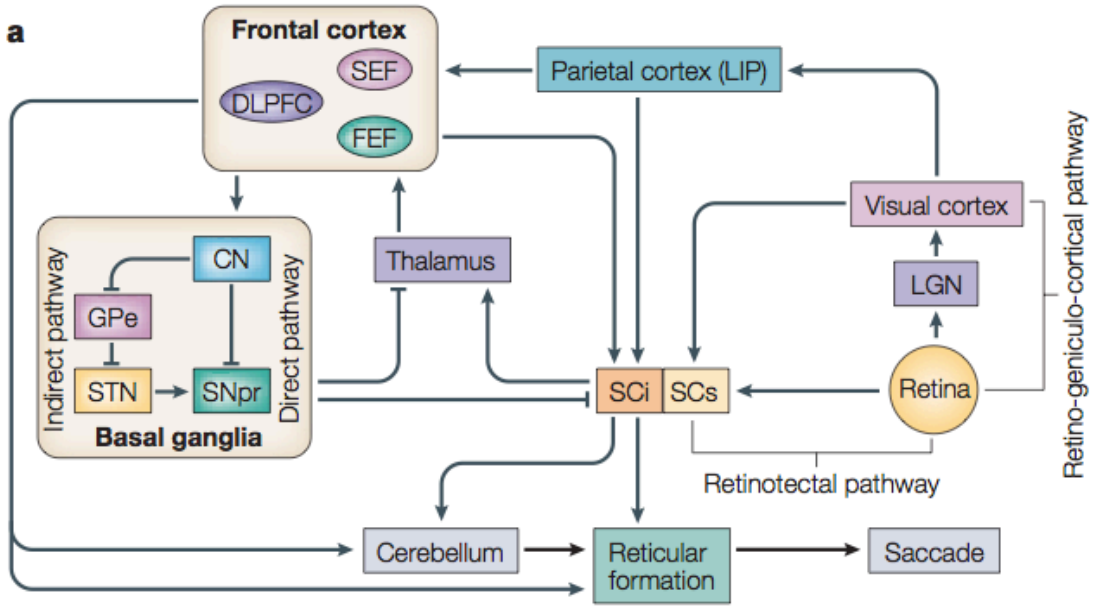

Figure 1.5: Major structures involved in controlling saccadic eye movements from cortical inputs to subcortical outputs. Frontal eye field (FEF), supplementary field (SEF), dorsolateral prefrontal cortex (DLPFC); lateral geniculate nucleus (LGN), superior colliculus intermediate layers (SCi), superior colliculus superficial layers (SCs), lateral intraparietal area (LIP), caudate nucleus (CN), substantia nigra pars reticulate (SNpr), globus pallidus (GPe), subthalamic nucleus (STN) (Munoz DP, Everling S. (2004) Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5:218-28. Review; permission 3371421244824, 4.17.14, Nature Publishing Group)

The LIP/PPC then projects to the oculomotor areas in the frontal cortex, such as the DLPFC, FEF, and SEF as well as the intermediate layers of the SC (Pare and Wutz, 2001; Ferraina et al., 2002; Schall 1997). The DLPFC plays a role in executive function and suppression of automatic, reflexive saccades (Fuster, 1997; Guitton et al, 1985). The FEF is a vital structure for voluntary saccades and the SEF plays a more mediating roll in the sequencing of saccades and decision-making (Coe et al 2002; Stuphorn et al, 2000, Sommer and Tehovnik, 1997). All of these oculomotor frontal cortical regions then project back to the SC, which completes a vital premotor circuit for saccadic generation (Everling and Munoz 2000; Shook et al, 1990; Selemon and Goldman, 1988). These frontal regions (DLPFC, FEF, SEF) also project to the basal ganglia, specifically the caudate nucleus (CN) (Hikosaka et al, 2000; Alexander et al 1986; Nakahara et al, 2001). GABA (γ-aminobutyric acid) neurons in the CN then either directly project to the substantia nigra pars reticulate (SNpr) or indirectly to the globus pallidus (GPe) and then on to the subthalamic nucleus (STN). The direct pathway passes through two inhibitory synapses which causes disinhibition of the SC and thalamus, while the indirect pathway leads to inhibition of these two areas (Alexander et al 1986, Hallett 1993).

Reflexive saccades (pro-saccades), which are made towards a visual stimulus that suddenly appears in the periphery, are mainly triggered by the posterior eye field in the PPC (Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny et al, 2004). In order to generate a voluntary saccade (anti-

saccade), these reflexive saccades will need to be inhibited first by the frontal cortex (i.e. DLPFC), before the voluntary movement can be executed correctly.

Models have been development to interpret the variability in reaction times for saccadic eye movements, one of which is called the accumulator model (Carpenter 1981; Trappenberg et al, 2001; Hanes and Schall, 1996; Gold and Shadlen, 2000; Ratcliff et al, 2003). This model posits that in order to initiate a movement, there must be some accumulation of baseline neural activity until it exceeds a threshold, which will then execute the movement. Electrophysiological studies have shown evidence for both baseline and post-target influences on the rise of activity in the FEF and SC to trigger a movement, which account for some of the variability in saccadic reaction times (Hanes and Schall, 1996; Gold and Shadlen, 2000; Pare and Hanes, 2003; Everling et al, 1999). When completing an anti-saccade trial, there are two processes that are racing towards threshold (Hallett 1978). First, after the onset of the stimulus a process initiates the automatic response to the target (pro-saccade), and then second process is initiated in the opposite direction to execute a voluntary anti-saccade. In order for this task to be performed correctly, the initial automatic response to the target (pro-saccade) must be inhibited in order to allow time for the second voluntary anti-saccade process to reach threshold. Inhibition of the FEF and SC must be intact prior to the stimulus onset. This suppression is represented in the accumulator model by a reduction in baseline neural activity prior to the target appearance (Figure 1.6b, solid line) (Munoz and Everling, 2004). If this inhibition is weak or impaired,

then baseline pre-target activity will accumulate prematurely and trigger an anti-saccade error (reflexive pro-saccade) (Figure 1.6b, dashed line) (Munoz and Everling, 2004). The DLPFC, which is close in anatomical proximity to the FEF, also plays a strong role in the preparation of saccadic eye movements, particularly regarding the inhibition of unwanted reflexive pro-saccades during an anti-saccade task (Pierrot-Deseilligny et al, 2005). Experiments in primates have also confirmed that the DLPFC is involved in saccadic inhibition (Hasegawa et al, 2004).

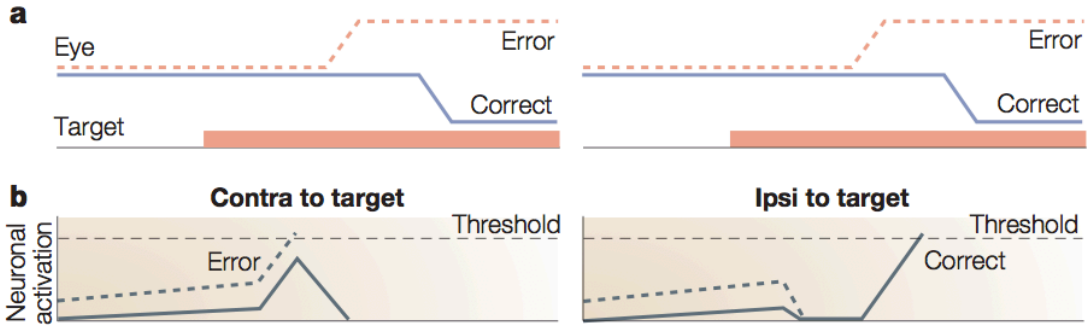

Figure 1.6: Accumulator model displaying the accumulation of saccade neural activity during anti-saccade trials. (a) Anti-saccade trial displaying correct (solid line) and error (dashed line) responses. (b) Neural activation for correct and error response. Neural activity in the brain contralateral to the target must be inhibited, while activity ipsilateral to the target must accumulate to threshold in order to execute a correct anti-saccade (Munoz DP, Everling S. (2004) Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5:218-28. Review; permission 3371421244824, 4.17.14, Nature Publishing Group)

Patients with focal cortical lesions provide valuable insight into the physiology of anti-saccade performance. Patients with lesions in the dorsolateral prefrontal cortex (DLPFC) have increased difficulty in the first step in the generation of the voluntary anti-saccade, which involves the initial suppression of the reflexive pro-saccade (step 1) before then making a visually guided voluntary saccade away from the stimulus (step 2) (Guitton et al., 1985; Pierrot-Deseilligny et al., 1991; Pierrot-Deseilligny, 2003; Walker et al., 1998). The DLPFC provides vital top-down input to the FEF and SC in order to inhibit the reflexive pro-saccade (step 1). Without the input of the DLPFC, the brain is not able to inhibit saccade neurons in the FEF and SC during the anti-saccade trials, which result in higher anti-saccade errors (Munoz and Everling, 2004). Several human lesion studies have shown an increase in errors during the anti-saccade task after DLPFC lesions, but may reveal no change in errors following a FEF lesion (Pierrot-Deseilligny et al., 1991; Ploner et al., 2005; Rivaud et al., 1994; Gaymard et al., 1999) – although the literature is somewhat equivocal on this topic. If the FEF is lesioned, suppression of the reflexive pro-saccade (step 1) remains intact, however, the ability to generate the voluntary anti-saccade (step 2) is now impaired (Gaymard et al., 1998; Davidson et al., 1999). The loss of neurons in the FEF due to the lesions effectively reduces neuronal input to the SC and prefrontal cortex. This lack of input increases the time that is typically needed to achieve saccadic threshold, and the time lag causes a latency or failure in initiation of the voluntary anti-saccade (Munoz and Everling, 2004).

G. Clinical utility of saccadic eye-movements

Neurologists have used eye-tracking and saccadic eye-movements as a diagnostic tool for many years, and it is rapidly becoming apparent that a myriad of neurological and psychiatric disorders are associated with a failed ability to *inhibit* saccades, or make a correct anti-saccade (Everling & Fischer, 1998). This perspective of looking at deficits in voluntary and reflexive oculomotor movements is best measured through the use of the anti-saccade task, due to the dependency of this task on the frontal cortex and basal ganglia structures (Everling & Fischer, 1998).

Disorders involving the basal ganglia such as Parkinson's and Huntington's disease have been evaluated with saccadic tasks. A notable deficit in Parkinson's disease is that these patients have difficulty generating voluntary eye responses (Lezak, 1995). Patients with Parkinson's have reportedly longer reaction times during correct anti-saccades trials, indicating the circuitry involved in executing this correct anti-saccade may activate more slowly in this patient population (Briand et al., 1999; Chan et al., 2005). The pro-saccade results from these patients, however, indicate that their reflexive responses toward stimuli are faster than controls. The inhibitory control deficits marked by this disease are well illustrated through the anti-saccade task, and efforts to implement this as an early diagnosis tool have been proposed (Vidailhet et al., 1994; Nilsson et al., 2013). Patients mildly affected with Huntington's disease have shown increased error rates during anti-saccade tasks as well, highlighting the detrimental effects of the disease on volitional

control and reflexive glances (Lasker et al., 1987). Evidence from these studies have posited that the frontal lobe and basal ganglia contribute to voluntary control (anti-saccade) more than to reflexive saccades (pro-saccade) (Lasker and Zee, 1997).

A large body of work has evaluated saccadic eye movements in schizophrenic patients, due to evidence that the frontal cortex is the primary region to source for the dysfunction of the disease (Levy, 1996; Pierrot-Deseilligny et al., 1991). The majority of clinical studies on this population have reported greater error rates and longer reaction time latencies of anti-saccades for the schizophrenics compared to controls subjects (Chementz et al., 1994; Fukushima et al., 1988; Fukushima et al., 1990; Rosse et al 1993; Sereno and Holzman, 1995). This behavior is very similar to patients with lesions in the prefrontal cortex, as evidenced by the differences found in the DLPFC when comparing the BOLD signal associated with anti-saccades between schizophrenics and controls (McDowell et al., 2002). Much like patients who have DLPFC lesions, schizophrenics may also have a handicapped ability to suppress the activity of saccade neurons in the SC and FEF during anti-saccade trials, as well as a reduced rate of activity accumulated that is needed to achieve threshold and successfully avert gaze away from the stimulus to produce the correct anti-saccade; the result is anti-saccade errors (Munoz and Everling, 2004).

Attention deficit hyperactivity disorder (ADHD) is a very common childhood disorder that is marked by a deficit in response inhibition (Barkley

1997). Children with ADHD also display higher anti-saccade error rates compared to age-matched controls (Munoz et al., 1999). These individuals have difficultly executing the first step in an anti-saccade sequence, suppressing the initial reflexive pro-saccade when the stimulus appears (Munoz et al., 2003). It is postulated that the increase in anti-saccade errors is due to deficits in top-down control of saccade neurons in the FEF and SC (Munoz and Everling, 2004). Increased reaction time variability during a simple go/no-go task was also found in this population indicating possible intermittent attentional lapses contribute to this impairment in response preparation, as opposed to a global CNS attentional deficit (Vaurio et al, 2009).

Prior studies have used eye-tracking to perform visual attention tasks in some areas of substance abuse, including daily smokers, alcohol-dependent subjects, and cocaine dependence with obsessive compulsive disorder (Munafo et al 2011; Khan et al, 2003; Rosse et al 1994). The aforementioned studies are representative of the many psychiatric and neurodegenerative disease studies that advocate the utility of saccadic eye movements as a diagnostic measure of disrupted attentional and inhibitory processes. The anti-saccade task is an excellent measure of inhibitory control function and generation of voluntary movements, such that top-down inhibitory control is required to reduce baseline activity of saccade neurons prior to stimulus onset, and impairment of this inhibition will subsequently lead to increases in anti-saccade errors (Munoz and Everling, 2004). Due to the specificity of this test in measuring frontal/cortical dysfunction, the anti-saccade task may provide

further utility in substance abuse disorders, where a lack of inhibitory control and impaired voluntary movement are commonly reported deficits (Fillmore and Rush, 2002; Bechara, 2005). Although many studies have measured anti-saccade performance through eye tracking in other psychiatric and neurological patient populations, this method has never been implemented as a measure of cue-reactivity and attentional bias in cocaine-dependent subjects, which is the primary goal of the current project.

H. Neuroanatomical overlap between saccadic function & cocaine impairment

The DLPFC is vital for saccadic inhibition during the generation of an anti-saccade (Pierrot-Deseilligny et al., 2005). Lesions to the DLPFC have shown an increase in anti-saccade errors, due to the inability to suppress the first step of anti-saccade generation when the target appears, the reflexive pro-saccade. It has been widely reported that one of the main areas of impairment from cocaine use is the DLPFC, which contribute to impulsive behavior and inhibitory control deficits (Fillmore and Rush, 2002; Jasinska et al., 2014). Collectively, this DLPFC dysfunction is expected to cause an increase in error rates and latencies in reaction times during anti-saccade trials in cocaine-dependent subjects, as has been similarly reported in patients with other frontal deficit disorders (Chementz et al., 1994; Chan et al., 2005; Sereno and Holzman, 1995).

I. Hypothesis & Specific Aims

The results from the current project may inform risk for relapse, and help as a battery of tests that can be utilized to screen for intervention (e.g. pharmacological therapies). Ultimately we seek to correlate the resulting saccadic profile to drug cues with other key variables of addiction severity to understand behavioral profiles for individual patients.

Specific Aim 1: To evaluate anti-saccade error rates during presentation of cocaine and neutral stimuli to cocaine dependent subjects vs. controls.

Hypothesis 1: Error rates across anti-saccade trials will be greater in the cocaine-dependent group relative to controls across all stimuli (main effect of group, general inhibitory control deficit).

Hypothesis 2: Error rates during anti-saccade trials will be greater in the cocaine-dependent group for drug-related vs. neutral cues relative to controls (interaction effect, attentional bias toward cocaine cues).

Specific Aim 2: To evaluate reaction time distributions during presentation of cocaine and neutral stimuli to cocaine dependent subjects vs. controls.

Hypothesis 3: Reaction time distributions during pro-saccade trials will be significantly faster on drug vs. neutral cues in cocaine dependent subjects relative to controls.

Hypothesis 4: Reaction time distributions during anti-saccade trials will show longer RT latencies during cocaine cues in cocaine dependent subjects relative to controls.

CHAPTER 2: ANTI-SACCADE ERROR RATES AS PREDICTORS OF RELAPSE IN COCAINE-DEPENDENT SUBJECTS

Introduction

Most substance dependent treatments are focused on preventing patients from relapsing back into their drug of choice. Despite many pharmacological and behavioral efforts, over 50% of these individuals drop out from treatment programs and inevitably relapse (Hattenschwiler et al., 2000; Franken and Hendriks, 1999). Studies identifying key factors that predict relapse are of great use in the addiction field (McKay, 1999, Donovan, 1996). Particularly regarding cocaine abuse, many relapse predictors have been tested including craving, demographic factors, length of substance use, and baseline urine results (Poling et al., 2007). Use of more neurocognitive measures, however, may serve as more precise predictors of relapse than these subjective measures of self-report (Kosten et al, 2006). The literature indicates an important role of attentional bias in substance use relapse (Franken 2003, Kacanagh et al., 2004; Marlatt and Gordon, 1985; Robinson and Berridge, 1993).

Attentional bias is the tendency to avert gaze toward a drug related stimulus compared to a neutral stimulus, and it is a well-studied cognitive process in addiction research (Marhe et al., 2013). There are few studies, however, that explore drug-related attentional biases with cocaine-dependent subjects. Some theories suggest that attentional bias plays a key role in drug maintenance and craving, and is therefore associated with relapse (Field and Cox, 2008). An established method of assessing craving and cocaine abusers response to cocaine stimuli is with a cue-reactivity paradigm (Carter

and Tiffany, 1999). A widely use measure of attentional bias is the cocaine Stroop task (Cox et al., 2006; Wuhr and Waszak, 2003). These studies have found that cocaine dependent individuals display attentional bias toward cocaine related cues (Vadhan et al., 2007). More notably, other studies have reported that this attentional bias toward salient drug stimuli is predictive of relapse in cocaine use (Marhe et al., 2012; Carpenter et al., 2006). Attentional processing of salient stimuli is poorly controlled in cocaine-dependent subjects due to frontal cortical impairments, which makes the stimulus a trigger for drug seeking (Miller and Cohen 2001). Cocaine related stimuli have been shown to impair inhibitory control, a frontally controlled action, in cocaine dependent individuals (Pike et al., 2013). It is typically understood to be an automatic (involuntary) process following the association of drug use with conditioned cues (Posner and DiGirolamo, 1998). Selective attention experienced during attentional bias paradigms, however, can also be voluntary, and a measure of attention such as saccadic eye movements would provide more sensitive physiological insight into cognitive processing of bias toward cocaine cues, including both reflexive (involuntary) and volitional processes (Franken, 2003).

Saccades, a key response in the oculomotor system to sensory stimuli, are rapid eye movements that move from one fixation point to another. When presented with a stimulus, the most common response is to orient gaze toward a salient cue, which is defined as a pro-saccade. With further instruction, however, direction can be given to look in the opposite direction of

a stimulus, which is known as an anti-saccade (Everling and Fischer, 1998). In order to accurately execute an anti-saccade, two innate processes must be intact and functional. First, the individual must process the cue and cue location, then suppress a reflexive response to attend to the stimulus (pro-saccade), and finally make a voluntary saccade to the opposite hemifield of the stimulus (anti-saccade) (Munoz and Everling, 2004). This two-stage process, primarily mediated by the dorsolateral prefrontal cortex (DLPFC) and frontal eye fields (FEF), are vital for producing correct anti-saccades. The DLPFC is vital for inhibitory control, and FEF for voluntary movement (Guitton et al., 1985, Gaymard et al., 1998). Therefore impairments to these frontal areas cause difficulty in proper execution of this task resulting in anti-saccade errors (Hasegawa et al., 2004; Coe et al., 2002; Stuphorn et al., 2000).

Anti-saccade errors as a measure of neural deficits are prevalent in many areas of psychiatry and neurology. Inhibitory control deficits marked by Huntington's disease are well illustrated through the anti-saccade task, and it has been suggested as an early diagnostic tool (Vidailhet et al., 1994; Nilsson et al., 2013). Patients mildly affected with Huntington's have shown increased error rates during anti-saccade tasks, highlighting the detrimental effects of the disease on volitional control and reflexive eye movements (Lasker et al., 1987). Notably, many studies have investigated error rates in patients with schizophrenia, due to evidence that the frontal cortex is a key region in the disease (Levy, 1996; Pierrot-Deseilligny et al., 1991). This population has well-established greater anti-saccade error rates compared to

age matched control subjects (Fukushima et al., 1990; Rosse et al., 1993; Sereno and Holzman, 1995). These anti-saccade error rates are similar to patients with lesions in DLPFC, suggesting that schizophrenics may also have impaired DLPFC inhibitory control, and therefore are unable to successfully avert gaze away from salient stimuli (Munoz and Everling, 2004).

It has been widely reported that one of the main areas of impairment from cocaine use is the DLPFC, which is related to impulsive behavior and inhibitory control deficits (Fillmore and Rush, 2002). Collectively, this DLPFC dysfunction is expected to cause an increase in error rates during anti-saccade trials in cocaine-dependent subjects, as has been similarly reported in patients with other frontal deficit disorders (Chementz et al., 1994; Chan et al., 2005; Sereno and Holzman, 1995). Taken together, this novel eye-tracking measurement of saccadic eye movements may provide further insight into attentional bias as a predictor of relapse in cocaine-dependent subjects, given that these cortical impairments are compromising voluntary control.

The goal of the present study is to develop a cocaine-specific attentional bias task using saccadic eye movement measurement. This analysis will focus on validating the following specific aim: To evaluate anti-saccade error rates during presentation of cocaine and neutral stimuli to cocaine dependent subjects vs. controls. Once validated, the task then may be used to evaluate new treatment interventions. Ultimately we seek to

correlate the resulting saccadic profile to drug cues with other key variables of addiction severity to understand behavioral profiles for each subject.

2. Materials and Methods

2.1 Subjects

This study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston. Subjects provided written consent for their participation and were fully informed of the nature of the research. The study enrolled male and females ages 18-60 years old, designated as either control subjects (n=41) or active cocaine-dependent subjects (n=46) that met current DSM-IV (SCID-1) criteria for cocaine dependence and reported using cocaine within the past 30 days [First, 1996]. Within the cocaine-dependent population, the majorities were African American (65%), male (85%), and employed at least part-time (91%). Within the control population, the majorities were African American (78%), male (51%), and employed (93%). Further demographics are shown in Table 2.1. The study was conducted at the University of Texas Health Science Center in Houston, where subjects were recruited through newspaper advertisements, flyers, public service announcements on television and radio, and notices mailed to local professionals. All subjects were urine tested for cocaine (benzoylecgonine), opiates, amphetamine, methamphetamine, benzodiazepines, and tetrahydrocannabinol using an E-Z split key cup II (Innovacon Company, San Diego, CA, USA) on each visit.

Eligible cocaine-dependent subjects had to submit at least one positive urine toxicology screen for the cocaine metabolite benzoylecgonine (BE) > 300ng/mL during the two day screening period. Subjects who were currently dependent on any psychoactive substance other than cocaine or nicotine were excluded. Further exclusionary criteria included current or past medical disorders affecting the central nervous system, and any Axis I disorders other than substance abuse or dependence. Chronic marijuana smokers, defined as smoking marijuana ≥ 10 times in past 30 days [Lindsay, 2009], were excluded to eliminate the potentially confounding role of heavy cannabis on cognitive performance [Lundqvist, 2005]. Cocaine-dependent subjects included both non-treatment-seekers as well as treatment seekers. The treatment seekers were tested on a baseline intake day, prior to the initiation of any intervention (e.g., medication or cognitive-behavioral therapy). Control subjects had urine-negative drug screens, no current or past DSM-IV axis I disorders (including substance dependence), and no medical disorder affecting the central nervous system. All subjects (cocaine and control) were free of alcohol at the time of testing as determined by a Breathalyzer test (Intoximeters, Inc., St. Louis, MO, USA). Female subjects were excluded if results from a urine pregnancy test were positive, however, no cases occurred during the study.

A total of nineteen subjects were excluded from the data analyses (7 cocaine; 12 controls): 16 because the eye tracker was unable to detect and/or consistently lock onto the subjects' pupil, and three due to an excessive

number of saccade errors (>80%), which indicated lack of motivation, inability to perform the task correctly, lack of instructional control, or some combination thereof. Two of these exclusions were further validated by the presence of low Shipley WAIS equivalent (IQ) scores below 80.

Table 2.1 Demographics: All results are means (std. deviations) p<0.05*, p<0.01**		
	Cocaine Dependent	**Control**
N	46	41
Age**	46.3 (8.4)	40.0 (11.3)
Gender N (%Male)**	39 (84.8)	21 (51.2)
Education (% College or Above)**	24%	63%
Shipley*	87.4 (13.6)	94.2 (15.1)
% Smokers	76.1	22.0
Cigarettes (days smoked/wk)**	6.6 (1.5)	1.3 (2.7)
Alcohol (days/week)**	3.4 (3.8)	1.6 (1.9)
Marijuana (days smoked/wk)**	3.9 (3.1)	0.9 (1.7)

2.2 Eye-Tracking Cocaine Attentional Bias Task

Each subject was tested using eye-tracking technology (MiraMetrix S2 Eyetracker, Vancouver, BC, 16ms eye reacquisition, 60Hz data rate) to measure performance on blocks of pro-saccade (look at stimulus) and anti-saccade (look away from stimulus) trials. The structure of the task began with a nine-point calibration procedure that was performed to map the eye-fixation position of each subject to designated screen coordinates. The calibration was considered valid if the maximum spatial error was less than 1 degree and the average error was less than 0.5 degrees.

Subjects began with a brief training session (16 pro-, 16 anti-saccade trials), in which the image shown was a textured grey box. The instructions were summarized on the screen explicitly, stating whether the subject was to look at or away from the image. Following training, the experimental session began. Each trial had the following structure: (1) orienting stimulus (cross hair; jittered 300-400ms to avoid anticipation effects); (2) cue = one of 6 unique cocaine images, 6 unique neutral images, or 6 neutral (gray) images, counterbalanced either to the left or right; (3) image cue removed from screen after 800ms; (4) followed by an intertrial interval (1600ms). For the pro-saccade trials, the subject was instructed to look *at* the image. Conversely for the anti-saccade trails the subject was told to look *away* from the image and fixate on the blank screen on the opposite side (Figure 2.1). On test days (e.g., 1 session), four counterbalanced blocks (2 pro-, 2 anti-saccade) were administered per session in a latin-square design, with 36 pro- and 36 anti-saccade trials in each. Cocaine-related images were matched as closely as possible to neutral images on visual characteristics such as color, background, and complexity. Each of the images (250 x 188 pixels) was presented on a 304 x 378mm screen, either 7^{o} to the left or right of the centered fixation cross. Each session of this task lasted 8-10 min. Trials interrupted with blinks (which render accurate measurement invalid) were captured, aborted, and then the trial was reinserted at the end of the test block. Thus each subject completed the same number of valid trials and no data were lost due to blinks (Patel et al., 2011).

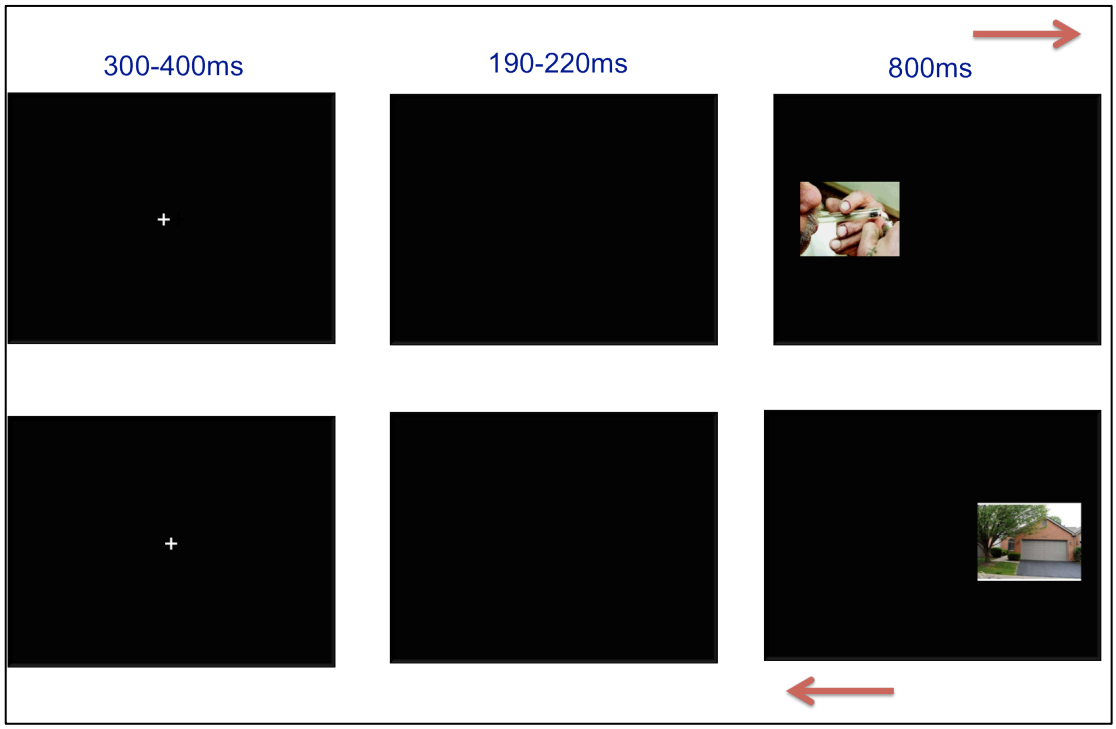

Figure 2.1: Eye-tracking anti-saccade task. The subject must attend away from the stimulus, to the opposite blank hemifield. (Pro-saccade task is identical, except the subject must look *toward* the stimuli)

Dependent Measures

This eye-tracking task captured two important indices: (1) pro- and anti-saccade errors (the latter defined as failure to inhibit a reflexive saccade towards the image and look in the opposite hemi-field), and (2) saccadic response times and latencies (the time it takes for the subject to break fixation and complete the appropriate saccade [pro- or anti-] after stimulus presentation). In order to keep the scope and focus of the report concise, only error rates will be reported in this chapter. Additionally, prior to beginning the attentional bias task, all subjects were given three

questionnaires to assess obsessive-compulsive behavior related to drug use, stress, and cocaine craving.

The Obsessive-Compulsive Cocaine Scale (OCCS) [Jardin, 2011; Vorspan, 2012] is a 14-item scale developed based on the Obsessive-Compulsive Drinking Scale, which focuses on separation and measurement of both obsessive and compulsive aspects of cocaine use. The present analyses focused on the obsessive factor score, as it has shown better predictive power related to cocaine use severity [Vorspan, 2012]. The Perceived Stress Scale (PSS) [Cohen, 1983; Cohen 1988] is 10-item scale widely used in health studies, developed to measure the degree to which individuals appraise their life as stressful. The scale has a 5-point Likert-type response format. The Visual Analogue Scale - Cocaine Craving (VAS-CC) is a brief 3-item instrument in which subjects mark a point on a 100 mm line to indicate NOT AT ALL or VERY MUCH to three cocaine-related questions: Right now, how much are you craving cocaine?, Over the last week on average how much have you been craving cocaine?, Over the last week how much did you crave cocaine when your craving was at its worst? [Sayette 2000]. The OCCS and VAS-CC was given to cocaine-using subjects only. All subjects completed the PSS.

2.3 Statistical Analyses

The following hypotheses were tested: (1) Error rates across anti-saccade trials will be greater in the cocaine-dependent group relative to

controls across all stimuli (2) Error rates during anti-saccade trials will be greater within the cocaine-dependent group on drug vs. neutral stimuli (interaction) (3) Error rates during anti-saccade trials will be greater in the cocaine-dependent group vs. the controls group, specifically in the presence of cocaine stimuli (interaction).

Initial linear effects mixed models using the R 'lmer' package examined the effects of group (cocaine-dependent, control), stimulus type (cocaine, neutral, shape), and the group x stimulus type interaction. Separate models were run for pro-saccade and anti-saccade error rates, as the direct comparison of the two trial types was not of interest in this study and has already been well-established in many disease models (Patel et al., 2012; Bowling et al., 2012; Hutton et al., 2002; Reuter et al., 2007).

The cocaine group was older than the control group, $t(85) = 2.95$, $p < .01$. This age difference is pervasive in studies of inner-city cocaine users, which are generally between 40 and 55 years old (Moeller, 2010, Haile, 2012, Kampman, 2013). Healthy control subjects in this age range without pathology are overwhelming employed and unable or unwilling to participate in research studies conducted during working hours. However, anti-saccade error rates increase with age (Shafiq-Antonacci, 1999). Thus the statistical models included age to control for the age difference between groups.

Initial demographic comparisons indicated that the two groups were different on age, education, and gender. Therefore, these three variables were examined as potential confounders, which are marked by the difference

between groups and a correlation of the confounder with the dependent variable (error rates) (Pocock et al., 2002). Pearson correlations indicated that only age was significantly correlated with anti-saccade error rates, and it was therefore the only confounder in the dataset. Therefore, age was included as a covariate in the statistical model, and the results indicated a significant difference in ages between the groups. The residuals from the initial linear model were examined for violations, with the Satterthwait approximation for degrees of freedom, of underlying assumptions that posed threats to stability and reliability, e.g., non-normality, heteroskedasticity, collinearity, and leverage. Any violations of normality of residuals were identified via Welch-Satterthwaite approximation, however, no violations were observed in this dataset. Post-hoc testing of significant main effects or interactions utilized testing of least-squared means using the R 'difflsmeans' command in order to establish factor-specific differences between and within groups, in which age was held constant. All post-hoc test outcomes were FDR corrected for multiple comparisons.

2.4 Heat Maps

Heat maps were designed as an additional visual tool to confirm the results found in Aim 1, and to more closely determined where subjects' gaze was directed on anti-saccade errors (e.g., at the drug stimulus, or elsewhere on the screen). Attentional allocation was examined in finer resolution by generating heat maps of eye positions in which raw XY eye coordinates were

calculated for each subject on anti-saccade trials with cocaine stimuli and anti-saccade trials with neutral stimuli. Separate heat maps were constructed for trials in which the stimulus appeared on the left and right side of the screen. All XY eye positions in which the subject's eyes were fixated on the crosshair in the middle of the screen (trial initiation) were removed from the dataset, e.g., all XY data points between 0.4 and 0.6 of the monitor screen were filtered out. After removing fixation data points, when combining all subjects within a group (control, cocaine) the datasets comprised over 10^6 data points in each group. The resulting heat maps were very dense and rich in eye movement patterns, however for some stimuli the differences were indistinguishable without multiple layers of filtering. Subsequently, the eye-movement data from all subjects in each group (cocaine and control) were collapsed together specifically for the cocaine-cue anti-saccade trials and shown in Figure 2.4.

2.5 Questionnaires

Correlational analyses were conducted between total anti-saccade errors across all stimuli and the PSS score, as well as between anti-saccade cocaine stimuli and the PSS score. The OCCS and VAS-CC were only conducted in the cocaine-dependent group. Specifically, pair-wise correlations were conducted between OCCS score and a difference score {(neutral + shape cue anti-saccade errors / 2) – cocaine cue anti-saccade errors} as well as between the VAS-CC and the difference score. Pro-

saccade error rate correlations were conducted in the same manner. The purpose of these correlations was to examine the possibly that cocaine-specific error rates were related to cocaine use, cocaine craving, or stress.

3. Results

3.1 Demographics

Shown in Table 2.1, cocaine-dependent subjects were older than controls (46.3 ± 8.4 vs. 40.0 ± 11.3 years, t (85) = 2.95, $p < .01$), differed in gender distribution compared with controls (85% male cocaine-dependent vs. 51% male controls, X^2 (1)= 11.41, $p < 0.00$), and had a lower educational level (12.1 ± 1.8 years for cocaine-dependent vs. 14.2 ± 2.3 years for controls, (t (77) = 4.47, $p < 0.00$). All subjects had normal or corrected-to-normal vision and none were color-blind. Pearson correlations of demographics (age $p<0.00$, education $p<0.96$, and gender $p<0.51$) with anti-saccade errors determined age to be the only confounding variable. Correlations with pro-saccade errors did not suggest any significant confounders. Therefore, none of these three variables were included in the pro-saccade statistical models.

3.2 Behavioral results during eye tracking

Analysis of errors including age as a covariate yielded a significant group x stimulus interaction (F [84, 167] = 4.81, $p< 0.01$). There was also a

main effect of group, indicated by significant differences in error rates between the two groups ($t = 2.63$, $p<0.01$) across all stimuli. A main effect of stimulus was also observed, shown by anti-saccade differences collapsing *across both groups* for cocaine > neutral cues ($t = 2.47$, $p<0.01$) and cocaine > shape cues ($t = 2.86$, $p<0.00$) (Figure 2.2). Overall, cocaine-dependent subjects made more errors during anti-saccade trials across all stimuli. Pro-saccade trials did not reveal any main effect of group ($F [84, 167] = 1.54$, $p< 0.22$), stimulus ($F [84, 167] = 0.09$, $p< 0.91$), or interaction of group x stimulus ($F [84, 167] = 0.41$, $p< 0.66$). Error rates for both groups and all stimuli types are shown in Table 2.2.

Table 2.2
Error Rates: All results are % ± SEM

Anti-saccade Trials			
	Cocaine Cue	Neutral Cue	Shape Cue
Cocaine Subject	40.94 ± 3.11	35.24 ± 2.96	28.35 ± 2.96
Control Subject	27.24 ± 3.3	28.35 ± 3.54	22.56 ± 3.24
Pro-saccade Trials			
	Cocaine Cue	Neutral Cue	Shape Cue
Cocaine Subject	3.26 ± 1.09	3.08 ± 1.30	3.89 ± 1.38
Control Subject	5.69 ± 1.34	5.79 ± 1.61	5.49 ± 1.25

Post hoc testing of specific interactions during anti-saccade trials indicated a significant difference of between groups ($p<0.03$) on trials with cocaine stimuli, but this difference was observed between groups ($p<0.48$) on trials with neutral stimuli. In addition, significant differences were observed within the cocaine group, between cocaine and neutral stimuli ($p<0.00$),

where significantly more errors were made on the cocaine stimulus vs. neutral or shape stimulus trials. Within the control group, no differences were observed between cocaine and neutral ($p<0.58$) or cocaine and shape stimuli ($p<0.21$). These raw p values were FDR corrected and all of the significant least-square mean tests remained significant after correction. All post-hoc results shown in Figure 2.3.

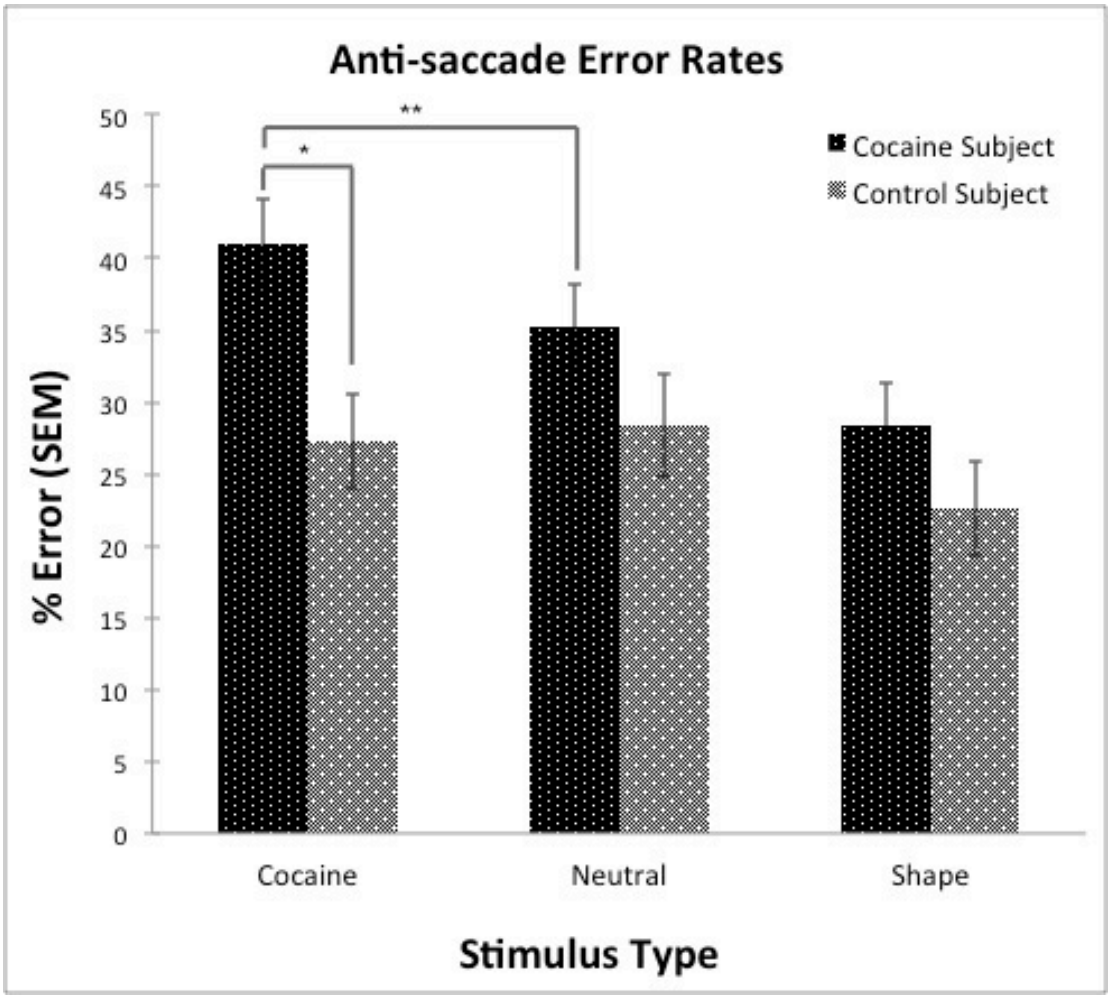

Figure 2.2: Anti-saccade error rate results of linear mixed-effects analysis

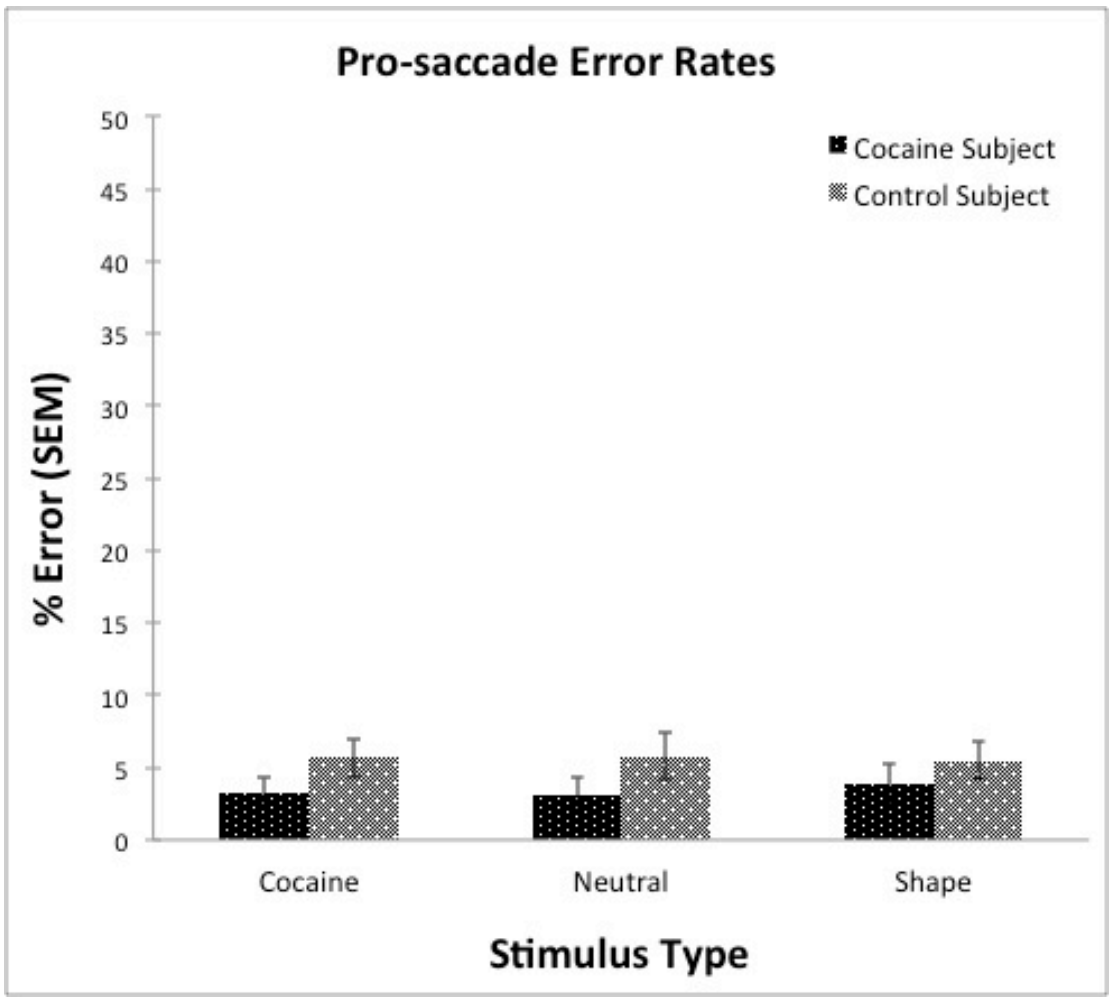

Figure 2.3: Pro-saccade error rate results of linear mixed-effects analysis

3.3 Heat Map Results

Figure 2.4 shows the data points across all subjects during anti-saccade cocaine trials from each respective group (cocaine & control), plotted in juxtaposition. During these trials, the subjects were instructed to look away from the stimulus (cocaine cue). The XY points found on the ipsilateral side are errors (i.e. points found on the left side during a left stimulus are error points). A greater density and an overall more erratic profile of XY points are found on the incorrect (or error) side of the screen for cocaine-dependent subjects vs. controls, which provides a visual reiteration of the results shown in Figure 2.2.

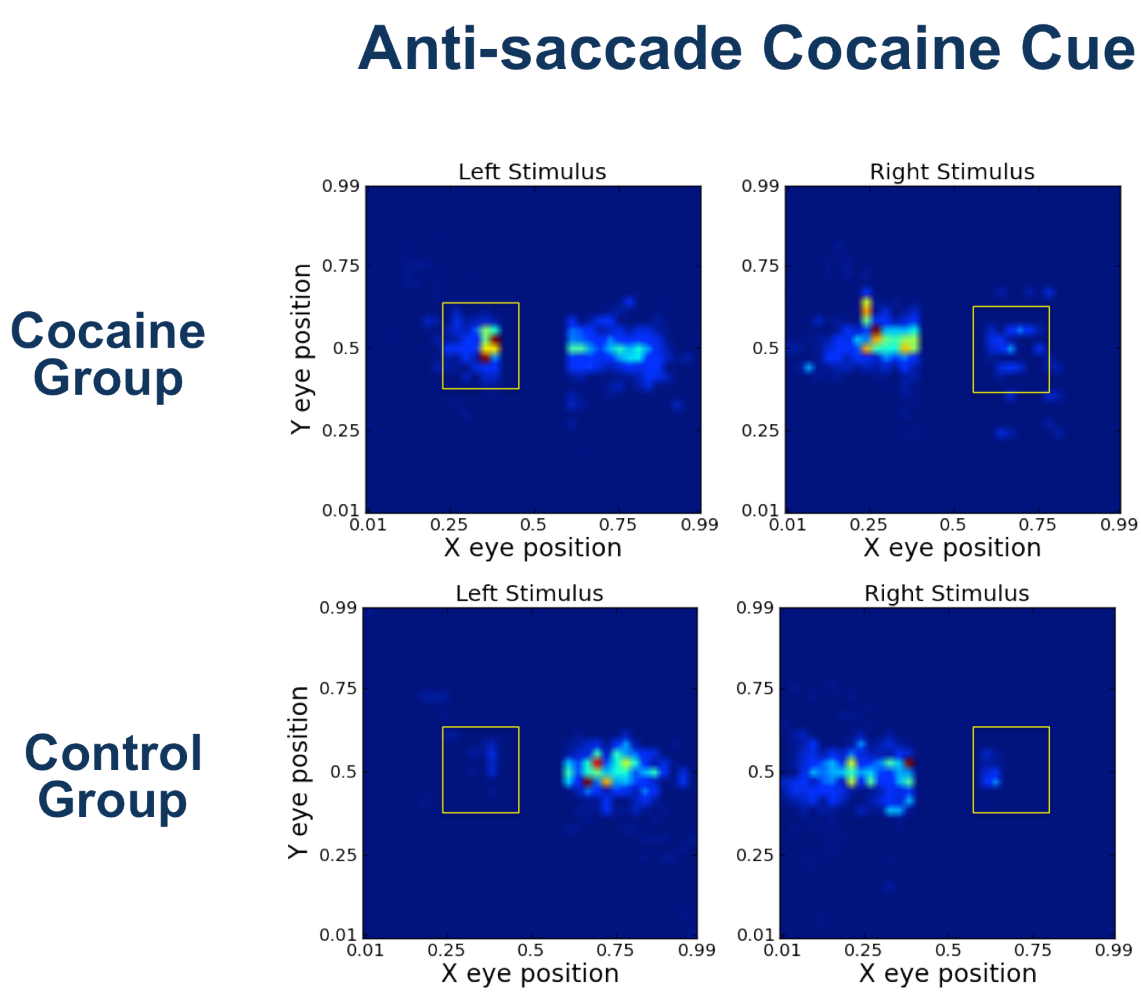

Figure 2.4: Heat maps for anti-saccade cocaine trials. Errors highlighted in boxes.

3.4 Questionnaires

Pair-wise correlations of total anti-saccade errors across all stimuli with total PSS score by group ($p<0.62$) as well as anti-saccade cocaine stimuli against the PSS total score by group ($p<0.29$) did not reveal any statistically significant results. Likewise, correlations between OCCS and difference score (neutral and shape errors - cocaine errors) ($p<0.06$) and VAS-CC with difference score ($p<0.47$) also failed to provide any substantial correlations with the error rates. Correlations between pro-saccade error rates across all stimuli with total PSS score by group ($p<0.93$) as well as pro-saccade cocaine stimuli against the PSS total score by group ($p<0.96$) did not reveal any significant results. Likewise, correlations between OCCS and difference score ($p<0.85$) and VAS-CC with difference score ($p<0.14$) also failed to provide any substantial correlations with the error rates.

4. Discussion

Prior experimentation has examined eye movements in cocaine dependent subjects (Demer et al., 1989). Studies that have investigated saccades within this population were limited to visual scanning paradigms (Rosse et al., 1997, Rosse et al., 1993). These studies reported that cocaine craving scores were inversely correlated with the number of preattentive fixations and saccades as well as positively correlated with the number of attentive fixations toward pictures of cocaine cues. Therefore, in order to advance the understanding of attention and eye movements in this substance

abuse population, this present study aimed to pinpoint quantitative measures of saccadic eye movements in cocaine-dependent individuals using an eye-tracking attentional bias task. This study evaluated both anti-saccades and pro-saccades during a cocaine picture attentional bias task, in which the primary dependent measure was the number of anti-saccade errors.

When healthy participants are instructed to compete an anti-saccade task, evidence shows that typically participants are more prone to errors during anti-saccade trials in comparison to pro-saccade trials (Everling and Fischer, 1998). This suggests that anti-saccade trials require an initial inhibition of reflexive orienting, which is then followed by a generation of a voluntary saccade to the opposite hemifield (Unsworth et al, 2011). Many studies have shown that individuals who engage in longstanding abuse of cocaine develop deficits in inhibitory control (Lane et al., 2007; Fillmore et al., 2013), therefore anti-saccade errors would be expected in this population. In following with the main hypotheses of the study, cocaine-dependent subjects made more overall anti-saccade errors indicating a deficit in inhibitory control, as well as more errors, specifically on trials with cocaine stimuli compared to neutral stimuli, indicating a strong attentional bias toward drug cues. The results support these hypotheses in that the cocaine-dependent group made more anti-saccade errors across all stimuli (cocaine, neutral, and shape), compared to control subjects. This provides evidence that cocaine-dependence subjects have poor inhibitory control over saccades and

sustained prefrontal cortex dysfunction, to the extent that these phenomena are sensitive to anti-saccade performance.

Cue-specific results showed a main effect of group (cocaine > control, 35% vs. 19% anti-saccade errors, $p<0.00$), such that cocaine-dependent subjects made significantly more errors during cocaine cues than controls. This operationally defined demonstration of attentional bias toward cocaine cues is consistent with findings in cocaine users on the picture and word emotional Stroop task (Hester et al, 2006). Importantly, results indicated a group x stimulus interaction, such that significantly greater errors towards cocaine-related vs. neutral stimuli (41% vs. 20% anti-saccade errors, $p<0.01$) were shown in cocaine-dependent subjects only; no difference were observed between cocaine and neutral stimuli in the control group. This differential outcome between groups on cocaine vs. neutral stimuli provides evidence of specificity of the attentional bias phenomena within this novel eye-tracking task; anti-saccade errors are greatest when cocaine users are viewing cocaine cues.

Pro-saccade error rates between groups were non-significant and very low across all stimuli (6% cocaine subjects vs. 3% control subjects). Error rate performance from the cocaine-dependent group was slightly better than controls, as shown in Table 2.2. Pro-saccade error rates were not of main interest to our hypothesis, but the uniformly low error rates argue against a non-specific global CNS dysfunction in the cocaine-dependent group, and provide evidence that anti-saccade error rates were not due to differences in

motivation or attention to the task, or disruptions of simple sensory function. This outcomes helps to validate the sensitivity of the anti-saccade task, in which the cocaine-dependent group performed significantly worse than controls, especially in the presence of cocaine cues. There is not any suggestion of gross CNS oculomotor dysfunction based on pro-saccade error rates (Munoz and Everling, 2004). While we do not have corroborative fMRI data the poor anti-saccade error rates suggest portions of the saccadic circuitry may be disrupted in cocaine dependence. Other studies have shown then when FEF is lesioned, the suppression of the reflexive pro-saccade remains intact, however, the ability to generate anti-saccades is impaired (Gaymard et al., 1998; Davidson et al., 1999). Furthermore, imaging results in healthy elderly subjects more prone to a decline in executive function indicate after cognitive decline, the aged FEF activity was associated with poor anti-saccade performance (Pa et al., 2014).

Correlations between the each of the questionnaires PSS, OCCS, VAS-CC and anti-saccade error rates respectively did not yield any statistically reliable results, although we did observe a trend on the OCCS. Cocaine has been shown to dysregulate the stress system and affect executive function when high levels of stress are evident (Fox et al, 2009). Therefore, we initially expected that higher PSS scores would be correlated with anti-saccade errors in the cocaine group. However, the results did not support this hypothesis. Poor anti-saccade performance has been reported for cocaine-dependent subjects who endorsed compulsive foraging for drugs

compared to cocaine users who did not endorse this behavior (Rosse et al., 1994). However, no anti-saccade differences were found between the entire group of cocaine dependent patients and controls alone. The current study did not make this subgroup distinction within the cocaine population, which may explain the weak correlation between error rates and OCCS score. Finally, the VAS-CC, which measured subjective craving, was not meaningfully correlated with anti-saccade error rates. Previous visual scanning studies have reported that heavy cocaine users displayed a 90s visual path pattern very similar to the entire cocaine-related picture they scanned (as opposed to a small portion) probably likely due to the associated reports of higher craving and greater interest in the cocaine image (Rosse et al., 1993). The lack of association of craving following testing and anti-saccade errors in this study may not be due a lack of stimulus effect on craving, rather the short period of stimulus presentation; the on-screen stimulus time of 800ms may not be sufficient to observe this phenomenon, rather inhibitory control deficits may have taken dominance during anti-saccade trials. The lack of association with more temporally distinct craving reports remains undetermined.

Collectively, the results support the primary hypotheses, and confirm that an eye-tracking based measure of attentional bias is a quick, noninvasive, and valid assessment of prefrontal deficits and attentional-bias to cocaine cues. It has sensitivity and specificity, and may prove useful in efforts toward relapse prevention. The predictive utility of attentional bias

toward drug-related cues has been documented in cocaine-dependent individuals (Carpenter et al., 2006) as well as in alcohol abusing subjects (Cox et al., 2007), smokers (Waters et al., 2003), and heroin users (Marissen et al., 2006). The consistency of this phenomenon is evident in predicting relapse in binge eating patients (Overduin et al., 1995), and symptom severity in individuals suffering from traumatic experiences, such as PTSD (Elsesser et al., 2005). By implementing this novel attentional bias eye-tracking task prior to any treatment efforts, researchers may be able to extract information regarding physiological and behavioral susceptibility to relapse, which may help tailor more specific treatment interventions. This information could, for example, be used to screen novel medications targeted at reducing the effect of cue-reactivity in salient situations, thereby reducing the likelihood of relapse, or serve as a predictive marker of successful abstinence or susceptibility to relapse following rigorous treatment efforts.

4.1 Limitations and Future Directions

One limitation of this study was heterogeneity in the subject population, such that when controlled, these factors would aid in the prediction of relapse even more precisely. Individuals were both treatment seeking and non-treatment seeking and ages varied with significant differences. We also did not account for any gender specific differences. We also do not know how the length of time of each subjects' cocaine use, both longitudinally and

acutely, relates to each of the outcomes. Furthermore, other measures of validation that are important in substance abuse research were not taken into account, such that we don't know if higher craving causing longer reaction times or if more frequent use attributes to higher error rates. We have, however, established that this task is sensitive and reliable, but due to these limitations, we do not know how well this tool predicts relapse at this point. Moving forward, we would like to extend this study to different subject populations and including more trials to further understand the predictive utility of this task and establish how versatile this tool can be across different disease populations. In addition, we would move forward with a study that implements an acute drug intervention or one that follows subjects throughout treatment and afterwards to validate relapse. These suggestions were beyond the scope of this project, but are necessary next steps in validating this tool as a predictive measure of relapse in addiction.

CHAPTER 3: SACCADIC REACTION TIME LATENCIES SHOW DEFICITS IN EXECUTIVE FUNCTION IN COCAINE-DEPENDENT SUBJECTS

1. Introduction

Drug abuse is disorder marked by chronic relapse and craving even after treatment efforts and prolonged periods of abstinence (Gawin and Kieber, 1986). Relapse is often triggered through environmental stimuli that was formerly associated with the self-administered drug of choice. These stimuli have a large influence on drug-seeking behavior, but evoking memories of emotions during drug administration, which induces craving for the drug and precipitates into reuse of the drug (Childress et al., 1999). Drug-evoked increases in dopamine, a key neurotransmitter involved with reward, is involved with the reinforcing effects of cue-elicited craving cocaine dependent individuals (Volkow et al, 2006). Experiments involving cocaine depending subjects have shown a strong physical reaction when presented with cocaine related cues (Childress et al., 1994, 1999; London et al., 2000), however, studies investigating attentional processing in cocaine addiction as a predictor of relapse have been limited (Franken et al., 2000). Studies, which have used the drug Stroop task, demonstrate that cocaine-dependent individuals exhibit attention bias toward cocaine related cues (Copersino et al. 2004; Hester et al 2006; Cox et al, 2006). Neuroimaging studies also report an association with drug-cue responses and craving in cocaine dependent individuals (Garavan et al, 2000; Hester et al, 2006; Hester and Garavan, 2004). The psychological symptoms of craving driven by these cocaine-related cues, such as people and places associated with the drug use, are strong factors in the relapse of cocaine addiction (O'Brien et al, 1998).

A sensitive method of measuring cognitive processes is through saccadic eye movements. Saccades are rapid eye movements that move from one fixation point to another. When presented with a stimulus, the most common response is to shift the gaze toward a salient cue, which is defined as a pro-saccade. With further instruction, however, direction can be given to look in the opposite direction of a stimulus, which is known as an anti-saccade (Everling and Fischer, 1998). In order to accurately execute an anti-saccade, two innate processes must be intact and functional. First, the individual must suppress a reflexive response to attend to the stimulus (pro-saccade), and second make a voluntary visually guided saccade to the opposite hemifield of the stimulus (anti-saccade) (Munoz and Everling, 2004). This two processes process, primarily mediated by the dorsolateral prefrontal cortex (DLPFC) and frontal eye fields (FEF), are vital for producing correct anti-saccades. The DLPFC is vital for inhibitory control, and FEF for voluntary movement (Guitton et al 1985, Gaymard et al 1998). Cocaine related stimuli have been shown to impair inhibitory control, a frontally controlled action, in cocaine dependent individuals (Pike et al, 2013). Therefore impairments to these frontal areas cause difficulty in proper execution of this task resulting in loss of attentional control and latencies in anti-saccade reaction times. In addition, pro-saccade reaction times, a strong measure of reflexive control, would provide insight into the saliency of cocaine cues and the bias experienced by the cocaine dependent subject.

Attentional control is vital for successful competition of the anti-saccade task (Hallet, 1978). A lapse in this attention most likely will lead to longer reaction times or an error. Typically reaction times are slower during anti-saccade trials (anti-

saccade cost) vs. pro-saccade due to the two-step process of initially inhibiting a pro-saccade then generating a voluntary saccade away from the target (Godijn and Kramer, 2007). Patient populations with attention control deficits, such as a lesion to the frontal eye field, have slower correct anti-saccade response times compared to controls (Gaymard et al, 1998). Schizophrenic patients also display this saccadic profile of longer anti-saccade reaction times compared to controls (McDowell and Clementz, 2001). Cocaine-dependent subjects display similar cortical deficits, such as compromised attention and voluntary control, and therefore are expected to also have slower anti-saccade response times compared to controls.

Historically, reaction time analyses have not examined the whole reaction time distribution, meaning that the central tendency is the point of focus and data components outside of the main Gaussian distribution are disregarded. This method, although widely used, may obscure unique findings and lead to a misinterpretation of similarity for two distributions that are actually very different (Whelan, 2008). Reaction time distributions, unlike Gaussian distributions, characteristically begin by rising on the left then decaying into a long positive tail on the right. This distribution can be described by an ex-Gaussian, which is a mixture of a Gaussian distribution and an exponential (Balota and Spieler, 1999). The ex-Gaussian distribution has three primary parameters: mu, sigma, and tau (Figure 3.1). Mu is the mean of the normal distribution, sigma represents the variation on the normal distribution, and tau describes the mean and variation of the exponential component in the distribution (Whelan, 2008; Vaurio et al., 2009; Hervey et al., 2006). Within the reaction time analysis of eye-movement patterns, mu and sigma

represent a distribution of faster responses (evaluation of pro-saccades), and tau provides more precise characterization for slower reaction times (anti-saccade performance).

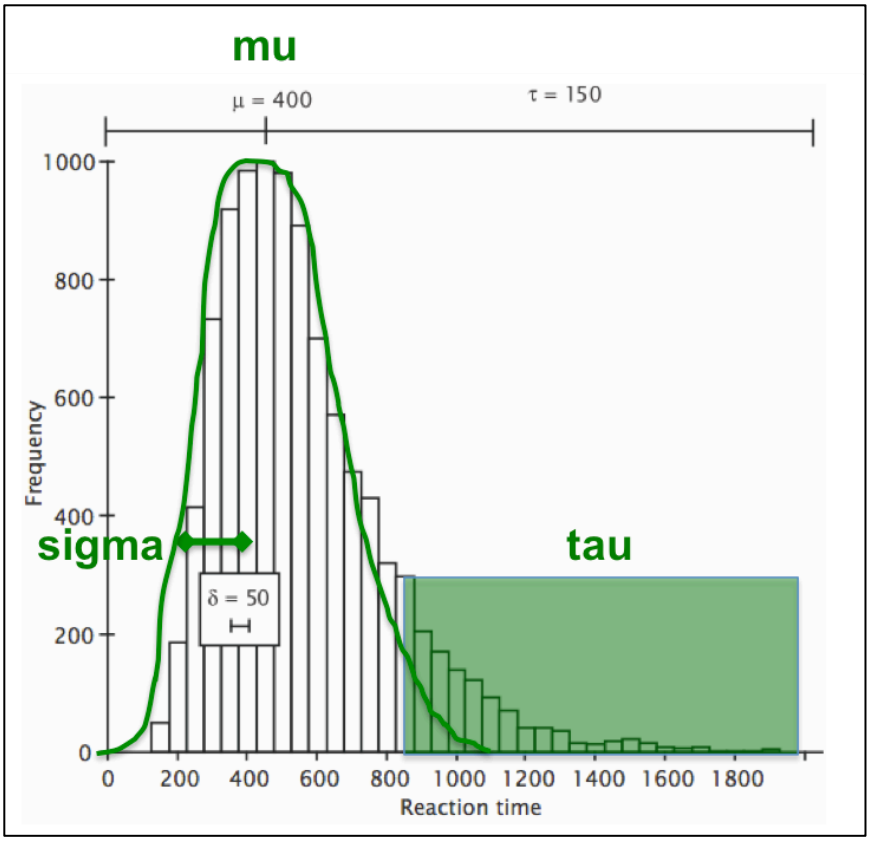

Figure 3.1: Ex-Gaussian distribution. (Adapted from Whelan, 2008).

In ADHD populations, the increased variability and longer latency has been shown in the tau component of the ex-Gaussian distribution, which has been hypothesized to be due to occasional lapses in attention or mind-wandering during the task (Leth-Steensen et al., 2000). During cocaine Stroop task, cocaine-dependent subjects showed greater tau on trials with cocaine-related words compared to controls (Liu et al, 2011) A similar profile of anti-saccade performance

is expected for cocaine dependent individuals during this eye-tracking attentional bias task due to the drug cue-related attentional distractions. On the other hand, craving and saliency evoked by cocaine cues may promote quicker reflexive attention toward the drug stimuli, indexed by faster pro-saccade reaction times in cocaine-dependent individuals.

This study examined reaction times during presentation of cocaine and neutral stimuli during pro-saccade and anti-saccade trials. The analysis focused on validating the following specific aims: To evaluate reaction time distributions during presentation of cocaine and neutral stimuli to cocaine dependent subjects vs. controls. The following hypotheses were tested: (1) Reaction time distributions during pro-saccade trials will be significantly faster on drug vs. neutral cues in cocaine dependent subjects relative to controls. (2) Reaction time distributions during anti-saccade trials will show longer RT latencies during cocaine cues for cocaine dependent subjects relative to controls.

2. Materials and Methods

2.1 Subjects

Subject details are identical those listed in the materials and methods of Chapter 2.

2.2 Eye-Tracking Cocaine Attentional Bias Task

Details of the eye-tracking task are identical to those listed in the materials and methods of Chapter 2.

Dependent Measures

This eye-tracking task captured two important indices: (1) pro- and anti-saccade errors (the latter defined as failure to inhibit a reflexive saccade towards the image), and (2) saccadic response times. Response time (RT) was defined as the time required to leave the 0.4x0.6 area of the screen, which was defined as the center surrounding the fixation cross, and then break the stimulus box on the left or right side of the screen. Subjects rarely fixated after making an anti-saccade error. Since the subjects would either continue to move their eyes or try to correct the error by averting gaze to the opposite side of the screen, RTs for error trials were not captured. The results of the error rates were reported in chapter 2, and therefore only response times will be reported in this chapter.

Additionally, prior to beginning the attentional bias task, all subjects were given three questionnaires to assess obsessive-compulsive behavior related to drug use, stress, and cocaine craving. The Obsessive-Compulsive Cocaine Scale

(OCCS) [Jardin, 2011; Vorspan, 2012] is a 14-item scale developed based on the Obsessive-Compulsive Drinking Scale, which focuses on separation and measurement of both obsessive and compulsive aspects of cocaine use. The present analyses focused on the obsessive factor score, as it has shown better predictive power related to cocaine use severity [Vorspan, 2012]. The Perceived Stress Scale (PSS) [Cohen, 1983; Cohen 1988] is 10-item scale widely used in health studies, developed to measure the degree to which individuals appraise their life as stressful. The scale has a 5-point Likert-type response format. The Visual Analogue Scale - Cocaine Craving (VAS-CC) is a brief 3-item instrument in which subjects mark a point on a 100 mm line to indicate NOT AT ALL or VERY MUCH to three cocaine-related questions: Right now, how much are you craving cocaine?, Over the last week on average how much have you been craving cocaine?, Over the last week how much did you crave cocaine when your craving was at its worst? [Sayette 2000]. The OCCS and VAS-CC was given to cocaine-using subjects only. All subjects completed the PSS.

2.3 Statistical Analyses

Initially, all impossible reaction times (<=100ms) and missing values were removed from the dataset. Kernel density plots for each of the 6 conditions, anti-saccade cocaine, anti-saccade neutral, anti-saccade shape, pro-saccade cocaine, pro-saccade neutral, pro-saccade shape, were created in order make comparisons of reaction time distributions between the two groups, shown as Figures 3.2-3.7 respectively. Since RT distributions are often not Gaussian (Whelan, 2008),

especially for anti-saccades, the Kolmogorov-Smirnov test (K-S test) was implemented, as it is non-parametric and makes no distributional assumptions. Group distributions were compared to evaluate reliable differences in RTs between the groups (Table 3.1). Significance values from the resulting K-S tests were then controlled for multiple comparisons through the use of Holm corrections on the raw p values.

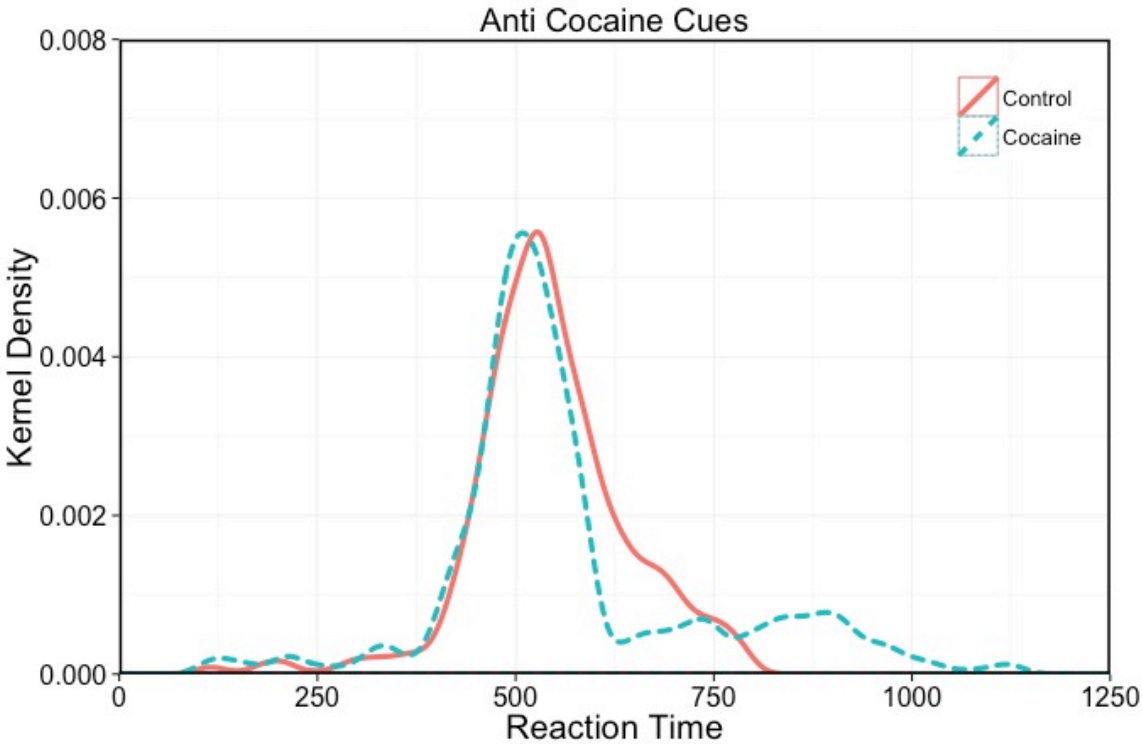

Figure 3.2: Anti-saccade cocaine RT distribution; KS test: p<0.00*

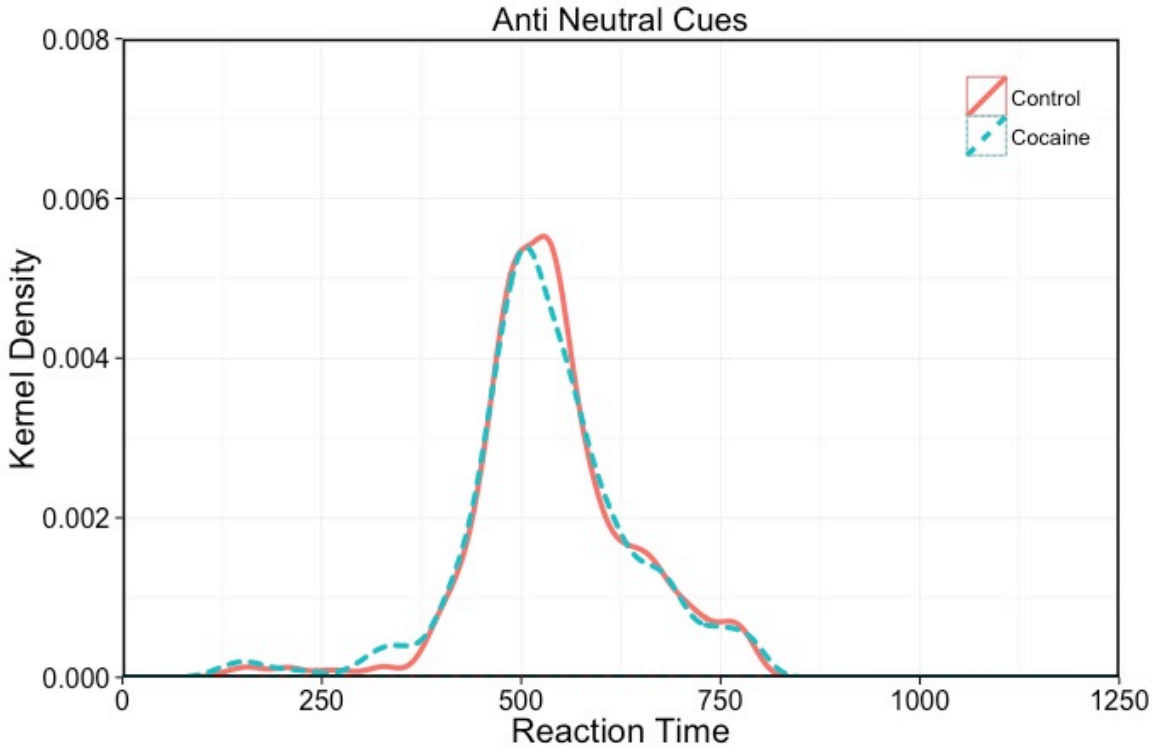

Figure 3.3: Anti-saccade neutral RT distribution

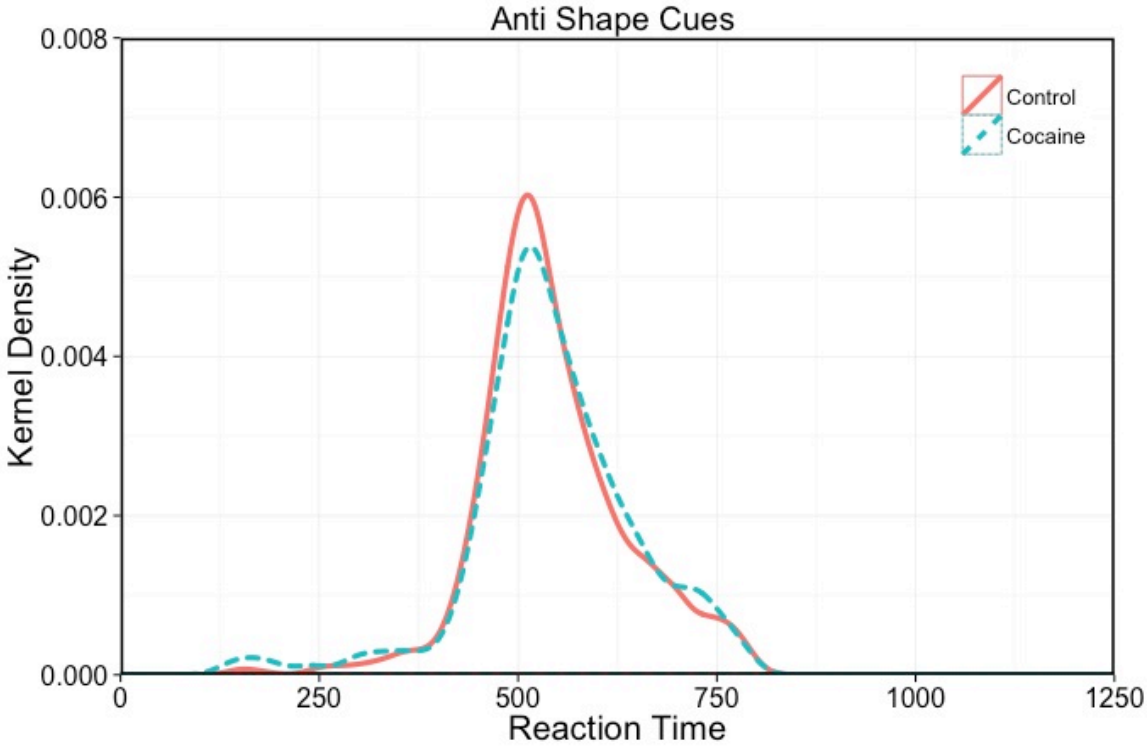

Figure 3.4: Anti-saccade shape RT distribution

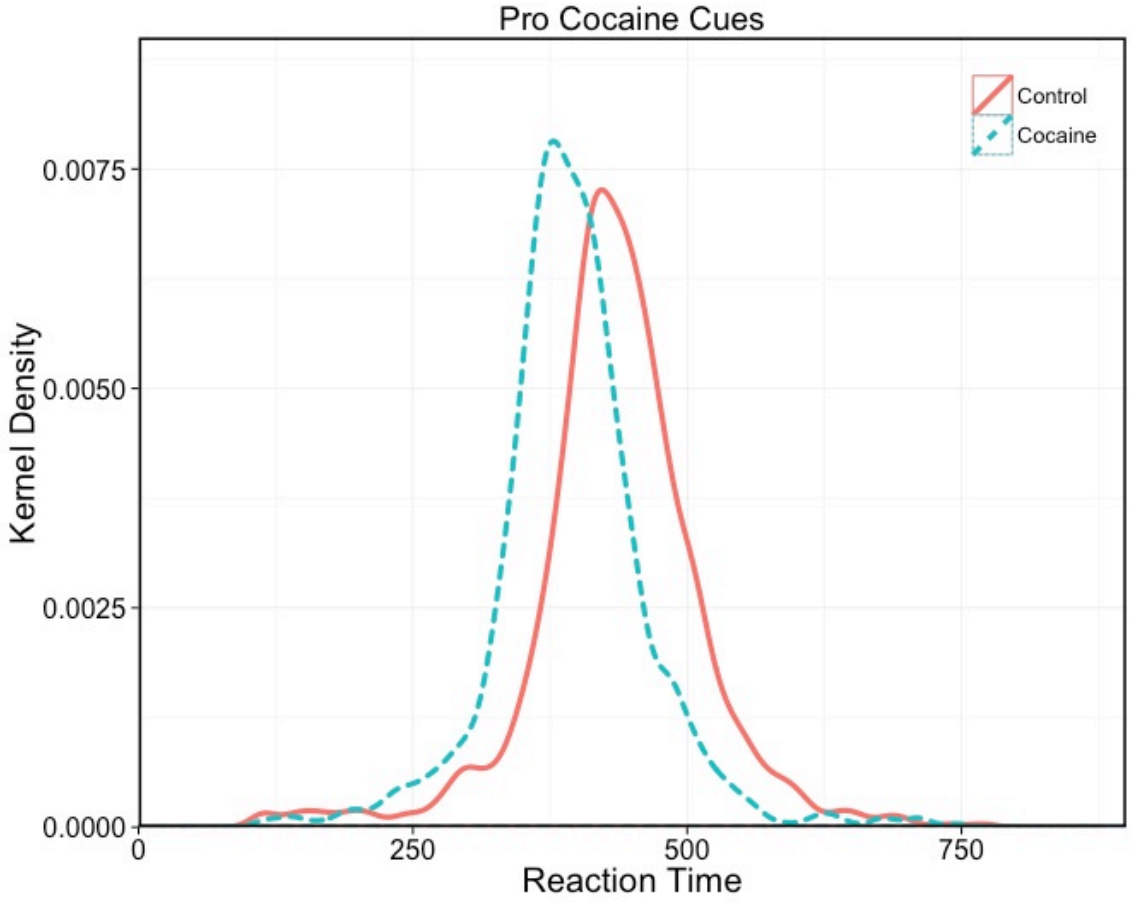

Figure 3.5: Pro-saccade cocaine RT distribution; KS test: p<0.00*

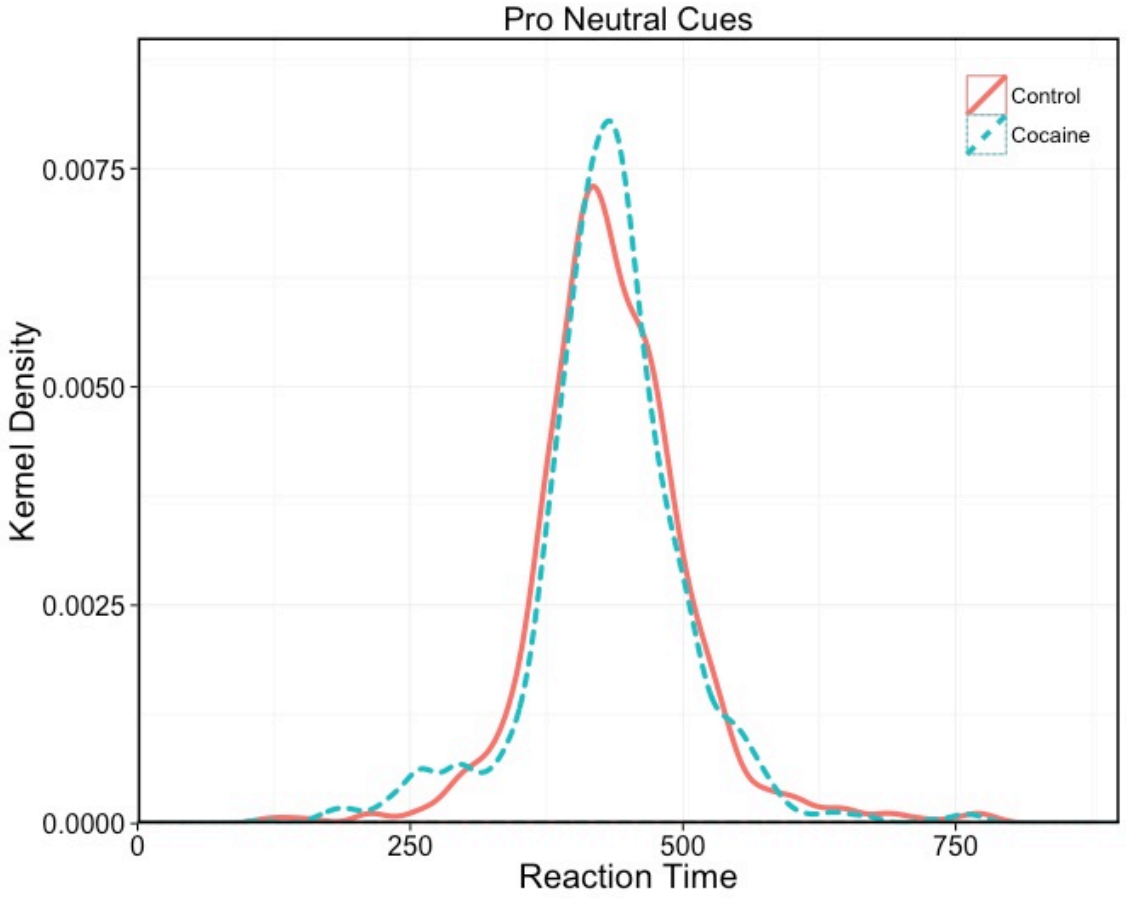

Figure 3.6: Pro-saccade neutral RT distribution

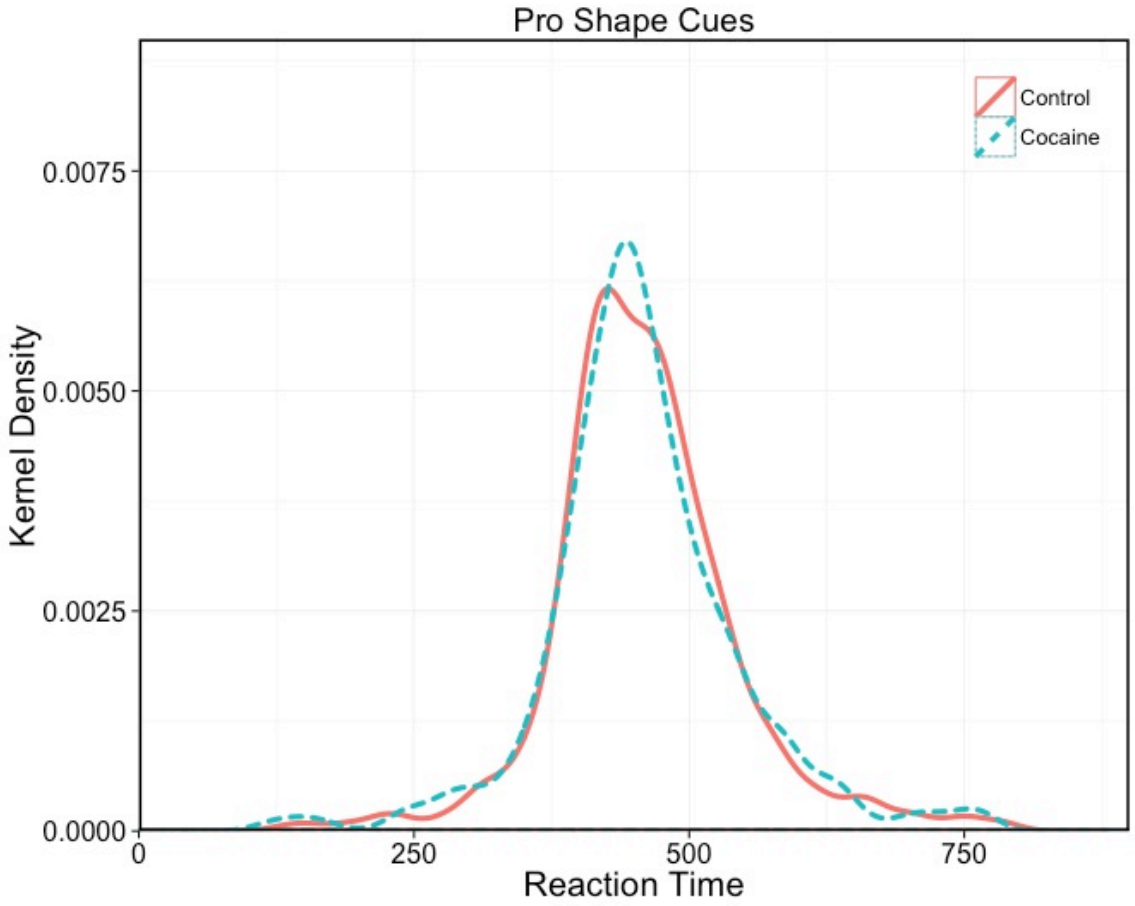

Figure 3.7: Pro-saccade shape RT distribution

As previously noted, RT distributions are frequently skewed and recent approaches have used ex-Gaussian analyses to examine both normal and non-normal tails of the distributions (Whelan, 2008; Hervey et al., 2006; Leth-Steensen et al., 2000). All three parameters of the ex-Gaussian model were evaluated, such that values for mu, sigma, and theta were generated for each of the 6 conditions as previously listed (Leth-Steensen et al. 1999). Mu is defined as the mean of the Gaussian, sigma, the standard deviation of the Gaussian, and tau, the mean and standard deviation of the exponential component (Unsworth et al, 2011).

The analysis evaluated the following hypotheses: (1) Reaction times (mu) during pro-saccade trials will be significantly faster on drug vs. neutral cues in cocaine dependent subjects relative to controls. (2) Reaction times (tau) during anti-saccade trials will show longer RT latencies during cocaine cues for cocaine dependent subjects relative to controls.

A mixed model using the R 'anova' command examined the effects of each parameter (mu, sigma, and tau) on group (cocaine-dependent, control), stimulus type (cocaine, neutral, shape), and the group x stimulus interaction (conducted simultaneously for pro-saccade and anti-saccade reaction times since both saccadic measures were of interest to our hypotheses). Demographic comparisons, shown in Table 2.1, indicated that the two groups were different on age, education, and gender. Therefore, these three variables were tested against ex-Gaussian reaction time values mu, sigma, & tau as potential confounders, which is defined as the difference between groups and a correlation of the confounder with the dependent variable (reaction times) (Pocock et al., 2002). Pearson correlations

indicated age was significantly correlated with mu, sigma, and tau ex-Gaussian reaction times, while gender and education were not. Therefore, age remained the sole confounder in this dataset and was included as a covariate in the ANOVA models. However, age was not a significant independent predictor in any results (mu, sigma, or tau). *Post hoc* comparisons used a two-sample t-test to evaluate the difference between groups on any significant main effects or interactions. The ANOVA models with *post hoc* testing were repeated for all three parameters of mu, sigma, and tau. Violations of normality of residuals and heterogeneity of variance between the groups were identified via Shapiro-Wilk test, q-q norm plots, and Bartlett's test of homogeneity of variances. No violations were observed for this dataset.

3. Results

3.1 Demographics

Shown in Table 2.1, cocaine-dependent subjects were older than controls (46.3 ± 8.4 vs. 40.0 ± 11.3 years, t (85) = 2.95, $p < .01$), differed in gender distribution compared with controls (85% male cocaine-dependent vs. 51% male controls, X^2 (1)= 11.41, $p < 0.00$), and had a lower educational level (12.1 ± 1.8 years for cocaine-dependent vs. 14.2 ± 2.3 years for controls, t (77) = 4.47, $p < 0.00$). All subjects had normal or corrected-to-normal vision and none were color-blind. Pearson correlations of demographics (age $p<0.03$, education $p<0.58$, and gender $p<0.80$) with anti-saccade ex-Gaussian reaction time parameters determined age to be the only confounding variable. Likewise, correlations

completed with pro-saccade errors (age p<0.00, education p<0.08, and gender p<0.48) suggested age as a significant confounder as well. Therefore, age was included as a covariate in this reaction time analyses for both anti-saccade and pro-saccade trails.

The cocaine group was older than the control group, t (85) = 2.95, $p < .01$. This age difference is pervasive in studies of inner-city cocaine users, which are generally between 40 and 55 years old (Moeller et al., 2010; Haile et al., 2012, Kampman et al., 2013). Healthy control subjects in this age range without pathology are usually employed and unable or unwilling to participate in research studies conducted during working hours.

3.2 Behavioral results during eye tracking

Group differences based on the K-S test were as follows for each stimulus condition: anti-saccade cocaine (p<0.00), anti-saccade neutral (p<0.47), anti-saccade shape (p<0.39), pro-saccade cocaine (p<0.00), pro-saccade neutral (p<0.21), and pro-saccade shape (p<0.51), Figures 3.2-3.7. Consistent with the experimental hypotheses, significant differences between the distributions for both anti-saccade and pro-saccade were only seen during presentation of cocaine cues (Table 3.1). Corrections for multiple comparisons preserved significance from the original results. Reaction times rates specifying peak RTs between groups and stimuli are shown in Table 3.2.

Table 3.1
Distributional differences as report by Komolgorov Smirnov test: p<0.05*

		K-S test
Anti-saccade	Cocaine	p < 0.00*
Anti-saccade	Neutral	p < 0.47
Anti-saccade	Shape	p < 0.39
Pro-saccade	Cocaine	p < 0.00*
Pro-saccade	Neutral	p < 0.21
Pro-saccade	Shape	p < 0.51

Table 3.2
Peak Reaction Times of Mu

		Cocaine Group	Control Group
Anti-saccade	Cocaine	452.24 ms	475.46 ms
Anti-saccade	Neutral	467.52 ms	482.28 ms
Anti-saccade	Shape	475.36 ms	485.42 ms
Pro-saccade	Cocaine	347.54 ms	388.36 ms
Pro-saccade	Neutral	383.19 ms	388.08 ms
Pro-saccade	Shape	399.81 ms	402.88 ms

Independent mixed model ANOVA's were conducted for each of the three ex-Gaussian reaction time parameters. Mean and variances for mu, sigma, and tau are listed in Table 3.3.

The ANOVA for mu yielded a main effect of stimulus ($F = 100.54$, $p<0.00$). Post hoc t-tests of mu reaction times between groups yielded non-significant differences on anti-saccade cocaine trials ($p<0.17$) and a statistically reliable difference on pro-saccade cocaine trials ($p<0.00$).

Table 3.3
Central tendency of mu, sigma, tau
All results are means (standard deviations).

		Cocaine Group			Control Group		
		mu	sigma	tau	mu	sigma	tau
Antisaccade	Cocaine	452.2 (81.5)	91.9 (58.6)	121.2 (45.7)	475.5 (72.3)	61.6 (31.6)	65.7 (36.5)
Antisaccade	Neutral	467.5 (73.3)	62.1 (31.6)	71.6 (42.3)	482.3 (77.8)	58.1 (24.5)	56.7 (26.3)
Antisaccade	Shape	475.4 (70.5)	62.7 (36.7)	68.5 (34.2)	485.4 (52.3)	55.1 (21.9)	54.4 (23.5)
Pro-saccade	Cocaine	347.5 (33.6)	37.9 (16.8)	46.7 (20.1)	388.4 (42.9)	46.1 (24.1)	46.3 (24.3)
Pro-saccade	Neutral	383.2 (38.3)	40.2 (13.1)	47.9 (18.6)	388.1 (36.3)	37.6 (16.4)	47.3 (25.6)
Pro-saccade	Shape	399.8 (47.4)	52.7 (23.1)	57.7 (24.4)	402.9 (42.6)	42.7 (19.6)	56.9 (22.7)

The ANOVA for sigma yielded a significant group x stimulus interaction ($F = 5.62$, $p<0.00$). Post hoc t-tests of sigma reaction times yielded a significant difference between groups on anti-saccade cocaine trials ($p<0.00$) and failed to show any reaction time group differences on pro-saccade cocaine trials ($p<0.08$). In general, there was greater variability on anti-saccade trials in the cocaine group.

The tau ANOVA yielded a main effect of group ($F = 13.5$, $p<0.00$), stimulus ($F = 35.7$, $p< 0.00$), and group x stimulus interaction ($F=13.6$ $p<0.00$). Post hoc t-tests of tau reaction times yielded a significant difference on anti-saccade cocaine trials ($p<0.00$) between groups and failed to show any reaction time differences on pro-saccade cocaine trails ($p<0.94$).

All post hoc tests were corrected for multiple comparisons through the use of Holm corrections on the raw p values. In general, as clearly shown in Figures 3.2, there were a greater number of longer RTs across the normal distribution for cocaine users on anti-saccade trials.

4. Discussion

Attentional bias toward drug-related cues has been previously reported for cocaine-dependent individuals (Bauer and Cox, 1998; Ehrman et al., 2002; Franken et al., 2003; Rosse et al., 1997, Liu et al., 2011). This population typically has many frontal cortical deficits due to drug use and attentional processes and inhibitory control are often compromised (Cocores et al, 1987; Daigre et al, 2013; Fillmore et al, 2002). When presented with drug related cues, this compromised attentional system may serves as a trigger for drug seeking, and lead to relapse. Saccdic eye movements are well-documented measures of attention (Posner and DiGirolamo, 1989). Studies that have investigated saccades within cocaine dependent individuals, however, are limited to visual scanning paradigms (Rosse et al., 1997, Rosse et al., 1993). Therefore, in order to advance the understanding of attention and eye movements in this substance abuse population, this study aimed to pinpoint quantitative measures of saccadic eye movements in cocaine-dependent individuals using an eye-tracking attentional bias task. We evaluated both anti-saccades and pro-saccades during a cocaine picture attentional bias task, in which one primary dependent measure was the reaction times on correct trials.

Longer RTs have been reported in other disease populations that have attentional deficits, such as autism (Nicolaas van der Geest et al., 2001), ADHD (Vaurio et al, 2009), and schizophrenia (Sereno and Holzman, 1995). It is the state of attention (engaged or disengaged) that may influence the trajectory of the saccade and thereafter the resulting saccadic reaction time towards a stimulus (Fischer and Weber, 1993). Therefore, an attentional system that is impaired, as in

cocaine dependence, may have notable modulations in RT in the face of salient stimuli.

Reaction times are an efficient method of studying sensorimotor transformation, such that during a saccadic task humans produce a skewed normal distribution, most similar to an ex-Gaussian distribution (Carpenter and Williams, 1995; Whelan, 2008). Further investigations into the three components that comprise the ex-Gaussian distribution (mu, sigma, and tau) allow a comprehensive method of reaction time analysis.

Anti-saccade and pro-saccade reaction time distributions were compared between groups and across all stimuli (cocaine, neutral, and shape). When cocaine-dependent subjects were presented with drug-related cues, their peak mu pro-saccade RTs were significantly faster compared to controls (347.54ms cocaine vs. 388.36ms; K-S test: $p<0.00$) (Table 3.2). Importantly, no differences in pro-saccade distributions between the groups were seen during presentation of neutral or shape cues, highlighting the specificity of the task toward cocaine cues. These faster reaction times are indicative of the salience of the cocaine cue to cocaine-dependent individuals. When individuals from this population are presented with a familiar cue, representative of their drug use, they attend toward it faster than an image with no incentive salience (Flagel et al, 2009). Attentional bias toward salient cues has been shown to be predictive of relapse in cocaine dependent populations (Franken et al., 2000). Therefore, these faster pro-saccades toward cocaine cues may be indicative of relapse in cocaine dependent subjects. When cocaine-dependent subjects were presented with cocaine-related cues, their anti-saccade

RTs were significantly slower compared to controls in the tau (right tail) component of the ex-Gaussian distribution. No differences in anti-saccade distributions between the groups were seen during presentation of neutral or shape cues, again highlighting task specificity. This longer latency in the presence of cocaine related cues is indicative of disrupted attention in the presence of the drug cue and possible inhibitory control impairments, such that it takes longer to look away from distracting salient stimuli in the periphery. Furthermore, this latency may indicate occasional lapses in attention similarly seen in patients with ADHD (Hervey et al., 2006; Leth-Steensen et al., 2000). These patients also exhibit variable and longer RTs in the tau component of the distribution. The observed differences may serve as an indicator of overall relapse risk potential in this population.

Collectively, the results support the three primary RT hypotheses, and confirm that an eye-tracking based measure of attentional bias is a quick, noninvasive, and sensitive assessment of prefrontal deficits and attentional-bias specific to cocaine cues. It may be implemented in efforts toward relapse prevention. The information gathered from this task can be compiled into a comprehensive profile, including the error rate analysis from Chapter 2, which then can be used to screen individuals on their potential to relapse in order to develop more effective plans of treatment for cocaine addiction.

4.1 Limitations and Future Directions

Details of limitations and future projects are identical to those listed in Chapter 2.

CHAPTER 4: CONCLUSIONS AND FUTURE DIRECTIONS

Relapse is a highly prevalent aspect of drug addiction, even after periods of prolonged abstinence, and a major barrier to successful treatment. Cocaine use impairs many areas of the reward circuit and frontal regions pivotal in attentional processing, craving, and inhibitory control, such as the mPFC and DLPFC (Garavan et al, 2000). Drug-seeking behavior is elicited by environment stimuli associated with the drug, or cue-reactivity, and it is repeated exposure to these cues that evoke craving and a drive to relapse (Koob & Volkow, 2009). Attentional bias, a form of cue-reactivity, toward cocaine-related stimuli may be predictive of relapse in cocaine dependent individuals (Marhe et al, 2012; Carpenter et al, 2006), but presently, there are few effective tools for predicting treatment outcomes and assessing risk for relapse in individuals who are addicted to cocaine.

Saccade eye movements are sensitive measures of attention and inhibitory control and involve intact functioning of circuits in the frontal and subcortical regions for successful execution. Due in part to frontal deficits in cocaine dependent subjects, saccadic eye movements are an excellent test to pinpoint the level of impairment in this population. Anti-saccade errors, in particular, are well documented in other diseases such as Schizophrenia and Huntington's as an indicator of inhibitory control deficits and have even been suggested as characteristic of an endophenotype (Nilsson et al., 2013, Pierrot-Deseilligny et al., 1991). Subjects with frontal deficits in the DLPFC have significant difficultly executing correct anti-saccade trials. Due to similar areas of dysfunction reported in cocaine users, poor anti-saccade performance and longer reaction times toward cocaine-related cues by cocaine-dependent subjects would be expected. The

results suggest that measuring performance on a cocaine-cue anti-saccade task (error rates and reaction times) may provide insights into physiological deficits and drug cue-saliency in cocaine addicted populations.

Cocaine dependent subjects and controls completed the attentional bias eye-tracking paradigm, and error rates during anti-saccade trials were evaluated. Cue-specific results showed a main effect of group (cocaine > control, 35% vs. 19% anti-saccade errors, $p<0.00$), such that cocaine-dependent subjects made significantly more errors on trials with cocaine cues than controls. This differentiated outcome between groups only in the presence of cocaine stimuli provides evidence of specificity of the attentional bias phenomena within this novel eye-tracking task. In addition, cocaine dependent subjects made more errors across all stimuli compared to controls. This is indicative of the inhibitory control deficits in the cocaine using population, and provides evidence of sensitivity of the present saccade test to capture these deficits.

Reaction times during both pro-saccade and anti-saccade correct trials were analyzed. Attentional control is often compromised if frontal circuitry is not intact, as is the case with many cocaine-using individuals (Bush, 2000). A lapse in attention during anti-saccade trials will most likely result in slower reaction times. Reaction times are well described by an ex-Gaussian distribution, which is a mixture of a Gaussian and exponential component (Balota and Spieler, 1999) composed of three components: mu, sigma, and tau. This technique evaluates the entire ex-Gaussian distribution, as opposed to the common evaluation of the overall mean and variance, in order to better describe important differences in RT distributions.

This analysis utilized only correct pro-saccade and anti-saccade trials. We observed significant distributional differences (KS tests $p<0.00$) between groups on cocaine cue trials for both anti-saccade and pro-saccade trials. For pro-saccade trials, cocaine-dependent subjects were significantly faster at responding to cocaine cues than controls. This is indicative of the cue-saliency toward cocaine cues. No differences between the groups were found during neutral cues. During anti-saccade trials, there was a marked difference between the groups in the tau tail portion of the distribution during cocaine-cues. Again, no differences between the groups were found during neutral cues. This difference in the tails of the distributions (tau), only shown in the cocaine-dependent group during cocaine cued trials, suggests that cocaine cues act as a distractor, which in addition to the voluntary control deficits in this population, result in slower saccadic reaction times on anti-saccade trials.

This dissertation aimed to develop a novel eye-tracking task using saccadic eye movements as a measure attentional bias and inhibitory control deficits in cocaine-dependent subjects, with an eye tracking tool to help predict relapse. The results suggest that error rates and reaction times are sensitive measures of attentional bias toward cocaine cues in this population. In addition, inhibitory control deficits, which have long been established as an adverse effect of chronic cocaine use, are pronounced when performing this task. Moving forward, we aim to establish individual subject profiles of these indices that, when evaluated in sum, can serve as a marker of relapse potential.

Future projects can assess the effects of pharmacotherapy to further extend the utility of this eye-tracking task. Cue-salience is an integral part of attentional bias, and additional physiological measures of cue reactivity such as heart rate and pupil diameter may be incorporated (Rohsenow et al., 1991; Robbins et al., 1999). Incorporating these variables will provide a more precise measurement and association of performance with craving and relapse potential. An acute pharmacological challenge with drugs known to modify saccades and/or cocaine abuse (levodopa/carbidopa) could also be examined. For example, levodopa has been shown to reduce anti-saccade error rates and slow pro-saccade reaction times in patients with Parkinson's disease (Hood et al., 2006), and haloperidol, a dopamine D2 antagonist, has been shown to increase antisaccade errors in cognitively nonimpaired schizophrenic patients (Babin et al., 2011). By implementing this novel task prior to medication and then directly after in cocaine-dependent subjects, acute differences in performance and potential improvement could be observed. In addition, implementation of this task with other substances of abuse, such as marijuana, would also enhance the validity and utility of this task as a predictive measure of relapse.

APPENDIX

Questionnaires:

1. Eye-tracking Consent
2. Obsessive-Compulsive Cocaine Scale (OCCS)
3. Perceived Stress Scale (PSS)
4. Visual Analogue Scale - Cocaine Craving (VAS-CC)

Addendum to Informed Consent

General Evaluation of Eligibility for Substance Abuse/Dependence Research

HSC-MS-05-0322

Eye Tracking Task

INVITATION TO TAKE PART

You have the option to participate in a non-invasive eye-tracking task. This is part of the screening for "General Evaluation of Eligibility for Substance Abuse/Dependence Research" conducted by Dr. F. Moeller and research staff with the Substance Abuse Research Center. This is information is collected to learn if you are eligible to take part in studies that are taking place in the University of Texas Health Science Center at Houston Substance Abuse Research Center. You can choose to take part in this eye tracking task or stop taking part at any time. A decision not to take part or stop taking part, at any time will not change the services available to you from the University of Texas Health Science Center at Houston or the Substance Abuse Research Center.

PURPOSE

The purpose of this screening is to learn if you qualify for a study that either provides treatment for substance abuse or helps provide information about substance abuse that potentially can lead to new treatments. You have been asked to participate in this evaluation either because you have used substances of abuse or you can serve as a comparison to people who use substances of abuse.

PROCEDURES

If you agree to take part in this eye tracking task you will be asked to look at a computer screen and making an eye movement toward (look at) or make an eye movement away (look away from) a picture shown on the screen. You will also be asked to fill out some questionnaires about stress and (if you are currently using drugs) about your drug use.

TIME COMMITMENT

Taking part in this additional task is voluntary. The total time commitment is about 1 hour of your time.

BENEFITS

You may receive no benefit from taking part in this study. The information collected will help determine if you qualify to take part in studies that are being conducted at the UT Substance Abuse Research Center.

KNOWN RISKS AND/OR DISCOMFORTS

There are no risks associated with the tasks you are asked to complete during eye tracking. You may become fatigued from concentrating on the computer screen. There is the possible risk of breach of confidentiality.

ALTERNATIVES

You have the alternative to not take part in this additional eye tracking task.

STUDY WITHDRAWAL

Your decision to take part is voluntary. You may decide to stop taking part at any time. A decision not to take part or stop being part of the screening process will not affect your eligibility for taking part in other research studies at this clinic.

If you withdraw from the study the information collected will not be used.

COSTS, REIMBURSEMENT AND COMPENSATION

There is no cost to take part in the study. You will be paid $5 for completing the task, and $20 for your time and to cover transportation costs.

If you receive a bill that you believe is related to your taking part in this screening, please contact the UT Substance Abuse Research Center research staff with any questions.

If you receive payment for taking part in this study please be informed that you will be asked to complete a copy W-9 form that will be forwarded to the accounting department as a requirement by the Internal Revenue Service. You will also be issued a 1099-Misc form from this study for tax reporting purposes.

CONFIDENTIALITY

You will not be personally identified in any reports or publications that may result from this screening. Any personal information about you that is gathered during this screening process will remain confidential to every extent of the law a special number (code) will be used to identify you in the study and only the investigator and research staff will know your name.

QUESTIONS

If you have questions at any time about this research study, please feel free to contact Dr. F. Moeller and research staff at the Substance Abuse Research Center at (713)500-2802 as they will be glad to answer your questions. You can contact the study team to discuss problems, voice concerns, obtain information, and offer input in addition to asking questions about the research.

SIGNATURES

Sign below only if you understand the information given to you about the research and choose to take part. Make sure that any questions have been answered and that you understand the study. If you have any questions or concerns about your rights as a research subject, call the Committee for the Protection of Human Subjects at (713) 500-7943. You may also call the Committee if you wish to discuss problems, concerns, and questions; obtain information about the research; and offer input about current or past participation in a research study. If you decide to take part in this research study, a copy of this signed consent form will be given to you.

_____

Printed Name of Subject

_____ _____

Signature of Subject Date

_____

Printed Name of Person Obtaining Informed Consent

_____ _____

Signature of Person Obtaining Informed Consent Date

CPHS STATEMENT: This study (HSC-05-0322) has been reviewed by the Committee for the Protection of Human Subjects (CPHS) of the University of Texas Health Science Center at Houston. For any questions about research subject's rights, or to report a research-related injury, call the CPHS at (713) 500-7943.

Obsessive Compulsive Cocaine Use Scale

Please indicate the number that represents how you feel about each question.

0= Never 1 = Almost Never 2 = Sometimes 3 = Fairly Often 4 = Very Often

1. When you're not using cocaine, how much of your time is taken up by ideas, thoughts, urges or images about cocaine?	0	1	2	3	4
2. How often do these thoughts occur?	0	1	2	3	4
3. How much do these ideas, thoughts, urges or images about using cocaine get in the way of your social life or work? Is there anything you don't or can't do because of them? [If you are not currently working, how much of your work would be affected if you were still working]	0	1	2	3	4
If yes, please explain _____					
4. How much upset does the ideas, thoughts, impulses, or images related to using cocaine cause you when you're not using cocaine?	0	1	2	3	4
5. How much effort do you make to stop these thoughts or try to turn your attention away from these thoughts? (Rate your effort made to lose these thoughts, not your success or failure in actually getting rid of them.).	0	1	2	3	4
6. How successful are you in stopping or changing your thoughts about cocaine when you're not using cocaine?	0	1	2	3	4
7. On average, how much did you spend on cocaine in the past week?	0	1	2	3	4
_____					
8. In the past week, how many days did you use cocaine?	0	1	2	3	4
If yes, how much _____					
9. How much does your cocaine use cause problems with your work? Is there anything that you don't or can't do because of your cocaine use? (If you are not working now, how much would you be affected if you were working?)	0	1	2	3	4
If yes, please explain _____					
10. How much does your cocaine use cause problems with your social life? Is there anything that you don't or can't do because of your cocaine use?	0	1	2	3	4

If yes, please explain _____

11. If something or someone was stopping you from using cocaine when you wanted to get high, how anxious or upset would you become?	0	1	2	3	4
12. How much of an effort do you make to resist getting high on cocaine? (Only rate your effort to resist, not your success or failure in actually controlling the urge to use cocaine).	0	1	2	3	4
13. How strong is the drive to use cocaine?	0	1	2	3	4
14. How much control do you have over the cocaine use?	0	1	2	3	4

Perceived Stress Scale

The questions in this scale ask you about your feelings and thoughts **during the last month**. In each case, you will be asked to indicate by circling *how often* you felt or thought a certain way.

Name _____ Date _____

Age _____ Gender (*Circle*): **M F** Other _____

	0 = Never	1 = Almost Never	2 = Sometimes	3 = Fairly Often	4 = Very Often
1. In the last month, how often have you been upset because of something that happened unexpectedly?	**0**	**1**	**2**	**3**	**4**
2. In the last month, how often have you felt that you were unable to control the important things in your life?	**0**	**1**	**2**	**3**	**4**
3. In the last month, how often have you felt nervous and "stressed"?	**0**	**1**	**2**	**3**	**4**
4. In the last month, how often have you felt confident about your ability to handle your personal problems?	**0**	**1**	**2**	**3**	**4**
5. In the last month, how often have you felt that things were going your way?	**0**	**1**	**2**	**3**	**4**
6. In the last month, how often have you found that you could not cope with all the things that you had to do?	**0**	**1**	**2**	**3**	**4**
7. In the last month, how often have you been able to control irritations in your life?	**0**	**1**	**2**	**3**	**4**
8. In the last month, how often have you felt that you were on top of things?	**0**	**1**	**2**	**3**	**4**
9. In the last month, how often have you been angered because of things that were outside of your control?	**0**	**1**	**2**	**3**	**4**
10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?	**0**	**1**	**2**	**3**	**4**

Please feel free to use the *Perceived Stress Scale* for your research.

Mind Garden, Inc.
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www.mindgarden.com

References

The PSS Scale is reprinted with permission of the American Sociological Association, from Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behavior, 24,* 386-396.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) *The Social Psychology of Health.* Newbury Park, CA: Sage, 1988.

Craving Scale (VAS-CC)

Please indicate how much you agree or disagree with each of the following statements by marking on the line between NOT AT ALL [0] and EXTREMELY [100]. The closer you place your mark to one end or the other indicates the strength of your answer. Please answer every question.

We are interested in how you are thinking or feeling right now.

Right now, how much are you craving cocaine?

0 ---------- 100

NOT AT ALL EXTREMELY

Over the last week on average how much have you been craving cocaine?

0 ---------- 100

NOT AT ALL EXTREMELY

Over the last week how much did you crave cocaine when your craving was at its worst?

0 ---------- 100

NOT AT ALL EXTREMELY

BIBLIOGRAPHY

Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Annu. Rev. Neurosci. 9: 357–381.

Amin Z, Constable RT, Canli T (2004). Attentional bias for valenced stimuli as a function of personality in the dot-probe task. Journal of Research in Personality 38: 15-23.

Andersen RA. (1997) Multimodal integration for the representation of space in the posterior parietal cortex. Philos. Trans. R. Soc. Lond 352:1421–1428.

Babin SL, Hood AJ, Wassef AA, Williams NG, Patel SS, Sereno AB (2011) Effects of haloperidol on cognition in schizophrenia patients depend on baseline performance: A saccadic eye movement study. Prog NeuroPsych Biol Psych 35: 1753-1764.

Back SE, Hartwell K, DeSantis SM, Saladin M, McRae-Clark AL, Price KL, Moran-Santa Maria MM, Baker NL, Spratt E, Kreek MJ, Brady KT (2010) Reactivity to laboratory stress provocation predicts relapse to cocaine. Drug Alcohol Depend 106: 21–27.

Balota DA, Spieler DH (1999) Word frequency, repetition, and lexicality effects in word recognition tasks: beyond measures of central tendency. J Exp Psychol Gen 128:32-55.

Barkley RA (1997) Behavioral inhibition, sustained attention, and executive

functions: constructing a unifying theory of ADHD. Psychol. Bull 121: 65–94.

Bauer D, Cox WM (1998) Alcohol-related words are distracting to both alcohol abusers and non-abusers in the Stroop color naming task. Addiction 93: 1539–42.

Bechara A (2005) Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nat Neuroscience 8:1458 - 63.

Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M (2003) Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. Neuroimage 19: 1085-94.

Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, Matochik JA, Kurian V, Cadet JL, Kimes AS, Funderburk FR, Ernst M (2003) Orbitofrontal cortex dysfunc- tion in abstinent cocaine abusers performing a decision-making task. Neuroimage 19: 1085–1094.

Bonson KR, Grant SJ, Contoreggi CS, Links JM, Metcalfe J, Weyl HL, Kurian V, Ernst M, London ED (2002) Neural systems and cue-induced cocaine craving. Neuropsychopharmacology 26: 376–386.

Bowling AC, Hindman EA, Donnelly JF (2012) Pro-saccade errors in the anti-saccade task: differences between corrected and uncorrected errors and links to neuropsychological tests. Exp Brain Res 216:169-79.

Breiter HC, Gollub RL, Weisskoff RM, Kennedy DN, Makris N, Berke JD, Goodman JM, Kantor HL, Gastfriend DR, Riorden JP, Mathew RT, Rosen BR, Hyman SE (1997) Acute effects of cocaine on human brain activity and emotion. Neuron 19:591–611.

Brewer JA, Worhunsky PD, Carroll KM, Rounsaville BJ, Potenza MN (2008) Pretreatment brain activation during stroop task is associated with outcomes in cocaine-dependent patients. Biol Psychiatry 64: 998–1004.

Briand KA, Strallow D, Hening W, Poizner H, Sereno AB (1999) Control of voluntary and reflexive saccades in Parkinson's disease. Exp. Brain Res. 129: 38–48.

Bush G, Luu P, Posner MI (2000) Cognitive and emotional influences in anterior cingulate cortex. Trends Cogn Sci 4: 215–222.

Carpenter KM, Schreiber E, Church S, McDowell D (2006). Drug Stroop performance: relationships with primary substance of use and treatment outcome in a drug-dependent outpatient sample. Addict Behav 31: 174–181.

Carpenter RH, Williams ML (1995) Neural computation of log likelihood in control of saccadic eye movements. Nature 377: 59–62.

Carpenter RHS (1981) Eye Movements: Cognition and Visual. Perception. eds Fischer, D. F. & Monty, R. A. 237–246, Erlbaum, Hillsdale, New Jersey.

Carter BL, Tiffany ST (1999) Meta-analysis of cue-reactivity in addiction research. Addiction 94:327–340

Chan F, Armstrong IT, Pari G, Riopelle RJ, Munoz DP (2005) Deficits in saccadic eye-movement control in Parkinson's disease. Neuropsychologia 43:784-96.

Childress AR, Ehrman R, McLellan A, MacRae J, O'Brien CP (1994) Can induced moods trigger drug- related responses in opiate abuse patients? Journal of Substance Abuse Treatment: 17–23.

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue-induced cocaine craving. Am J Psychiatry 156:11–18.

Childress AR, Mozley PD, McElgin W, Fitzgerald J, Reivich M, O'Brien CP (1999) Limbic activation during cue- induced cocaine craving. American Journal of Psychiatry: 11–18.

Clementz BA, McDowell JE, Zisook S (1994) Saccadic system functioning among schizophrenia patients and their first-degree biological relatives. J Abnorm Psychol 103: 277-87.

Cocores JA, Davies RK, Mueller PS, Gold MS (1987) Cocaine abuse and adult attention deficit disorder. Journal of Clinical Psychiatry 48: 376-377.

Coe B, Tomihara K, Matsuzawa M, Hikosaka O (2002) Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. J. Neurosci 22: 5081–5090.

Cohen S, Williamsom G. (1988) Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) The Social Psychology of Health. Newbury Park, CA: Sage.

Cohen, S. and Williamson, G. Perceived Stress in a Probability Sample of the United States. Spacapan, S. and Oskamp, S. (Eds.) The Social Psychology of Health. Newbury Park, CA: Sage, 1988.

Cohen, S., Kamarck, T., and Mermelstein, R. (1983). A global measure of perceived stress. Journal of Health and Social Behavior 24: 386-396.

Cooney NL, Litt MD, Cooney JL, Pilkey DT, Steinberg HR, Oncken CA (2007) Alcohol and tobacco cessation in alcohol-dependent smokers: analysis of real-time reports. Psychol Addict Behav 21:277–286

Copersino ML, Serper MR, Vadhan N, Goldberg BR, Richarme D,Chou JCY, Stitzer M, Cancro R (2004) Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. Psychiatry Res: 209–218.

Cosgrove KP (2010) Imaging receptor changes in human drug abusers. Curr Top Behav Neurosci 3: 199–217.

Cox WM, Fadardi JS, Pothos EM (2006) The addiction-stroop test: Theoretical considerations and procedural recommendations. Psychol Bull: 443–476.

Cox WM, Pothos EM, Hosier SG (2007). Cognitive-motivational predictors of excessive drinkers' success in changing. Psycho- pharmacology (Berl) 192: 499–510.

Daigre C, Roncero C, Grau-López L, Martínez-Luna N, Prat G, Valero S, Tejedor R, Ramos-Quiroga JA, Casas M (2013) Attention deficit hyperactivity disorder in cocaine-dependent adults: a psychiatric comorbidity analysis. Am J Addict 22: 466-73.

Davidson MC, Everling SL, Munoz DP (1999) Comparison of pro- and anti-saccades in primates. III. Reversible activation/inactivation of frontal eye field and superior colliculus. Soc. Neurosci 25: 147.

Davis M and Whalen PJ (2001) The amygdala: vigilance and emotion. Mol Psychiatry 6(1):13-34.

Demer JL, Volkow ND, Ulrich I, Krajewski K, Davis CM, Porter FI. Eye movements in cocaine abusers (1989) Psychiatry Res 29:123-36.

Donovan DM (1996). Assessment issues and domains in the prediction of relapse. Addiction 91: S29–S36.

Ehrman RN, Robbins SJ, Bromwell MA, Lankford ME, Monterosso JR, O'Brien CP (2002) Comparing attentional bias to smoking cues in current smokers, former smokers, and non- smokers using a dot-probe task. Drug Alcohol Depend 67: 185–91.

Elsesser K, Sartory G, Tackenberg A (2005) Initial symptoms and reactions to trauma-related stimuli and the development of posttraumatic stress disorder. Depress Anxiety 21:61-70.

Epstein DH, Marrone GF, Heishman SJ, Schmittner J, Preston KL. (2009) Tobacco, cocaine, and heroin: craving and use during daily life. Addict Behav 35:318–324

Ersche KD, Barnes A, Jones PS, Morein-Zamir S, Robbins TW, Bullmore ET (2011) Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. Brain 134: 2013–2024.

Everitt BJ, Belin D, Economidou D, Pelloux Y, Dalley JW, Robbins TW (2008) Review. Neural mechanisms underlying the vulnerability to develop compulsive drug-seeking habits and addiction. Phil Trans Royal Soc London B Biol Sci 363: 3125–3135.

Everitt, B (1997) Craving cocaine cues: cognitive neuroscience meets drug addiction research. Trends Cogn. Sci. (Regul. Ed.) 1: 1-2.

Everling S, Dorris MC, Klein RM, Munoz DP (1999) Role of primate superior colliculus in preparation and execution of anti-saccades and pro-saccades. J. Neurosci. 19: 2740–2754.

Everling S, Fischer B (1998)The anti-saccade: a review of basic research and clinical studies. Neuropsychologia 36:885-99.

Everling S, Munoz DP (2000) Neuronal correlates for preparatory set associated with pro-saccades and anti-saccades in the primate frontal eye field. J Neuroscii 20:387-400.

Ferraina S, Paré M, Wurtz RH (2002) Comparison of cortico- cortical and cortico-collicular signals for the generation of saccadic eye movements. J. Neurophysiol 87: 845–858.

Field M, Cox WM (2008). Attentional bias in addictive behaviors: a review of its development, causes, and consequences. Drug Alcohol Depend 97: 1–20.

Fillmore MT, Rush CR (2002) Impaired inhibitory control of behavior in chronic cocaine users. Drug Alcohol Depend 66: 265-73.

Fillmore MT, Rush CR. The Impact of Disulfiram Treatment on the Reinforcing Effects of Cocaine: A Randomized Clinical Trial

First MB, Spitzer RL, Gibbon M, Williams J (1996) Structured Clinical Interview for DSM-IV Axis I Disorders – Patient Edition. New York, Biometrics Research Department, New York State Psychiatric Institute.

Fischer B, Breitmeyer B (1987) Mechanisms of visual attention revealed by saccadic eye movements. Neuropsychologia 25:73–83.

Fischer B, Weber H (1993) Express saccades and visual attention. Behav Brain Sci 16: 553–610.

Fox HC, Jackson ED, Sinha R (2009) Elevated cortisol and learning and memory deficits in cocaine dependent individuals: relationship to relapse outcomes. Psychoneuroendocrinology. 34:1198-207.

Franken IH (2003) Drug craving and addiction: integrating psychological and neuropsychopharmacological approaches. Prog Neuropsychopharmacol Biol Psychiatry 27: 563-79.

Franken IH, Stam CJ, Hendriks VM, van den Brink W. (2003) Neurophysiological evidence for abnormal cognitive processing of drug cues in heroin dependence. Psychopharmacology 170: 205–12.

Franken IHA (2003) Drug craving and addiction: integrat- ing psychological and neuropsychopharmacological approaches. Prog Neuropsychopharmacol Biol Psychiatry 27: 563–79.

Franken IHA, Hendriks VM (1999). Predicting outcome of inpatient detoxification of substance abusers. Psychiatr Serv 50: 813–817.

Franken IHA, Van Strien JW, Nijs IM (2006) Effect of hedonic tone on event-related potential measures of cognitive processing. Psychiatry Research: 233–239.

Franklin TR, Acton PD, Maldjian JA, Gray JD, Croft JR, Dackis CA, O'Brien CP, Childress AR (2002) Decreased gray matter concentration in the insular, orbitofrontal, cingulate, and temporal cortices of cocaine patients. Biol Psychiatry 51: 134–142.

Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M (1988) Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. Biol Psychiatry. 23: 670-7.

Fukushima J, Fukushima K, Morita N, Yamashita I (1990) Further analysis of the control of voluntary saccadic eye movements in schizophrenic patients. Biol Psychiatry 28: 943-58.

Fuster JM (1997) The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe, Raven, New York.

Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 157: 1789–1798.

Garavan H, Pankiewicz J, Bloom A, Cho JK, Sperry L, Ross TJ, Salmeron BJ, Risinger R, Kelley D, Stein EA (2000) Cue-induced cocaine craving: neuroanatomical specificity for drug users and drug stimuli. Am J Psychiatry 157: 1789-98.

Gawin FH, Kleber HD (1986) Abstinence symptomatology and psychiatric diagnosis in cocaine abusers. Clinical observations. Arch Gen Psychiatry: 107–113.

Gaymard B, Ploner CJ, Rivaud-Péchoux S, Pierrot-Deseilligny C (1999) The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. Exp Brain Res 129:288-301.

Godijn R, Kramer AF (2007) Anti-saccade costs with static and dynamic targets. Percept Psychophys 69:802-15.

Gold JI, Shadlen MN (2000) Representation of a perceptual decision in developing oculomotor commands. Nature 404: 390–394.

Grefkes C, Fink GR (2005) The functional organization of the intraparietal sulcus in humans and monkeys. J Anat 207: 3–17.

Guitton D, Buchtel HA, Douglas RM (1985) Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. Exp Brain Res 58: 455-72.

Haile CN, De La Garza R 2nd, Mahoney JJ 3rd, Nielsen DA, Kosten TR, Newton TF (2012) The Impact of Disulfiram Treatment on the Reinforcing Effects of Cocaine: A Randomized Clinical Trial. PLoS One: 7(11).

Hallett M (1993) Physiology of basal ganglia disorders: an overview. Can. J. Neurol. Sci. 20: 177–183.

Hallett PE (1978) Primary and secondary saccades to goals defined by instructions. Vision Res 18:1279-96.

Hanes DP, Schall JD (1996) Neural control of voluntary movement initiation. Science 274: 427–430.

Hanlon CA, Canterberry M (2012) The use of brain imaging to elucidate neural circuit changes in cocaine addiction. Subst Abust Rehabil 3: 115-128.

Hanlon CA, Wesley MJ, Porrino LJ (2009) Loss of functional specificity in the dorsal striatum of chronic cocaine users. Drug Alcohol Depend 102: 88–94.

Hattenschwiler J, Ruesch P, Hell D (2000). Effectiveness of inpatient drug detoxification: links between process and out- come variables. Eur Addict Res 6: 123–131.

Hervey AS, Epstein JN, Curry JF, Tonev S, Eugene Arnold L, Keith Conners C, Hinshaw SP, Swanson JM, Hechtman L (2006) Reaction time distribution analysis of neuropsychological performance in an ADHD sample. Child Neuropsychology: 125–140.

Hester R, Dixon V, Garavan H (2006) A consistent attentional bias for drug-related material in active cocaine users across word and picture versions of the emotional Stroop task. Drug Alcohol Depend: 251–257.

Hester R, Garavan H (2004) Executive dysfunction in cocaine addiction: evidence for discordant frontal, cingulate, and cerebellar activity. The Journal of Neuroscience: 11017–11022.

Hester R, Luijten M (2013) Neural correlates of attentional bias in addiction. CNS Spectr 6:1-8.

Hikosaka O, Takikawa Y, Kawagoe R (2000) Role of the basal ganglia in the control of purposive saccadic eye movements. Physiol. Rev. 80: 953–978.

Holmqvist K, Nystrom M, Andersson R, Dewhurst R, Jarodzka H, Van de weijer J. Eye Tracking: A Comprehensive guide to methods and measures. Oxford 2011.

Hood AJ, Amador SC, Cain AE, Briand KA, Al-Refai AH, Schiess MC, Sereno AB (2007) Levodopa slows .pro-saccades and improves anti-saccades: an eye movement study in Parkinson's disease. J Neurol Neurosurg. Psychiatry: 565-70.

Hutton SB (2008) Cognitive control of saccadic eye movements. Brain and Cognition 68:327-40.

Hutton SB, Joyce EM, Barnes TR, Kennard C (2002) Saccadic distractibility in first-episode schizophrenia. Neuropsychologia 40:1729-36.

Hyman SE, Malenka RC, Nestler EJ (2006) Neural Mechanisms of Addiction: The role of reward-related learning and memory. Annu Rev Neurosci 29:565-98.

Ito R, Robbins TW, Everitt BJ (2004) Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. Nat. Neurosci. 7: 389–97

Jardin BF, Larowe SD, Hall BJ, Malcolm RJ (2011) The Obsessive Compulsive Cocaine Scale: assessment of factor structure, reliability, and validity. Addict Behav 36:1223-7.

Jasinska AJ, Stein EA, Kaiser J, Naumer MJ, Yalachkov Y (2014) Factors modulating neural reactivity to drug cues in addiction: a survey of human neuroimaging studies. Neurosci Biobehav Rev. 38:1-16.

Kampman KM, Pettinati HM, Lynch KG, Spratt K, Wierzbicki MR, O'Brien CP (2013) A double-blind, placebo-controlled trial of topiramate for the treatment of comorbid cocaine and alcohol dependence. Drug Alcohol Depend 133:94-9.

Kavanagh DJ, Andrade J, May J (2004) Beating the urge: implications of research into substance-related desires. Addict Behav 29: 1359–72.

Khan SA, Ford K, Timney B, Everling S (2003) Effects of ethanol on anti-saccade task performance. Exp Brain Res 150:68-74.

Kilts CD, Gross RE, Ely TD, Drexler KP (2004) The neural correlates of cue-induced craving in cocaine- dependent women. Am J Psychiatry. 161:233–241.

Kilts CD, Schweitzer JB, Quinn CK, Gross RE, Faber TL, Muhammad F, Ely TD, Hoffman JM, Drexler KP (2001) Neural activity related to drug craving in cocaine addiction. Arch Gen Psychiatry 58: 334–341.

Koob GF (1992) Drugs of abuse: anatomy, pharmacology, and function of reward pathways. Trends Pharmacol Sci 13: 177–184.

Koob GF, Volkow ND (2009) Neurocircuitry of addiction. Neuropsychopharmacology 35: 216-238.

Kosten TR, Scanley BE, Tucker KA, Oliveto A, Prince C, Sinha R et al (2006). Cue-induced brain activity changes and relapse in cocaine-dependent patients. Neuropsychopharmacology 31: 644–650.

Krawczyk DC (2002) Contributions of the prefrontal cortex to the neural basis of human decision making. Neurosci Biobehav Rev 26: 631–664.

Kufahl PR, Li Z, Risinger RC, Rainey CJ, Wu G, Bloom AS, Li SJ (2005) Neural responses to acute cocaine administration in the human brain detected by fMRI. Neuroimage 28:904–914.

Lane SD, Moeller FG, Steinberg JL, Buzby M, Kosten TR (2007) Performance of cocaine dependent individuals and controls on a response inhibition task with varying levels of difficulty. Am. J. Drug Alcohol Abuse 33: 717–726.

Lasker AG, Zee DS (1997) Ocular motor abnormalities in Huntington's disease. Vision Res 37: 3639-45.

Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS (1987) Saccades in Huntington's disease: initiation defects and distractibility. Neurology 37:364-70.

Leigh, RJ, Zee D (1983) The Neurology of Eye Movements. Philadelphia: F.A. Davis.

Leth-Steensen C, Elbaz ZK, Douglas VI (1999) Mean response times, variability, and skew in the responding of ADHD children: a response time distributional approach. Acta Psychol (Amst): 167-90.

Leth-Steensen C, Elbaz ZK, Douglas VI (2000). Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. Acta Psychologica 104: 167–190.

Levy, DL (1996) Location, location, location: the pathway from behavior to brain locus in schizophrenia. Psychopathology: The evolving science of mental disorder. New Tork: Cambridge University Press. pp. 100-126.

Lezak MD (1995) Neuropsychological Assessment. Oxford Univ. Press, Oxford.

Lindsay JA, Stotts AL, Green CE, Herin DV, Schmitz JM (2009) Cocaine dependence and concurrent marijuana use: a comparison of clinical characteristics. Am J Drug Alcohol Abuse: 193-198.

Liu S, Lane SD, Schmitz JM, Green CE, Cunningham KA, Moeller FG. (2011) Increased intra-individual reaction time variability in cocaine-dependent subjects: role of cocaine-related cues. Addict Behar 37: 193-7.

Liu S, Lane SD, Schmitz JM, Waters AJ, Cunningham KA, Moeller FG. (2011) Relationship between attentional bias to cocaine-related stimuli and impulsivity in cocaine-dependent subjects. Am J Drug Alcohol Abuse 37: 117-22.

London ED, Ernst M, Grant S, Bonson K, Weinstein A (2000) Orbitofrontal cortex and human drug abuse: functional imaging. Cerebral Cortex: 334–342.

Lundqvist T (2005) Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol Biochem Behav: 319-30.

Maas LC, Lukas SE, Kaufman MJ, Weiss RD, Daniels SL, Rogers VW, Kukes TJ, Renshaw PF (1998) Functional magnetic resonance imaging of human brain activation during cue-induced cocaine craving. Am J Psychiatry 155: 124–126.

Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH (2013) Individual differences in anterior cingulate activation associated with attentional bias predict cocaine use after treatment. Neuropsychopharmacology. 38:1085-93.

Marhe R, Waters AJ, Van de Wetering BJM, Franken IHA (2013). Implicit and explicit drug-related cognitions during detoxifica- tion treatment are associated with drug relapse: an ecological momentary assessment study. J Consult Clin Psychol 81:1-12.

Marissen MAE, Franken IHA, Waters AJ, Blanken P, van den Brink W, Hendriks VM (2006) Attentional bias predicts heroin relapse following treatment. Addiction 101: 1306–1312.

Marlatt GA, Gordon JR. Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors. New York: Guilford Press; 1985.

Matochik JA, London ED, Eldreth DA, Cadet JL, Bolla KI (2003) Frontal cortical tissue composition in abstinent cocaine abusers: a magnetic resonance imaging study. Neuroimage 19: 1095–1102.

McDowell JE, Brown GG, Paulus M, Martinez A, Stewart SE, Dubowitz DJ, Braff DL (2002) Neural correlates of refixation saccades and anti-saccades in normal and schizophrenia subjects. Biol. Psychiatry 51: 216–223.

McDowell JE, Clementz BA (2001). Behavioral and brain imaging studies of saccadic performance in schizophrenia. Biological Psychology 57: 5−22.

McKay JR (1999). Studies of factors in relapse to alcohol, drug and nicotine use: a critical review of methodologies and findings. J Stud Alcohol 60: 566–576.

Miller EK, Cohen JD (2001) An integrative theory of prefrontal cortex function. Ann Rev Neurosci 24: 167–202.

Moeller FG, Steinberg JL, Schmitz JM, Ma L, Liu S, Kjome KL, Rathnayaka N, Kramer LA, Narayana PA (2010) Working memory fMRI activation in cocaine dependent subjects: association with treatment response. Psychiatry Res: 174-82.

Munafò MR, Roberts N, Bauld L, Leonards U (2011) Plain packaging increases visual attention to health warnings on cigarette packs in non-smokers and weekly smokers but not daily smokers. Addiction 106: 1505-10.

Munoz DP, Armstrong IT, Hampton KA, Moore KD (2003) Altered control of visual fixation and saccadic eye movements in attention-deficit hyperactivity disorder. J. Neurophysiol 90: 503–514.

Munoz DP, Everling S. (2004) Look away: the anti-saccade task and the voluntary control of eye movement. Nat Rev Neurosci 5:218-28. Review.

Munoz DP, Hampton KA, Moore KD, Goldring JE (1999) Control of Purposive Saccadic Eye Movements and Visual Fixation in Children with Attention-Deficit Hyperactivity Disorder. Current Oculomotor Research: 415-423

Nakahara H, Doya K, Hikosaka O (2001) Parallel cortico-basal ganglia mechanisms for acquisition and execution of visuomotor sequences — a computational approach. J. Cogn. Neurosci. 13: 626–647.

Nilsson MH, Patel M, Rehncrona S, Magnusson M, Fransson PA (2013) . Subthalamic deep brain stimulation improves smooth pursuit and saccade performance in patients with Parkinson's disease. J Neuroeng Rehabil 10:33.

O'Brien CP, Childress AR, Ehrman R, Robbins SJ (1998) Conditioning factors in drug abuse: can they explain compulsion? J Psychopharmacol: 15-22.

O'Brien CP, Gardner EL (2005) Critical assessment of how to study addiction and its treatment: human and non-human animal models. Pharmacol Ther 108:18–58.

Olds J, Milner P (1954) Positive reinforceent produced by electrical stimulation of septal area and other regions of rat brain. J Comp Physiol Psychol 47: 419–427.

Overduin J, Jansen A, Louwerse E (1995) Stroop interference and food intake. Int J Eat Disord 18:277-85.

Pa J, Dutt S, Mirsky JB, Heuer HW, Keselman P, Kong E, Trujillo A, Gazzaley A, Kramer JH, Seeley WW, Miller BL, Boxer AL (2014) The functional oculomotor network and saccadic cognitive control in healthy elders. Neuroimage. 2014 Mar 24.

Paré M, Hanes DP (2003) Controlled movement processing: superior colliculus activity associated with countermanded saccades. J. Neurosci. 23: 6480–6489.

Paré M, Wurtz RH (2001) Progression in neuronal processing for saccadic eye movements from parietal cortex area LIP to superior colliculus. J. Neurophysiol 85: 2545–2562.

Patel SS, Jankovic J, Hood AJ, Jeter CB, AB (2012) Reflexive and volitional saccades: biomarkers of Huntington disease severity and progression. J Neurol Sci 313:35-41.

Pierrot-Deseilligny C, Milea D, Müri RM (2004) Eye movement control by the cerebral cortex. Curr Opin Neurol 17: 17-25.

Pierrot-Deseilligny C, Müri RM, Nyffeler T, Milea D (2005) The role of the human dorsolateral prefrontal cortex in ocular motor behavior. Ann N Y Acad Sci 1039: 239-51.

Pierrot-Deseilligny C, Müri RM, Ploner CJ, Gaymard B, Demeret S, Rivaud-Pechoux S (2003) Decisional role of the dorsolateral prefrontal cortex in ocular motor behaviour. Brain 126: 1460–1473.

Pierrot-Deseilligny C, Rivaud S, Gaymard B, Agid Y (1991) Cortical control of reflexive visually-guided saccades. Brain 114: 1473–1485.

Pike E, Stoops WW, Fillmore MT, Rush CR (2013) Drug-related stimuli impair inhibitory control in cocaine abusers. Drug Alcohol Depend 133:768-71.

Ploner CJ, Gaymard BM, Rivaud-Péchoux S, Pierrot-Deseilligny C (2005) The prefrontal substrate of reflexive saccade inhibition in humans. Biol Psychiatry 57: 1159-65.

Pocock SJ, Assmann SE, Enos LE, Kasten LE (2002) Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med: 2917-30.

Poling J, Kosten TR, Sofuoglu M (2007). Treatment outcome predictors for cocaine dependence. Am J Drug Alcohol Abuse 33: 191–206.

Posner MI and DiGirolamo G (1989) Conflict, target detection, and cognitive control. In: Parasuraman, R. (Ed.), The Attentive Brain. MIT Press, Cambridge, pp. 401- 423.

Posner MI and DiGirolamo GJ (1998) Executive attention: conflict, target detection, and cognitive control. The Attentive Brain (p 201-423).

Powell J, Gray JA, Bradley BP, Kasvikis Y, Strang J, Barratt L, Marks I (1990) The effects of exposure to drug-related cues in detoxified opiate addicts: a theoretical review and some new data. Addict. Behav 15: 339 – 354.

Ratcliff R, Cherian A, Segraves M (2003) A comparison of macaque behavior and superior colliculus neuronal activity to predictions from models of two-choice decisions. J. Neurophysiol. 90: 1392–1407.

Reuter B, Jäger M, Bottlender R, Kathmann N (2007) Impaired action control in schizophrenia: the role of volitional saccade initiation. Neuropsychologia 45:1840-8.

Reuter-Lorenz PA, Hughes HC, Fendrich R (1991). The reduction of saccadic latency by prior offset of the fixation point: An analysis of the gap effect. Perception & psychophysics 49: 167–175.

Risinger RC, Salmeron BJ, Ross TJ, Amen SL, Sanfilipo M, Hoffmann RG, Bloom AS, Garavan H, Stein EA (2005) Neural correlates of high and craving during cocaine self-administration using BOLD fMRI. Neuroimage 26:1097–1108.

Rivaud S, Müri RM, Gaymard B, Vermersch AI, Pierrot-Deseilligny C (1994) Eye movement disorders after frontal eye field lesions in humans. Exp Brain Res 102:110-20.

Robbins SJ, Ehrman RN, Childress AR, O'Brien CP (1999) Comparing levels of cocaine cue reactivity in male and female outpatients. Drug Alcohol Depend: 223-30.

Robinson TE, Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 18: 247–91.

Rohsenow DJ, Niaura RS, Childress AR, Abrams DB, Monti PM (1990) Cue reactivity in addictive behaviors: theoretical and treatment implications. Int J Addict: 957-93.

Rosse RB, Fay-McCarthy M, Collins JP, Risher-Flowers D, Alim T, Deutsch S (1993) Transient compulsive foraging behavior associated with crack cocaine use. American Journal of Psychiatry 150: 155–156.

Rosse RB, Johri S, Kendrick K, Hess AL, Alim TN, Miller M, Deutsch SI (1997) Preattentive and attentive eye movements during visual scanning of a cocaine cue: correlation with intensity of cocaine cravings. J Neuropsychiatry Clin Neurosci 9:91-3.

Rosse RB, McCarthy MF, Alim TN, Deutsch SI (1994) Saccadic distractibility in cocaine dependent patients: a preliminary laboratory exploration of the cocaine-OCD hypothesis. Drug Alcohol Depend 35:25-30.

Rosse RB, Miller MW, Hess AL, Alim TN, Deutsch SI (1993) Measures of visual scanning as a predictor of cocaine cravings and urges. Biol Psychiatry 33:554-6.

Rosse RB, Schwartz BL, Kim SY, Deutsch SI (1993) Correlation between anti-saccade and Wisconsin Card Sorting Test performance in schizophrenia. Am J Psychiatry 150: 333-5.

Sayette M, Shiffman S, Tiffany ST (2000) The measurement of drug craving. Addiction: S189-S210.

Schall JD (1997) Visuomotor areas of the frontal lobe. Cereb. Cortex 12: 527–638.

Selemon LD, Goldman-Rakic PS (1988) Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: evidence for a distributed neural network subserving spatially guided behavior. J. Neurosci 8:4049–4068.

Sereno AB, Holzman PS (1995) Anti-saccades and smooth pursuit eye movements in schizophrenia. Biol Psychiatry. 37: 394-401.

Shafiq-Antonacci R, Maruff P, Whyte S, Tyler P, Dudgeon P, Currie J (1999) The effects of age and mood on saccadic function in older individuals. J Gerontol B Psychol Sci Soc Sci 54:P361-8.

Shiffman S, Waters AJ (2004) Negative affect and smoking lapses: a prospective analysis. J Consult Clin Psychol 72:192–201

Shook BL, Schlag-Rey M, Schlag J (1990) Primate supplementary eye field: I. Comparative aspects of mesencephalic and pontine connections. J. Comp. Neurol. 301: 618–642.

Sim ME, Lyoo IK, Streeter CC, Covell J, Sarid-Segal O, Ciraulo DA, Kim MJ, Kaufman MJ, Yurgelun-Todd DA, Renshaw PF (2007) Cerebellar gray matter volume correlates with duration of cocaine use in cocaine-dependent subjects. Neuropsychopharmacology 32: 2229–2237.

Sinha R (2001) How does stress increase risk of drug abuse and relapse. Psychopharmacology 158:343–359.

Sinha R (2008) Chronic stress, drug use, and vulnerability to addiction. Ann N Y Acad Sci. 1141:105-30.

Sinha R, Garcia M, Paliwal P, Kreek MJ, Rounsaville BJ (2006) Stress-induced cocaine craving and hypothalamic-pituitaryadrenal responses are predictive of cocaine relapse outcomes. Arch Gen Psychiatry 63:324–331

Sinha R, Lacadie C, Skudlarski P, Fulbright RK, Rounsaville BJ, Kosten TR, Wexler BE (2005) Neural activity associated with stress-induced cocaine craving: a functional magnetic resonance imaging study. Psychopharmacology 183: 171– 180.

Sinha R, Shaham Y, Heilig M (2011) Translational and reverse translational research on the role of stress in drug craving and relapse. Psychopharmacology (Berl) 218:69-82.

Sommer MA, Tehovnik EJ (1997) Reversible inactivation of macaque frontal eye field. Exp. Brain Res 116: 229–249.

Stuphorn V, Taylor TL, Schall JD (2000) Performance monitoring by the supplementary eye field. Nature 408: 857–860.

Trappenberg TP, Dorris MC, Munoz DP, Klein RM (2001) A model of saccade initiation based on the competitive integration of exogenous and endogenous signals in the superior colliculus. J. Cogn. Neurosci 13:256–271.

Unsworth N, Spillers GJ, Brewer GA, McMillan B (2011) Attention control and the anti-saccade task: A response time distribution analysis. Acta Psychol (Amst) 137:90-100.

Vadhan NP, Carpenter KM, Copersino ML, Hart CL, Foltin RW, Nunes EV (2007) Attentional bias towards cocaine-related stimuli: relationship to treatment-seeking for cocaine dependence. Am J Drug Alcohol Abuse 33:727–736.

Van der Geest JN, Kemner C, Camfferman G, Verbaten MN, van Engeland H (2001) Eye movements, visual attention, and autism: a saccadic reaction time study using the gap and overlap paradigm. Biol Psychiatry 50:614-9.

Vaurio RG, Simmonds DJ, Mostofsky SH (2008) Increased intra-individual reaction time variability in attention-deficit/hyperactivity disorder across response inhibition tasks with different cognitive demands. Neuropsychologia: 2389-96.

Vidailhet M, Rivaud S, Gouider-Khouja N, Pillon B, Bonnet AM, Gaymard B, Agid Y, Pierrot-Deseilligny C (1994) Eye movements in parkinsonian syndromes. Ann Neurol 35:420-6.

Volkow ND, Fowler JS, Wang GJ, Telang F, Logan J, Jayne M, Ma Y, Pradhan K, Wong C, Swanson JM (2010) Cognitive control of drug craving inhibits brain reward regions in cocaine abusers. Neuroimage 49: 2536–2543.

Volkow ND, Wang GJ, Fischman MW, Foltin RW, Fowler JS, Abumrad NN, Vitkun S, Logan J, Gatley SJ, Pappas N, Hitzemann R, Shea CE (1997) Relationship between subjective effects of cocaine and dopamine transporter occupancy. Nature 386: 827–830.

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C (2006) Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci: 6583-8.

Vorspan F, Bellais L, Romo L, Bloch V, Neira R, Lépine JP (2012) The Obsessive-Compulsive Cocaine Scale (OCCS): a pilot study of a new questionnaire for assessing cocaine craving. Am J Addict: 313-9.

Walker R, Husain M, Hodgson TL, Harrison J, Kennard C (1998) Saccadic eye movement and working memory deficits following damage to human prefrontal cortex. Neuropsychologia 36: 1141–1159.

Waters AJ, Shiffman S, Sayette MA, Paty JA, Gwaltney CJ, Balabanis MH (2003) Attentional bias predicts outcome in smoking cessation. Health Psychol 22: 378–387.

Westheimer G (1954) Mechanisms of saccadic eye movements. Am Arch Opthalmol 52:710–724.

Whelan R (2008) Effective analysis of reaction time data, The Psychological Record: 58 (3).

Wilson SJ, Sayette MA, Fiez JA (2004) Prefrontal responses to drug cues: a neurocognitive analysis. Nat Neurosci 7: 211–214.

Wühr P, Waszak F (2003) Object based attentional selection can modulate the Stroop effect. Mem Cognit 31: 983-94.

VITA

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