The Road to Recovery: A Neural Characterization of Cocaine Abstinence

by

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Abstract

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Ryan Patrick Bell

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Cocaine addiction is a significant public health issue with an outsized effect on the individual and society at large. A principal reason for the immense social and personal costs associated with cocaine addiction is the difficulty in remaining abstinent. Utilizing diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI), current cocaine dependence has been associated with deficits in white matter integrity and atypical neural activation in multiple cognitive control regions. However, while the neurobiological and behavioral deficits associated with current cocaine dependence have been well-characterized, it is relatively unknown if these deficits persist after the cessation of cocaine use. To elucidate neurobiological functioning during cocaine abstinence, we conducted three experiments utilizing either DTI or fMRI methodology in cocaine dependent (CD) individuals at varying periods of abstinence. The results of these investigations show that as a group, abstinent CD individuals do not display the same neurobiological deficits as current users. We speculate that the absence of these deficits may be partly due to the intensive drug-treatment programs the participants were enrolled in. However, when we conducted subject-level examinations, we found that abstinent CD individuals displayed neurobiological functioning related to the duration of abstinence. We postulate then that continued abstinence may be responsible for an amelioration of

neurobiological deficits or reflect preexisting differences that allow for extended abstinence. Additionally, we observed participant-level differences that were not a function of duration of abstinence leading us to speculate that recovery occurs at temporally different rates in some individuals. Overall, it appears that while a majority of recovering individuals do not display the neurobiological deficits associated with current cocaine users, there exists a subset of individuals that continue to display these deficits. We hypothesize that those individuals who continue to display neurobiological deficits will have the greatest risk of cocaine relapse.

Dedication

This dissertation is dedicated to my parents, Patricia and Milton Bell, and the rest of my lovely southern family. Without their love and support none of this would have been possible. They always believed in me and allowed me to follow whatever path I chose.

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GENERAL INTRODUCTION

A persistent problem with cocaine dependence is that at least 1 in every 4 cocaine dependent (CD) individuals will return to drug use after periods of abstinence (Simpson et al., 2002). Understanding the neurobiology of relapse or, more particularly, the neurobiology of those who successfully avoid relapse is thus an important issue with clear therapeutic implications. Here, I provide an introduction describing the significant costs of cocaine dependence to the American health care and criminal justice system and, most importantly, the significant costs of cocaine addiction to the individual. I will discuss the proposed neurobiological processes responsible for the "high" that occurs after cocaine intake and how this "high" is both more attractive to some individuals and not pleasant at all to others. Additionally, this document will help to elucidate how extended cocaine use is believed to result in significant neuroadaptations and how these neuroadaptations go a long way toward explaining the devastating loss of personal control associated with severe cocaine dependence. It will also be discussed how specific genetic and environmental factors may predispose an individual to be more likely to not only initially experiment with using cocaine, but also continue to use the drug in increasing amounts. Additionally, this introduction will explore specific childhood factors that may serve as risk factors for increased drug use and dependence. Finally, I will discuss some of the prominent theories on drug addiction in the current literature. Specifically, I will address how these theories explain the tremendous consequences associated with drug addiction and the commonalities that exist between the various theories.

By providing this introduction, I intend to offer enough background information on what constitutes drug addiction and how this process proceeds so that the reader may be able to better understand the physiological state of an individual when they are dependent upon a substance.

From that standpoint, this thesis will investigate whether an individual after acquiring cocaine dependence, is able to recover from the substantial changes that have been discussed in this introduction. Although there is tentative agreement among researchers about what factors lead to and result from drug addiction, there is relatively little information on whether these factors can be reversed or attenuated after cocaine abstinence. Therefore, this work will focus primarily on how cognitive deficits that have been identified in current cocaine users are present in formerly cocaine-dependent individuals after various lengths of drug abstinence. Additionally, we will investigate whether the neural activations in the regions where these deficits have been identified in current CD individuals can predict resistance to relapse in abstinent CD individuals.

Prevalence and Significance of Substance Dependence and Cocaine Use

Drug dependence is a significant public health problem in the United States with 22.2 million persons aged 12 or older (8.9% of the population) being classified with substance dependence or abuse in 2008 (Administration, 2009). Specifically, cocaine presents a particularly severe problem. According to the 2008 National Survey on Drug Use and Health, approximately 36.8 million Americans aged 12 and older had tried cocaine at least once in their lifetimes, representing 14.7% of the population in this age bracket. Approximately 5.3 million individuals (2.1%) had used cocaine in the past year and 1.9 million (0.7%) had used cocaine within the past month according to the most recent Substance Abuse and Mental Health Services Administration survey (Administration, 2009). While the number of cocaine users is relatively small, the social cost and speed of addiction to cocaine are of utmost concern. It is estimated that over 11% of federal and state government budgets (374 billion in 2005) are spent dealing with the consequences of tobacco, alcohol and other substance use, abuse and dependence (The

National Center on Addiction and Substance Abuse at Columbia University, 2009). Data from the Drug Abuse Warning Network (DAWN), a national system for reporting drug-related emergency room visits shows that cocaine is the most frequently mentioned illicit substance; 548,608 out of 1,742,887 emergency room visits for illicit drug use involved cocaine. Using data from the National Comorbidity Survey (Kessler, R.C. National Comorbidity Survey: Baseline (NCS-1), 1990-1992), Wagner and Anthony (2002) showed that the peak values for cocaine dependence are between the ages of 23 and 25. Additionally, it was shown that 5-6% of cocaine users become dependent upon cocaine within their first year of use with 15-16% of cocaine users converting to cocaine dependence within 10 years of first use. This compares with 8% of marijuana users becoming dependent and 12-13% of alcohol users becoming dependent within 10 years of first use. These findings provide evidence of the relative quickness at which individuals become dependent upon cocaine after their first use when compared to other abusable substances and amounts to 1 in every 16-20 cocaine users becoming dependent upon the drug within the first year of cocaine usage. The quickness with which dependence develops could be explained by the relatively short half-life of cocaine which means that the drug's effects do not last for long which leads to binge taking behavior where the drug is taken repeatedly over a short period of time by users (O'Brien, 2001). The speed at which dependence develops after the initial usage of cocaine is matched by the extreme difficulty in stopping its use after dependence has developed. A study conducted by the National Institute on Drug Abuse showed that 1 in 4 people who enter treatment for cocaine addiction will still be using cocaine on a weekly basis 5 years after treatment (Simpson et al., 2002). For individuals who use any type of drug, it is estimated that less than 20% of those individuals will develop dependence to any particular substance regardless of the substance used (Anthony, 1994).

Neurobiology of Cocaine Addiction

To understand why so many individuals return to cocaine abuse after periods of abstinence, it is important to first understand the neurobiological processes that occur in the cortical and subcortical regions of the brain after an individual has ingested cocaine. The primary neurotransmitter associated with the rewarding effects of using cocaine is the catecholamine dopamine (DA) (Di Chiara and Imperato, 1988). Cocaine is believed to achieve its rewarding effects primarily through actions that take place in the mesocorticolimbic dopaminergic system which originates in DA neurons of the ventral tegmental area (VTA) and projects to the nucleus accumbens (NAc) (Moore and Bloom, 1978), ventral pallidum (Napier and Maslowski-Cobuzzi, 1994), prefrontal cortex, hippocampus, amygdala and olfactory tubules (Swanson, 1982) (see Figure 1). DA neurons in the VTA receive excitatory inputs from the PFC, laterodorsal tegmental nuclei, lateral hypothalamus and bed nucleus of stria terminalis (Geisler and Wise, 2008) and inhibitory inputs from GABAergic neurons within the VTA, and distally from the NAc and the ventral pallidum (see (Mameli and Luscher, 2011) for review). Specifically, it has been proposed that there are three stages of neuronal activity that give rise to the rewarding properties of cocaine. The first stage neurons are non-DA and are located in the anterior bed nuclei of the medial forebrain bundle (Wise, 1980; Wise and Bozarth, 1984; Wise and Rompre, 1989). These neurons are responsible

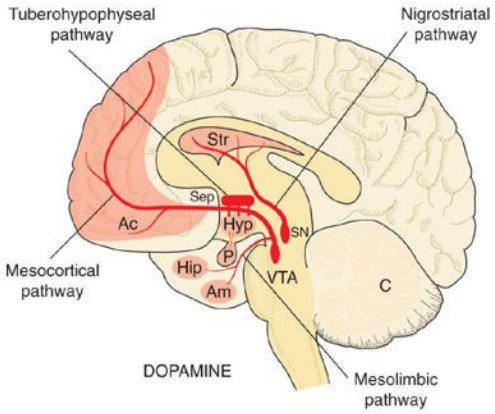

Figure 1. Dopamine Pathways. Ac, nucleus accumbens; Am, amygdaloid nucleus; C, cerebellum; Hip, hippocampus; Hyp, hypothalamus; P, pituitary gland; Sep, septum; SN, substantia nigra; Str, corpus striatum; Th, thalamus; VTA, ventral tegmental area. Reprinted with permission from Rang & Dale's Pharmacology. – 7th ed.

for conducting the initial reward signal. (Wise, 1980; Wise and Bozarth, 1984; Wise and Rompre, 1989). The first stage neurons synapse onto the second stage neurons which lie at a point of convergence with the DA cell bodies in the VTA and DA axon terminals in the NAc (Wise, 1980; Wise and Bozarth, 1984; Wise and Rompre, 1989). It is at these second stage neurons that it has been proposed that cocaine produces its rewarding effects resulting in the cocaine "high". The final, third stage neurons are hypothesized to carry the reward signal beyond the NAc and have been found to be critical for the expression of reward-related and incentive-related behaviors (Inglis et al., 1994). These third stage neurons use the endogenous opioid peptide enkephalin as their primary neurotransmitter and project to the ventral pallidum (Heimer et al., 1991; McAlonan et al., 1993). The primary rewarding properties of cocaine are mediated by elevated extracellular DA levels in the reward synapses of the NAc shell (Rodd-Henricks et al., 2002). These elevated extracellular DA levels have been observed through the administration of cocaine-like drugs which inhibited DAT (Dopamine transporter) and blocked reuptake of DA (Ritz et al., 1987; Volkow et al., 1996). This hypothesis is supported by evidence showing that microinjections of DA antagonists into the NAc, but not into other brain areas that are also involved with dopamine and reward processing, block intravenous cocaine self-administration in laboratory animals (Phillips et al., 1983). Utilizing positron emission tomography (PET), Volkow et al. (1996) showed that in humans, intravenous cocaine injections blocked between 60-77% of DAT sites and that the self-reported "high" by the participants was correlated with the degree of DAT occupancy and was dependent upon the amount of cocaine in the striatum. Furthermore, ablation of DA terminals in the NAc of rats has been shown to result in significantly decreased cocaine self-administration (Gerrits and Van Ree, 1996). More specifically, the shell region of the NAc is believed to be involved in the early reinforcing

properties of cocaine, while the core region of the NAc is involved in maintaining learned drug-taking (Suto et al., 2009; Veeneman et al., 2012). However, recent evidence in rats suggests that the dorsolateral striatum may also be involved in the early reinforcing aspects of cocaine with the dorsolateral striatum involved with the motivation to take cocaine, while the NAc shell is involved with the rewarding aspects of cocaine (Veeneman et al., 2012). Cocaine dependence, however, is a complex disorder that is believed to arise through enhancement of DA activity throughout the mesocorticolimbic system (Wise, 1996). The amygdala and the hippocampus are believed to play a role in the conditioned learning that takes place in addiction with the amygdala (See, 2005) and the ventral hippocampus (Rogers and See, 2007) involved with stimulus-reward associations and the dorsal hippocampus being involved with stimulus-stimulus associations that may be important for contextual learning (Fuchs et al., 2007). The prefrontal cortex, anterior cingulate and insula all contribute to executive functioning, cognitive control and the regulation of emotional responses (Chambers et al., 2009; Garavan, 2010). Therefore, it appears that the primary rewarding properties of cocaine occur through actions in the mesolimbic dopaminergic system, specifically, the "high" resulting from the ingestion of cocaine results from the blocking of DAT by the substance which leads to a large concentration of dopamine within the striatum. However, cocaine addiction is hypothesized to occur through more widespread actions that take place throughout the mesocorticolimbic dopaminergic system and will be discussed in later sections.

Neurotoxicity

Extended and persistent cocaine use has been shown to cause neurotoxicity in users, but the exact mechanisms underlying this neurotoxicity are relatively unknown. Cocaine use has

been observed to induce vasoactive effects that result in the disruption of cerebral blood flow (CBF) (Volkow et al., 1988). Ren et al. (2011) showed that mice who were repeatedly injected with cocaine displayed cerebral microischemia in the arteriolar branches of the cerebral microvascular of the somatosensory cortex. Similarly, Sharma et al. (2009) showed that intravenous administration of cocaine in rats produced hyperthermia, elevated mean arterial blood pressure, increased blood-brain barrier permeability, brain edema, increased serotonin levels, increased cerebral blood flow, and increased upregulation of glial fibrillary acidic protein (GFAP) activity. The authors hypothesized that these actions could result in neurotoxicity that could be irreversible in nature and could possibly be responsible for neurodegenerative changes that are believed to result from extended cocaine use. Examples of neurodegenerative changes that could result from repeated cocaine use are reduced gray matter volume (Ersche et al., 2011a; Franklin et al., 2002; Hanlon et al., 2011; Sim et al., 2007) and increased white matter (WM) hyperintensities (Bartzokis et al., 1999) that have been observed in current CD individuals when compared to non-using controls. Most strikingly, after a single "binge" use of cocaine, a patient with a past history of drug dependence but no history of cocaine dependence was diagnosed with bilateral WM hyperintensities of the palladi and splenium of the corpus callosum (CC) attributed to the cocaine overdose (De Roock et al., 2007).

Neuroadaptations as a Cause of Addiction

Despite the identification of the neurotransmitters and the cortical and subcortical structures involved with the rewarding effects of drug use, reward itself is inadequate to fully explain drug addiction. This is primarily due to the observation that the intense feelings of reward associated with the early stages of drug use do not continue into the later stages of

compulsive drug-taking (Everitt and Robbins, 2005; Koob and Le Moal, 2008). Instead, the later stages of drug addiction are characterized by habitual, compulsive drug-taking that is theorized to be driven by automatic habit formation rather than reward-seeking (Everitt et al., 2008; Koob and Volkow, 2010). The transition from reward-based drug-taking to compulsive drug-taking is proposed to occur as a result of various neuroadaptations in the mesocorticolimbic dopamine system. (Everitt et al., 2008; Koob and Le Moal, 2008; Koob and Volkow, 2010; Robinson and Berridge, 2008). It has been shown that neuroadaptations that occur as a result of drug administration can begin as early as the very first instance of cocaine use (Ungless et al., 2001). However, we are not suggesting that an individual becomes physically and psychologically addicted after only one trial of cocaine. The most likely scenario is that these early, reversible forms of neuroplasticity are instrumental in initiating more enduring forms of neuroplasticity. If cocaine use is continued, these changes become more concrete and are hypothesized to then result in the compulsive, habitual drug- taking that is characteristic of drug addiction.

The neuroadaptations resulting from persistent cocaine use can help to explain how an individual who initially begins using a drug for the rewarding effects of the substance, slowly degenerates to a point where he or she is no longer capable of controlling their drug use. The end result of these neuroadaptations appears to be the last stop for the recreational cocaine user, a point where he or she is no longer in control of their use and for the rest of their life will carry the burden of addiction. Everitt and Robbins (2005) theory maintains that drug addiction is comprised of a switch from voluntary drug use to compulsive/habitual drug intake. The acquisition stage of drug use consists of individuals initially taking a drug because of its rewarding effects (Campbell and Carroll, 2000). However, in the escalation/dysregulation stage, a drug is taken in a compulsive/habitual manner that is hypothesized to result from an interaction

between Pavlovian and instrumental learning processes (Everitt et al., 2008). Pavlovian conditioning, in the context of drug addiction, refers to when previously neutral environmental stimuli become associated with drug use and become conditioned stimuli (drug cues). An example of this process would be the repeated use of a lighter to use drugs causes the sight of the lighter by itself to trigger cocaine craving. When these drug cues are combined with the reinforcing effects of drugs, the presentation of drug cues alone can act as a reinforcer and can produce drug-seeking or drug-taking behavior (Pavlovian instrumental transfer).

The switch from voluntary to habitual drug-seeking and drug-taking can be understood through two distinct but temporally interrelated processes. The first neuroadaptation that is hypothesized to cause the transition to compulsive drug-taking is a priming mechanism referred to as metaplasticity, a process where glutamatergic synapses become more susceptible to future plasticity through the neurobiological effects of cocaine use (Lee and Dong, 2011). Specifically, it has been proposed that this metaplasticity occurs through the recruitment of "silent synapses" within the NAc. The term silent synapses refers to synaptic connections in which only N-methyl-D-aspartic acid receptor (NMDAR) facilitated responses can be observed while alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) are not easily detected. The creation of silent synapses is considered a form of metaplasticity because they provide an increased amount of plasticity substrates which are then highly susceptible to long-term potentiation (LTP) (Kerchner and Nicoll, 2008). The recruitment of these silent synapses is hypothesized to result in increased LTP that leads to a strengthening of cocaine-associated memories based upon the steadily increasing relationship between drug use and reward (Lee and Dong, 2011). This process is thought to occur because of increased DA receptor activation in the VTA as a result of cocaine use, which produces an increase in NMDAR excitatory postsynaptic

potentials which then generate NMDAR-dependent LTP resulting in the creation of silent synapses in the NAc (Luscher and Malenka, 2011). Supporting evidence for the creation of silent synapses as a result of cocaine use in the NAc comes from experimental results documenting the appearance of silent glutamatergic synapses after in-vivo cocaine administration in rats (Huang et al., 2009). In addition, self-administered cocaine in rats has also been shown to increase NMDAR-dependent LTP in the bed nucleus stria terminalis (Dumont et al., 2005).

It is also hypothesized that these silent synapses may be responsible for the recruitment of specific AMPARs (Lee and Dong, 2011). There is evidence that AMPA-mediated LTP occurs even before the recruitment of silent synapses. A single *in vivo* exposure to cocaine has been shown to induce LTP of AMPA-mediated excitatory neurotransmission in dopamine neurons located in the VTA for at least five days (Ungless et al., 2001). This potentiation of synaptic AMPARs in the VTA may occur in part through an increase in NMDAR signaling which is then dependent upon the presence of the neurotransmitter orexin (Borgland et al., 2006). When cocaine was self-administered by rats rather than passively introduced, strengthened AMPAR transmission was observed for up to three months in the VTA (Chen et al., 2008) suggesting that self-administration is an integral part of the increased LTP that occurs as a result of cocaine use. In contrast to the VTA, injections to the NAc require repeated cocaine administrations which first results in depressed potentiation but then after 10 days of withdrawal results in increased potentiation that coincides with increased AMPAR surface expression (Kourrich et al., 2007). Therefore, it seems that the VTA is involved in early short-lived changes in the mesocorticolimbic system while the NAc is involved in slower and longer lasting changes.

There is also evidence for the involvement of NMDA signal transduction components in cocaine-induced neuroadaptations. Extracellular signal-regulated kinase (ERK) has been observed in neuroplasticity related to learning and memory (Adams and Sweatt, 2002). Single and repeated doses of cocaine have been shown to increase ERK phosphorylation in the NAc, amygdala, bed nucleus of the stria terminalis and prefrontal cortex which are all areas of the mesocorticolimbic dopamine system (Thomas et al., 2008). Using animal models, it has been shown that (ERK) activity and its effects on downstream gene transcription are responsible for the psychomotor sensitization caused by cocaine administration (Girault et al., 2007). Finally, evidence exists for a contribution of Brain-derived neurotrophic factor (BDNF) to cocaine-induced synaptic plasticity. BDNF is involved in synaptic plasticity (Thoenen, 1995) as well as continued functioning of midbrain dopamine neurons (Hyman et al., 1991) and can be found in the VTA (Seroogy et al., 1994), basolateral amygdala, bed nucleus of the stria terminalis (Dawson et al., 2001; Meredith et al., 2002) and prefrontal cortex (Altar et al., 1997). A single injection of BDNF directly into the VTA of rats trained to self-administer cocaine resulted in enhanced cocaine cue responding even after thirty days since cessation of cocaine use (Lu et al., 2004). This suggests that BDNF-induced neuroplasticity as a result of cocaine use contributes to both cocaine craving and relapse through enhanced responsiveness of VTA dopamine neurons to cocaine cues.

The evidence suggests that one of the more significant consequences of extended cocaine use is increased LTP production through the recruitment of silent synapses in the NAc. Increased LTP in response to cocaine consumption could help explain the strong learned associations that are gradually formed between cocaine related stimuli and the physiologically rewarding actions of cocaine. This learning is incorporating all of the various elements of drug-taking, including

the surrounding environment and the assorted tools associated with the drug-taking ritual. However, after repeated use, cocaine is unable to elicit the reward that was once experienced by the individual but unfortunately the neural circuitry has changed to a point where that reward is expected and therefore sought out. At this point, the neuroadaptations that have occurred have resulted in cocaine-related stimuli being able to trigger drug-taking behavior because of the strong learned associations that occurred during the earlier stages of drug addiction (Everitt et al., 2008).

The second major neuroadaptation to occur helps to explain why, from a physiological standpoint, an individual continues to take drugs in response to learned associations created during the early stages of drug abuse despite the obvious adverse consequences that are associated with continued drug use. This neuroadaptation is a gradual activation change from ventral to dorsal striatal activation in response to drug cues that is hypothesized to result from extended cocaine use and is believed to be responsible for the transition to habitual drug-seeking and taking. While increased LTP as a result of persistent drug use helps to solidify the link between drug use and reward, the transition from ventral to dorsal striatal activation to drug cues appears to represent the change in behavior associated with drug use. Instrumental behaviors are behaviors in which the result is completely dependent upon an action. It is theorized that instrumental behaviors are controlled by two separate and distinct systems referred to as the action-outcome (A-O) and stimulus-response (S-R) systems. The A-O system deals with behavior that is conducted with outcome-expectancy, that is, behavior that is based upon an awareness of the outcome. In contrast, the S-R system refers to behavior that is initiated by environmental stimuli with little regard to the actual outcome (Yin et al., 2006a). To put it more clearly, S-R behavior refers to actions that are commonly thought of as habits, that is, behavior

that is conducted with little or no conscious processing. The primary subcortical structure hypothesized to be responsible for the control of habitual behavior is the dorsal striatum. The role of the dorsal striatum in habit formation was explored through a lesion study which showed that rats that had received a lesion to the dorsolateral striatum did not develop S-R behavior and instead continued to engage in A-O behavior while rats without the lesion developed S-R behavior (Yin et al., 2006b). Thorn et al. (2010) showed that activity in dorsolateral striatal neurons in rats was positively correlated with increased habitual learning on a T-maze task. Further evidence comes from a human study utilizing a free-operant task which showed that right putamen activation corresponded with the formation of habitual behavior (Tricomi et al., 2009). The dorsolateral striatum in rats is hypothesized to be a homologue of the putamen in humans (Balleine and O'Doherty, 2010). A proposed model for the transition from reward to habit based cocaine intake is that striatal reactivity to drug cues switches from predominantly ventral to predominantly dorsal activation and that this switch is mediated by dopaminergic innervation (Everitt et al., 2008). This switch is hypothesized to occur through ventral striatal "spiraling" connections between midbrain dopamine neurons and gradually more progressive regions of the dorsal striatum (Haber et al., 2000; Ikemoto, 2007). Several studies conducted in non-human primates have provided evidence for this ventral to dorsal transition occurring with extended cocaine use. In non-human primates who were trained to self-administer cocaine, it was found that monkeys that had used cocaine for extensive periods of time expressed higher dopamine receptor 2 (D2) binding in dorsal rather than ventral regions of the striatum (Nader et al., 2002). Similarly, rhesus monkeys who self-administered cocaine in larger amounts expressed higher DAT binding in the dorsal striatum relative to the ventral striatum (Letchworth et al., 2001). Porrino et al. (2004) measured rates of glucose utilization in the striatum of monkey's that were

trained to self-administer cocaine. During the initial stages of cocaine self-administration, the monkeys exhibited decreased functional activity primarily in the ventral striatum. However, with a more extended exposure to cocaine, this decreased functional activity spread to the dorsal regions of the striatum. Additional evidence for the role of the dorsal striatum in cocaine dependence comes from rat models of cocaine addiction. In rats that were self-administering cocaine, it was shown that rats who engaged in extended cocaine intake did not demonstrate extinction of cocaine-seeking even after devaluation of the drug-taking link, whereas rats that did not have extended cocaine intake did demonstrate extinction after devaluation of the outcome. Furthermore, when rats with extended cocaine intake had the dorsolateral striatum inactivated, they became sensitive again to the devaluation of the outcome. The authors interpreted the data as indicative of extended cocaine seeking resulting in habitual, rather than goal-directed behavior and of dorsolateral striatal activation being responsible for controlling habitual responding (Zapata et al., 2010). Belin et al. (2008) demonstrated that in rats that had progressed to a stage of cue-controlled drug seeking for cocaine, their drug seeking behavior was dramatically reduced after inactivation of the dorsal striatum through the injection of a DA receptor antagonist and lesioning the contralateral NAc core. Thus, ventral striatal activity to drug cues is thought to underlie the early stages of drug-taking where the drug is taken for its rewarding properties and the user still has some control over his or her drug use. In contrast, dorsal striatal activity to drug cues is thought to underlie the latter stages of drug use where the drug is taken in a compulsive/habitual manner that is not mediated solely by reward and would characterize a state of drug addiction.

Heritability of Drug Addiction

It has been postulated that addiction to illicit substances, specifically the neurobiological effects of cocaine, may be based on heritable genes. Bierut et al. (1998) found that siblings of CD probands had an elevated risk of developing cocaine dependence (risk ratio, 1.71). However, a majority of studies have not identified a specific heritable influence of cocaine dependence. It is possible that cocaine addiction itself is not genetically disposed but rather the propensity for addiction to abusable substances is itself due to genetic variation. In a study examining 1,196 male twin pairs from the Virginia Twin Registry on the use of six different illicit substances, it was shown that there were no substance-specific genetic effects (Kendler et al., 2003). The authors went on to show that any genetic or environmental risks for substance abuse pertained to all classes of drugs. Additionally, a study of 3,372 twin pairs from the Vietnam Era Registry found that there was a shared vulnerability factor across marijuana, sedatives, stimulants, heroin and psychedelics without any specific vulnerability for any particular substance (Tsuang et al., 1998). Furthermore, a longitudinal study looking at the sons of males with or without substance use disorders (SUD) found that a lifetime diagnosis of SUD was observed significantly more often in the sons of males with SUD's than in the sons whose fathers did not have SUD's (42.8% vs. 29.9%, $p = .012$) (Vanyukov et al., 2009). Both Cadoret et al. (1995) and Cadoret et al. (1986) showed that adopted children's drug dependence and or abuse was correlated with a diagnosis of alcohol dependence in the biological parent. A study examining 231 probands with dependence on opioids, cocaine, cannabis, and/or alcohol and 61 control probands and their 1267 adult first-degree relatives showed an eight-fold increased risk of substance abuse among the relatives of probands with substance abuse disorders across the whole range of substances examined (Merikangas et al., 1998). A community based study that compared CD individuals and their siblings against a non-using control group and their siblings, found that siblings of CD

individuals had significantly increased prevalence of drug use when compared to the non-using comparison group (Bierut et al., 2008). Finally, a study assessing cocaine dependence in dependent and non-dependent siblings, which were grouped into four clusters based upon degree of cocaine use, found the following heritability estimates: heavy users; cocaine predominant (h^2 =.39), heavy users; mixed drug injectors (h^2=.44), heavy users; later onset of cocaine dependence (h^2=.50) and moderate cocaine and opioid abuse (h^2=.32) (Kranzler et al., 2008). Therefore, it appears that there is a heritable risk to drug addiction across a spectrum of substances rather than a specific heritable risk for cocaine addiction. However, it should be noted that heritability is not adequate to understand all personal choices in life. Although there may be general heritable traits that are passed down, individual genetic and environmental differences still exist among individuals that are crucial to understanding personal preferences.

General Candidate Genes for Drug Addiction

Evidence supporting the concept of general heritable risks for drug addiction comes from genetic studies showing risk genes that are non-specific to any particular class of drugs, but rather, to dependence across all substances. Variants of neuronal nicotinic acetylcholine receptors (nAChRs) subunit genes have been associated with dependence to nicotine, alcohol and cocaine (Li and Burmeister, 2009). The Dopamine Receptor D4 (DRD4) has been associated with impulsivity, risk-taking and heroin, cocaine and alcohol dependence (Kreek et al., 2005). As stated previously, dopamine is involved with reward functioning and therefore genetic variations in genes that encode for proteins involved in the dopaminergic system could be responsible for vulnerability to multiple substance dependencies. Dopamine D2 receptors are encoded by the DRD2 gene and a polymorphism in the DRD2 gene called Taq1A can result in

reduced DRD2 receptor binding in the striatum (Thompson et al., 1997). Individuals that have reduced DRD2 may suffer from a reduction in D2 receptors and may thus be more prone to use substances that would increase dopaminergic activity. The Taq1A polymorphism has been associated with an increased risk for polysubstance abuse, heroin use, cocaine dependency, psychostimulant polysubstance abuse, smoking, and a predisposition to alcoholism (Khokhar et al., 2010). It may be that there are general genetic and environmental risk factors for substance dependence across all individuals. However, individuals who abuse cocaine do show neurobiological and personality differences that are separate from individuals who abuse heroin which will be discussed in more detail in subsequent sections (Badiani et al., 2011). Whether these differences are a consequence of the usage of the predominant drug of abuse or reflect preexisting differences remains to be seen. Regardless, there appears to be polysubstance risk genes within the general population for susceptibility to drug dependence. It may also be that there are more specific risk genotypes for individual drugs of abuse that remain to be clarified.

Candidate Genes Specifically for Cocaine Use and Addiction

Although much of the evidence suggests that general genetic influences are responsible for drug addiction, it is still possible that there are specific genetic factors that can help explain a personal preference for cocaine. One candidate gene thought to be associated specifically with cocaine dependence is dopamine transporter 1 (DAT1). The variable-number tandem repeat (VNTR) in intron 8 is a polymorphism in DAT1 that was shown to be positively associated with cocaine dependence in a sample of CD individuals in Sao Paulo, Brazil (Caine et al., 2002; Guindalini et al., 2006). Animal knock-out (KO) models have also found dopamine receptor D2 (DRD2) and brain-derived neurotrophic factor (BDNF) to be involved in cocaine dependence.

DRD2 is involved in the synaptic transmission of the neurotransmitter dopamine and was shown to be involved in limiting the rate of high-dose self administration of cocaine in KO models (Caine et al., 2002). However, a study examining only DRD2 and DAT1 polymorphisms in African-American CD individuals and non-using controls did not find any association between these polymorphisms and cocaine dependence (Lohoff et al., 2010). BDNF is involved in the regulation of synaptic plasticity and KO models have shown that BDNF originating from NAc neurons is responsible for regulating cocaine self-administration and is involved in cocaine relapse after the discontinuation of use (Graham et al., 2007). Additionally, BDNF KO mice were shown to have reduced cocaine-conditioned place preference and decreased locomotor activity in the first hour after cocaine injection when compared to wild type mice (Hall et al., 2003). Human studies have shown that in the cortex of human CD individuals, exon 4 and exon 1-specific BDNF mRNA levels (BDNF1) were found to be reduced 40% when compared to non-using controls (Jiang et al., 2009). Another possible protein involved in cocaine addiction is nerve growth factor (NGF). NGF is a neurotrophin involved in the survival and function of cholinergic neurons (Lad et al., 2003). NGF serum levels are significantly decreased in CD individuals (Angelucci et al., 2007). Additionally, deletion of the α4 subunit gene for nAChRs resulted in a prolonged motor response to cocaine in KO mice (Marubio et al., 2003). It has been proposed that nAChRs are part of the regulation of dopamine release and are therefore involved in cocaine self-administration levels and reinforcement of the rewarding effects of cocaine (Li and Burmeister, 2009). Supporting this, the non-synonymous coding polymorphism rs16969968 of the CHRNA5 gene that is responsible for encoding the α5 subunit of nAChR has been shown to provide a protective factor against cocaine dependence (Grucza et al., 2008). Homer proteins have been shown to play a role in cocaine-induced neuroplasticity by regulating glutamate

signaling (Szumlinski et al., 2006). A single nucleotide polymorphism (SNP) in the Homer1 gene, rs6871510 was identified as a potential risk factor for cocaine dependence in an African American population (Dahl et al., 2005). Finally, a genome-environmental risk-prediction analysis showed that the GBE1 gene along with personal and environmental factors were significant risk factors for the development of cocaine dependence (Wei et al., 2012). These studies have shown that in both human cocaine addiction and animal models of cocaine addiction there are numerous genes that appear to be involved with the risk for and the continuation of cocaine addiction. This polygenetic presentation of cocaine dependence appears to reflect the complicated nature of who presents a risk for addiction and implies that numerous neurotransmitter systems are involved in this disorder.

Individual Factors Associated with Cocaine Addiction

In addition to the possibility that specific genes are involved in cocaine addiction, there is also evidence suggesting that specific personal factors are responsible for the choice of cocaine. First, individuals who abuse stimulants typically display greater impulsivity and greater attention and executive function deficits than individuals who abuse heroin (Ersche et al., 2006; Lundqvist, 2005). However, whether these differences are reflective of pre-existing deficits or a result of psychostimulant use remain to be elucidated. Evidence in support of low impulse control predating cocaine use comes from Dalley et al. (2007). This study showed that rats that exhibited high impulsivity would increase cocaine self-administration but not heroin self-administration. In a study looking at the effect of environment on heroin or cocaine choice, rats were trained to self-administer both heroin and cocaine either in their living environment (resident rats) or were transferred to another setting to self-administer (non-resident rats). When

given an opportunity to choose between heroin and cocaine, most resident rats preferred heroin while non-resident rats preferred cocaine (Caprioli et al., 2009). Similarly, in humans who abused both heroin and cocaine, a majority of users would use heroin at home (73%) and cocaine when they were outside of the home (67%) (Caprioli et al., 2009). Therefore, it would seem that individuals who primarily use cocaine have specific environmental reasons for this choice. It might be that individuals who are predisposed to using cocaine are more extroverted in nature while individuals who prefer heroin are more introverted. In a study that clustered cocaine users by their amount of substance use, it was found that individuals who were heavy users of cocaine and heavy users who injected both cocaine and heroin have the highest prevalence of major depressive disorder, antisocial personality disorder and posttraumatic stress disorder when compared against individuals who used less of a substance and against non-using controls (Kranzler et al., 2008). Personality was assessed in a sample of young cocaine users in Barcelona, Spain (mean age = 23.8) using the Temperament and Character Inventory-Revised version (TCI-R). The authors postulated that cocaine users who have low levels of self-directedness, low levels of cooperativeness, high levels of self-transcendence in the TCI-R, high levels of cocaine usage and a comorbid psychiatric diagnosis may represent a specific phenotype of cocaine users (Herrero et al., 2008). Although individuals may have an equal chance of becoming dependent on any illicit substance, it would seem that there are clear environmental factors that may predispose an individual towards cocaine use rather than other substances.

Childhood Factors Relating to Substance Abuse/Dependence

Along with genetic and environmental factors that may predict substance dependence, specific childhood behaviors have been hypothesized as risk phenotypes for the development of

substance dependence later in life. Using data from a 25-year longitudinal study on a cohort of 1,265 New Zealand children who had data collected at three intervals consisting of middle childhood (7-9 years), adolescence (14-16 years) and young adulthood (18-25 years) researchers found that children diagnosed with conduct problems in middle childhood were at an increased risk for substance abuse/dependence in young adulthood (Fergusson et al., 2007). Using the same cohort of children, Fergusson et al. (2008) found that the frequency of cannabis use in adolescence and young adulthood was the strongest predictor of illicit drug abuse/dependence in young adulthood. This does not necessarily mean that marijuana is a "gateway" drug that leads to harder drug use, rather, it could be that individuals predisposed to drug use would start with the most readily available and socially acceptable illicit substance. It seems that a diagnosis of conduct disorder is a strong predictor of future substance abuse/dependence in adulthood while attention-deficit hyperactivity disorder (ADHD) is somewhat less predictive. Evidence for this hypothesis comes from a longitudinal study on a sample of 1,512 male and female twin pairs from the Minnesota Twin Family Study which found that conduct disorder was strongly predictive of substance use disorders by the age of 18 (odds ratio > 4.27). This study also found that the hyperactivity/impulsivity subtype of ADHD was predictive of cannabis abuse/dependence although not to the same degree as conduct disorder (Elkins et al., 2007). It is worth noting that in the above study, a diagnosis of cannabis abuse/dependence was the only illicit substance measured in the 18 year old cohort while in the 11-14 year old cohort, all illicit substance use was measured. The authors reported that this was because by the age of 18, most individuals who used illicit substances had a comorbid diagnosis of cannabis abuse/dependence and therefore was the only substance measured. Although ADHD is not the only childhood disorder associated with substance abuse, it has been shown to be somewhat prevalent in adult

substance abusers (Ohlmeier et al., 2008). Additionally, a longitudinal study relying on self-reports looked at the relationship between childhood inattention/hyperactivity symptoms and adolescent substance use while also controlling for psychiatric comorbidity, temperament and environmental risk factors and found that inattention/hyperactivity symptoms were associated with regular cannabis use and a higher risk for experimentation with harder drugs such as stimulants and sedatives in male participants (Galera et al., 2008). However, it does not seem that the symptoms of ADHD can fully explain why an individual would become dependent upon illicit substances. A longitudinal study examining 481 children found that individuals with high levels of both hyperactivity/impulsivity/inattention and conduct problems had the highest levels of hard drug use, marijuana dependence symptoms and hard drug dependence. Furthermore, children who had the highest levels of hyperactivity/impulsivity/inattention but lower conduct problems had the lowest rates of the above mentioned substance use (Flory et al., 2003). Additionally, in a sample of 217 Hispanic eighth-grade adolescents, it was shown that individuals with both high levels of ADHD and conduct disorder were at a greater risk for developing early substance abuse than adolescents with ADHD and without conduct disorder. However, another finding of the study was that adolescents diagnosed with ADHD who had high levels of hyperactivity symptoms were at greater risk for alcohol and drug use compared to adolescents with low levels of hyperactivity symptoms whether or not there was conduct disorder symptoms present (Lopez et al., 2008). In somewhat disagreement with the above findings, another study of 142 ADHD diagnosed children found that the inattention and not the impulsivity dimension of ADHD predicted later substance abuse better than childhood antisocial behaviors (Molina and Pelham, 2003). It is important to note that impulsivity was measured in this study using only 3 items from the DSM-IV and, therefore, may not have adequately

measured the impulsive symptoms. The same study also showed that development of conduct disorder by the time of adolescence in the ADHD group was predictive of the highest levels of substance use and associated problems. A possible explanation for why ADHD and conduct disorder continuously appear in models of predictive factors for substance abuse is because of the high levels of comorbidity (30–50%) between the disorders that has been observed in both epidemiological and clinical samples (Biederman et al., 1991; Szatmari et al., 1989). One way of interpreting the disagreement between whether ADHD alone, conduct disorder alone, or ADHD and conduct disorder are more or less predictive of adolescent substance is through the cascade model proposed by Martel et al. (2009). In the cascade model, problematic temperament such as low reactive control would increase the risk for inattention/hyperactivity. This inattention/hyperactivity would then increase the risk for delinquency and conduct problems, which would then increase the risk for substance abuse and this sequence of behaviors would then be responsible for mediating the relationship between family risk status and adolescent substance abuse. This model was tested through a longitudinal study of 674 children from families that include a father with a diagnosis of alcohol dependence and found that the measure of reactive control was significantly related to the inattention/hyperactivity and disruptive behaviors as well as to the development of substance abuse in the cohort (Martel et al., 2009). Therefore, low reactive control was predictive of the development of inattention/hyperactivity and the inattention/hyperactivity was predictive of the development of conduct problems. However, disruptive behavior was suppressive of any effect of inattention/hyperactivity on the formation of substance abuse. The authors suggested that conduct problems could be more predictive of substance abuse in adolescents than inattention/hyperactivity. Finally, reactive control, inattention/hyperactivity and disruptive behaviors were found to be responsible for a

partial mediation of the path from family risk to adolescent substance abuse (Martel et al., 2009). Therefore, it would seem that ADHD and conduct disorder can interact in a specific fashion that would make children more susceptible to drug use. It is possible that this is manifested either through more risk-taking, lower impulse control or a tendency to engage in antisocial behaviors or is a result of an interaction of these behavioral phenotypes. A crucial area of research would then be to identify children most at risk for drug addiction so that necessary steps can be taken to ensure they do not fall into the vicious cycle of addiction. Importantly, because of limited resources available for childhood interventions, it would be necessary to reduce the broad phenotypes (high risk-taking, low impulse control, antisocial behavioral) to a more specific phenotype that targets those at the greatest risk for developing substance dependence.

Theories of Addiction

The following section will describe some of the more prominent theories of how drug dependence develops in individuals. This section will not attempt to refute or support any of the following theories. Rather, the main focus is to objectively present the hypotheses currently available in the drug addiction literature.

Genotypic Theories of Addiction

Iacono et al. (2008) have proposed that individuals are predisposed towards addiction because they possess a propensity towards behavioral disinhibition. They have proposed a single trait referred to as externalizing (EXT) which encompasses traits that would reflect behavior disinhibition across a broad spectrum and could apply to various compulsive and or antisocial disorders such as substance use disorder (SUD), anti-social personality disorder, conduct

disorder and ADHD disorder. Individuals possessing this EXT trait would be more likely to engage in impulsive behaviors that, depending on their environment, could lead to SUD's. Furthering this idea of a genetic and environmental component to cocaine addiction are Hiroi and Agatsuma (2005) who argue that an underlying disposition makes you susceptible to addiction. However, if cocaine is not available then you will not become addicted to cocaine but the traits will still be evident and may present in the form of personality disorders related to impulsivity or compulsivity. Evidence for this theory comes from an adoption study that showed a diagnosis of antisocial personality disorder in the biological parents correlated with adoptee aggressiveness, conduct disorder, antisocial personality disorder, and eventually drug abuse and/or dependence in the adoptee (Cadoret et al., 1986; Cadoret et al., 1995). In a study that clustered cocaine users by their amount of substance use, it was found that individuals who were heavy users of cocaine and heavy users who injected both cocaine and heroin have the highest prevalence of major depressive disorder, antisocial personality disorder and posttraumatic stress disorder when compared to individuals who used less of a substance and against non-using controls (Kranzler et al., 2008).

Dopaminergic Theories of Addiction

Knowing that there is more than likely a genetic component to addiction and that this component can apply to a wide range of behavioral disinhibition and not just cocaine addiction, what is the possible link between impulsivity and cocaine addiction? Two current theories focus on the main neurotransmitter that is associated with cocaine addiction, dopamine. The Anhedonia hypothesis was put forth by Roy A. Wise who argues that normal brain dopamine levels are responsible for everyday motivation while phasic elevations of dopamine are crucial

for reinforcement learning and produce learned associations between rewards and stimuli (Wise, 2008). Wise showed that laboratory animals treated with dopamine antagonists are able to initiate an activity but do not continue their activities because they are not reinforced (Wise, 2008). With the knowledge in hand that dopamine is intrinsically necessary for reward, it could be that individuals suffering from impulsivity have lower than normal dopaminergic functioning and therefore are more prone to seek out activities that would enhance dopaminergic function. In line with the Anhedonia hypothesis, Kenneth Blum proposed the reward deficiency syndrome (RDS). In RDS, the individual engages in addiction based upon his or her genetic makeup at birth but is influenced by multiple environmental elements that may include family, friends, educational status, economical position, environmental pollutants, and the availability of psychoactive drugs (Blum et al., 2000). Blum believes that the reason for the predisposition to addiction occurs because of a low level of dopamine functioning that leads the person to actively seek out stimulating or rewarding activities that would lead to feelings of well-being.

Systems Level Theory of Addiction

We next examine a systems level model of addiction. Antoine Bechara's model of addiction focuses on two different aspects of decision making (Bechara, 2005). This model consists of both an impulsive and reflective system of decision making. The impulsive system is based upon immediate affect and emotional responses to stimuli. The impulsive system is primarily concerned with the amygdala and how it codes stimuli and is concerned with the immediate response to a stimulus. In drug addicts, the amygdala is hyperactive and thus causes an exaggerated response to drug stimuli that can lead to neurobiological changes in how drug use is processed cognitively (Bechara, 2005). The reflective system is primarily associated with the

functioning of the ventral medial prefrontal cortex (VMPC) and is more concerned with long-term outcomes associated with decision making. The VMPC has been postulated to be responsible for how information is recalled and can help pick the correct or desired response for an individual based upon previous experiences. In cocaine addicts, the reflective system is theorized to be hypoactive and is therefore unable to adequately gauge performance based upon the long-term consequences because negative behaviors and their consequences do not carry the same importance as someone who is not addicted to drugs. Therefore, the cocaine addict codes information incorrectly and is unable to correctly learn how to inhibit their behavior because of deficits in the VMPC. Bechara therefore hypothesizes that addiction stems from a hyperactive impulsive system that exaggerates the importance of using cocaine and stimuli associated with using the drug and a hypoactive reflective system that is unable to inhibit socially undesirable responses because long-term consequences are not properly coded. However, there are varying levels of addiction whereas some individuals have decision-making deficits that are similar to those with lesions of the VMPC, decision-making deficits that are somewhat like those with damage to the VMPC and those who have decision-making abilities that are on par with non-using individuals. Those with abilities similar to non-using individuals may be physically addicted to drugs, but are still able to hold down jobs and be a "functioning" addict. These differences may be genetic and would occur before drug use begins.

Addiction as a Result of Vulnerability and Neural Changes in the Striatum

It is postulated by Everitt and Robbins (2005); Everitt et al. (2008) that drug addiction arises from a period where a drug is initially taken for its reinforcing reward effects, a time period that is referred to as "drug-taking" and primarily involves the NAc shell region. In the

beginning stages of addiction, it is believed that a neural shift in behavioral control takes place from the prefrontal cortical areas to the striatum. This shift is theorized to evolve from the neurotoxicity of drug use on prefrontal cortical structures and thus forces subcortical areas to be responsible for behavioral control. Eventually, after the drug is administered for an extended amount of time the behavior of the drug-taking individual transitions to a pattern of drug-seeking. This drug-seeking period involves behavior that is motivated by the rewarding effects of the drug but also by drug-related cues that act as conditioned reinforcers. This early period of drug-seeking involves the NAc core and its afferents from the basolateral amygdala which together form part of the ventral striatum. This initial period of drug-seeking is characterized by goal-directed drug seeking behavior that follows an instrumental response-outcome contingency which refers to behavior that is not yet automatic or compulsive but guided by the principle that taking drugs produces rewarding effects. Following the early stage of drug-seeking behavior is conduct that is guided by a stimulus-response instrumental process that is characterized by actions involved in seeking out the drug that are actually triggered and maintained by drug cues. This period of addiction would be best characterized as the time period when the addict is engaged in habitual and compulsive drug-seeking, an automatic process where self-control is nearly all lost. The actual act of using drugs has become devalued at this point. It is hypothesized that this time period is characterized by a migration from ventral striatal activation that is involved with the initial drug-seeking to dorsal striatal activity that characterizes the habitual, compulsive drug-seeking portion of drug addiction that serves to maintain the addiction. This theory also holds that an impulsive predisposition leaves an individual more prone to escalate cocaine self-administration and at an increased risk for relapsing into drug use. A predisposition towards impulsivity is explained by low numbers of D2/D3 dopamine receptors

in the ventral striatum. In contrast, animal models of the sensation-seeking phenotype have been shown to have higher initial cocaine self-administration than the impulsive phenotype rats (Belin et al., 2008). It is therefore explained that initial drug use does not cause addiction, but rather, persistent drug use would lead to addiction in a specific subset of the population that is estimated to be about 20% (Anthony, 1994) and is caused by some interaction between impulsivity and sensation seeking.

Incentive Sensitization Theory of Addiction

Robinson and Berridge (2008) proposed a model of addiction where dependence is caused by persistent drug abuse that causes physiological changes in neural processing. These changes result in a sensitization to the incentive motivational effects of drugs (compulsive "wanting") and stimuli associated with the drugs or drug use but does not sensitize circuits involved with how much an individual likes a drug. This process is hypothesized to result in a heightening of the incentive salience of drugs and the cues associated with drug use and leads to addiction. The sensitization takes place on brain circuits that are involved in Pavlovian conditioned incentive motivational processes and can be particular to a certain place or time. However, this theory does not provide evidence about what specific changes cause incentive sensitization. Stimuli that are paired with a reward obtain incentive properties when they display three specific characteristics 1) They can elicit approach towards them (Pavlovian conditioned approach behavior) 2) They can strengthen ongoing behavior by eliciting cue-triggered "wanting" for their associated unconditioned rewards (Pavlovian instrumental transfer) 3) They can act as reinforcers in their own right (Conditioned reinforcement). Additionally, this sensitization may also lead to compulsive behavior in other activities such as sex, gambling and

food. Robinson & Berridge argue that addiction cannot be explained by a simple stimulus-response theory because addicts are very flexible in obtaining their drugs and do not simply engage in the same sequence of events every day to get the drugs that they desire and argue that this is not the core issue with addiction. Additionally, they argue that this sensitization can persist long after the individual has stopped taking the drug and is a reason why addicts continue to want a drug long after use has stopped and may lead to relapse. Finally, this theory posits that there are significant cognitive behavioral deficits that result in a loss of control and lead to poor decision making in the addicts. Therefore, the loss of behavioral control combined with a sensitization to the effects of drugs and stimuli associated with drug use are responsible for the development of drug addiction.

Opponent Process as Motivation for Addiction

The opponent process theory of addiction byKoob and Le Moal (2008) defines addiction as 1) a compulsion to seek and take a drug 2) loss of control in limiting intake and 3) emergence of a negative emotional state when the drug is withdrawn. This theory maintains that addiction is comprised of both impulsive and compulsive elements that exist in three stages 1) preoccupation/anticipation 2) binge/intoxication and 3) withdrawal/negative effects. Impulsivity is believed to be the predominant factor in the early stages of addiction while compulsivity is more dominant at the later stages of addiction. The shift from impulsivity to compulsivity coincides with a shift from positive reinforcement driving the motivation for drugs to negative reinforcement driving the motivation for drugs. Koob and Le Moal (2008) maintain that different drugs produce different patterns of addiction because they focus on different stages of the pattern of addiction as described above. This theory is based upon the opponent process

theory of motivation which is described by an a-process and a b-process (Solomon and Corbit, 1974). The a-process consists of habituation to affective and or hedonic stimuli while the b-process focuses on the withdrawal from the affective and or hedonic stimuli. The two processes act in balance with each other to reduce the intensity of pleasurable experiences so that the system can generate new ways of reinforcing behavior that changes with different situations. In terms of drug-taking, the a-process is the initial acute effects that occur from taking a drug (pleasurable experiences) and would be counteracted by the b-process that serves to dampen the initial acute effects (withdrawal) so that new behaviors for pleasurable experiences can be sought. Addiction occurs when the b-process is no longer functioning properly and leads to a negative emotional state which then results in compulsive drug-taking. This process is believed to be caused by both within-system neuroadaptations and between-system neuroadaptations. The within-system neuroadaptations occur within the reward circuits and would neutralize the pleasurable effects of the drugs and involve a heightened and prolonged withdrawal response. The between-system neuroadaptations involve circuits that are activated by the reward circuits and would serve to attenuate the rewarding effect of drug-taking. Examples of within-system neuroadaptations would consist of decreases in sensitivity to natural reinforcers and decreased functioning of dopaminergic neurotransmitter systems. These decreases in reward functioning would contribute to a negative emotional state that is associated with drug abstinence and lead to relapses in drug-taking. Between-system neuroadaptations are believed to include increased release of stress hormones in response to drug-taking and inactivation of anti-stress systems that can persist into prolonged abstinence. These between-system neuroadaptations may lead to a prolonged negative emotional state that helps to maintain and prolong addiction. Therefore, drug addiction is conceptualized as a state where the normal opponent processes are disrupted by

drug-taking which results in a new state of functioning that is identified primarily through increased reward thresholds, revised motivational schemas and recruitment of anti-reward systems that would lead to a state of compulsive drug-taking or addiction.

Directions for Study

Drug addiction (with cocaine addiction in particular) is a significant public health problem in the United States of America. Along with the calculable costs of drug addiction that are associated with treatment and criminal punishment, there exists the incalculable costs associated with the damage to communities and society in general. Understanding the neurobiological actions and consequences of cocaine addiction are therefore of utmost concern as they provide an idea of what exactly needs to be treated for successful recovery to occur. Along with understanding the physiological changes that result from extended cocaine abuse, it is just as important to understand the factors that may lead an individual to take cocaine in a fashion that would lead to addiction. By identifying the variables associated with an increased risk for cocaine addiction, it may be possible to intervene before the individual engages in experimental drug use that could lead to addiction. After a comprehensive exploration of the available research, a picture emerges of a variety of factors that are believed to be responsible for initially predisposing an individual towards drug abuse. These factors consist of heredity, candidate genes and childhood behavior that can interact to form a devastating phenotype resulting in a heightened susceptibility to cocaine addiction for affected individuals. Numerous twin, sibling and family studies have provided evidence that individuals who have parents or siblings that abuse drugs are more likely themselves to also suffer from substance dependence. Furthermore, numerous candidate genes have been identified that may predispose an individual

to find more enjoyment from drug-taking. Even more specifically, candidate genes have been identified that are specific to cocaine addiction. This would make sense as cocaine use results in a very specific physiological reaction that is not enjoyable to all individuals. It has been shown that certain childhood factors are predictive of drug addiction in general. Examples of childhood behavioral factors that can predispose an individual towards drug addiction include low impulse control, high risk-taking and the presence of conduct disorder. Low impulse control and a predilection for risk-taking can lead to an individual being more likely to engage in drug use because they are unable or unwilling to adequately gauge the consequences of repeated drug use. Furthermore, an affinity for risk-taking could mean that an individual might find pleasure in indulging in illegal substances and the presence of antisocial personality disorder could mean they would also be undeterred by the legal and social ramifications of drug use. It should be stated that the presence of these behavioral factors in an individual does not automatically mean that he or she will initiate drug use. Instead, these behavioral factors should serve as warning signs for an increased likelihood of drug use early in life. While these behavioral factors do indeed predict drug use, they are inadequate in explaining why an individual would continue to abuse drugs. This is primarily because although these factors may explain why an individual would be more likely to initiate drug use, they do not explain why an individual would continue to maintain drug use despite substantial negative consequences. This is because to continue drug use, the individual must receive some kind of reward from continued use. Therefore, there must be a biological component to drug use to explain why drug intake would be more rewarding to some individuals and not to others. An example of a possible biological factor that could predispose an individual to cocaine addiction is being more susceptible to the rewarding effects of the drug of choice. This affinity for the rewarding effects of drugs would lead an individual to

take drugs in larger and more consistent amounts than others that do not have the same specific genetic predispositions. Finally, there is also evidence that the environment an individual is in may result in more drug use as the specific drug or opportunities to take the drug are more prevalent in that environment. However, this is not enough to explain the later stages of drug abuse where the drug is taken in a compulsive/habitual manner despite immense negative social and personal consequences. After the individual has taken a substance for an extended period of time, specific neuroadaptations begin to develop in the users brain which leads to an altered state of functioning that causes the neurobiological system to be dependent upon continued drug use. These neuroadaptations are hypothesized to consist of increased LTP in the NAc resulting from the biological effects of cocaine and a transition from ventral to dorsal striatal activation regulating drug use. Specifically, these neuroadaptations are believed to be responsible for the transition from reward-based to habit-based cocaine seeking and taking that is representative of the later stages of cocaine dependence.

With a clearer understanding of the risk factors for cocaine use, and the biological effects of extended cocaine use, the next chapters will focus on the specific cognitive and biological deficits that are found in current cocaine users and whether these deficits ameliorate with cocaine abstinence. Although a majority of research has focused on the behavioral and neurobiological deficits associated with current cocaine dependence, studies have also examined whether these deficits persist in abstinent CD individuals. Former stimulant abusers have displayed behavioral deficits in attention and motor skills even after one year of drug abstinence when compared to their non-drug abusing twins (Toomey et al., 2003). Additionally, abstinent polysubstance cocaine abusers showed behavioral deficits on multiple measures of inhibitory control when compared to non-using controls (Verdejo-Garcia et al., 2007). Multiple studies have also

examined whether CD individuals display neurostructural deficits after cocaine abstinence. Abstinent CD patients have shown reduced gray matter volume in multiple cortical regions including the prefrontal cortex (Fein et al., 2002; Matochik et al., 2003), lateral and medial aspects of the orbitofrontal cortex and right cingulate gyrus (Matochik et al., 2003) when compared against non-using controls. However, Connolly et al. (2013) showed that abstinent CD individuals with durations of abstinence greater than 35 weeks displayed higher gray matter volumes than drug-naïve controls. Additionally, (Hanlon et al., 2011) found that abstinent CD individuals showed higher gray matter density when compared to current CD individuals. Utilizing a modified STROOP task and positron emission tomography, (Bolla et al., 2004) showed that recently abstinent CD individuals displayed less activation in the left anterior cingulate cortex and right lateral prefrontal cortex and greater activation in the right anterior cingulate cortex during the conflict condition as compared to non-using controls. Another positron emission tomography study showed that recently abstinent CD patients showed greater activation while performing the Iowa Gambling Task in the right orbitofrontal cortex and less activation in the right dorsolateral prefrontal cortex and left medial prefrontal cortex when compared against non-using controls (Bolla et al., 2003). However, CD individuals with more extended periods of abstinence have shown increased neural activation measures when compared to a non-drug abusing cohort. Connolly et al. (2012) utilized a Go/No-Go motor response inhibition task to examine cortical activations in abstinent CD individuals and found that both the short- and long-term abstinence groups displayed greater cortical activity than drug naïve controls when performing a successful motor response inhibition in multiple cortical structures associated with response inhibition.

Therefore, the work completed thus far on recovering cocaine addicts shows somewhat conflicting evidence depending on the task, abstinence length and research methodology employed. Here we sought to help clarify the behavioral and neurobiological functioning of abstinent cocaine dependent individuals by utilizing relatively large cohorts of individuals and multiple research methodologies. Specifically, our research employed two different neuroimaging techniques consisting of diffusion tensor imaging (DTI) and functional magnetic resonance imaging (fMRI). DTI is a passive neuroimaging technique that provides information about the structural integrity of WM. This methodology provides information about structural integrity by analyzing the flow of water molecules through white matter tissue using fractional anisotropy (FA) as the dependent variable (Beaulieu, 2002). The FA value varies from 0 (completely isotropic) to 1 (free diffusion in one direction only). A FA value closer to 0 is typically interpreted as less structural integrity while a value closer to 1 is thought to be indicative of greater structural integrity. The second methodology that we intend to employ in this thesis is fMRI. fMRI is a type of MRI that measures the magnetic susceptibility of blood when an individual is typically performing a task (Huettel, 2009). Specifically, this methodology looks at the difference between oxygenated and deoxygenated hemoglobin levels to obtain the blood oxygen level dependent (BOLD) contrast (Greve, 2011). The BOLD contrast is believed to reflect the neural activity associated with the performance of a task. Utilizing these two methodologies, this thesis focuses on whether individuals, after cocaine cessation, recover neural function and structure that has been shown to be compromised in current CD individuals. Additionally, I will explore whether dorsal striatal activation is able to predict relapse behavior. Focusing on whether recovery occurs, and how and whom it occurs in, will help us to better understand how drug addiction can be treated.

CHAPTER 1

Assessing White Matter Integrity as a Function of Abstinence Duration in Former Cocaine-Dependent Individuals.

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Key Words: Diffusion Tensor Imaging, Relapse, Cingulum, Corpus Callosum, Fractional Anisotropy

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ABSTRACT

Current cocaine-dependent users show reductions in white matter (WM) integrity, especially in cortical regions associated with cognitive control that have been associated with inhibitory dysfunction. A key question is whether these white matter differences are present following abstinence from drug use. To address this, WM integrity was examined using diffusion tensor imaging (DTI) obtained on 43 cocaine abstinent patients (abstinence duration ranged between five days and 102 weeks) and 43 non-using controls. Additionally, a cross-sectional comparison separated the patients into three groups (short-term, mid-term and long-term) based upon duration of cocaine abstinence. The 43 cocaine abstinent patients showed lower fractional anisotropy (FA) in the left anterior callosal fibers, left genu of the corpus callosum, right superior longitudinal fasciculus, right callosal fibers and the superior corona radiata bilaterally when compared against non-using controls. Higher FA in the cocaine abstinent patients was observed in the splenium of the corpus callosum and right superior longitudinal fasciculus. Differences between the cocaine abstinent groups were observed bilaterally in the inferior longitudinal fasciculus, right anterior thalamic radiation, right ventral posterolateral nucleus of the thalamus, left superior corona radiata, superior longitudinal fasciculus bilaterally, right cingulum and the WM of the right precentral gyrus. The results identified WM differences between cocaine abstinent patients and controls as well as distinct differences between abstinent subgroups. The findings suggest that specific white matter differences persist throughout abstinence while other, spatially distinct, differences discriminate as a function of abstinence duration. These differences may, therefore, represent brain changes that mark recovery from addiction.

1. INTRODUCTION

A persistent problem with cocaine dependence is that most users will often return to drug use after periods of abstinence (Bossert et al., 2005). Understanding the neurobiology of relapse or, more particularly, the neurobiology of those who successfully avoid relapse is thus an important issue with clear therapeutic implications. However, there is relatively little empirical research on the neurobiological characteristics of successful abstainers. Exceptions include a positron emission tomography study (Bolla et al., 2004) which showed less activation in the left anterior cingulate cortex and right lateral prefrontal cortex and greater activation in the right anterior cingulate cortex during performance on a modified Stroop task in recently abstinent cocaine dependent (CD) patients when compared to non-using controls. Another positron emission tomography study showed that recently abstinent CD patients showed greater activation while performing the Iowa Gambling Task in the right orbitofrontal cortex and less activation in the right dorsolateral prefrontal cortex and left medial prefrontal cortex when compared against non-using controls (Bolla et al., 2003). An fMRI study showed decreased activation in the putamen, anterior cingulate, parahippocampal gyrus amygdala, mesencephalon and thalamus while increased activation was observed in prefrontal and parietal cortical regions involved in attentional processes in abstinent CD patients when compared against non-using controls during performance of a verbal working memory task (Tomasi et al., 2007). Additionally, another fMRI study found positive correlations between self-reported duration of abstinence and activation during a cognitive control task in the left posterior cingulate cortex, left ventral medial prefrontal cortex and right putamen (Brewer et al., 2008). Abstinent CD patients have shown reduced gray matter volume in the prefrontal cortex (Fein et al., 2002; Matochik et al., 2003), lateral and

medial aspects of the orbitofrontal cortex and right cingulate gyrus (Matochik et al., 2003) when compared against non-using controls. Finally, utilizing diffusion tensor imaging (DTI), Xu et al. (2010) found that self-reported days of cocaine abstinence were positively correlated with increased fractional anisotropy (FA) in the right superior longitudinal fasciculus, right body of the CC, right posterior limb of the internal capsule and the left cerebellum that was measured before entering a treatment program for CD. Additionally, Xu et al. (2010) split their sample into a short term abstinent group (mean duration of abstinence = 2.5 weeks) and a long-term abstinent group (mean duration of abstinence = 7.3 weeks) and found that the long-duration group had significantly higher FA than the short-duration group. All of these studies examined CD patients at relatively early stages of abstinence (mean = 7.3 weeks was the longest period of abstinence) and thus little is known about the effects of long-term abstinence.

Neuroimaging studies of currently-using CD individuals have shown differences in brain function (Hanlon et al., 2009; Kaufman et al., 2003; Garavan et al., 2008; Li et al., 2007), gray matter volume (Sim et al., 2007; Franklin et al., 2002), and white matter (WM) between CD individuals and healthy controls. With regard to WM, structural magnetic resonance imaging (MRI) has found an increased number of WM hyperintensities in CD individuals compared to healthy controls (Bartzokis et al., 1999) and to opiate dependent patients (Lyoo et al., 2004). A single period of intense cocaine use may even cause WM hyperintensities. After a single "binge" use of cocaine, a patient with a past history of drug dependence but no history of CD was diagnosed with bilateral WM hyperintensities of the palladi and splenium of the corpus callosum (CC) attributed to the cocaine overdose (De Roock et al., 2007).

DTI has been used to identify WM differences in current CD users. DTI provides information about WM integrity based upon the flow of water molecules through white matter

tissue using FA as the dependent variable (Beaulieu, 2002). The FA value varies from 0 (completely isotropic) to 1 (free diffusion in one direction only). Studies utilizing DTI have found lower FA in the WM of the inferior prefrontal cortex (Lim et al., 2002; Romero et al., 2010), internal capsule (Lim et al., 2008), genu of the CC (Moeller et al., 2005) and the isthmus, body and splenium of the CC (Ma et al., 2009; Lim et al., 2008) in current cocaine users when compared to non-using controls. Increased FA has been observed in current users compared to controls in the WM of the anterior cingulate (Romero et al., 2010). A DTI study also demonstrated that better performance on executive functioning measures was associated with higher FA in the left frontal callosal fibers and that faster performance on a set-shifting task was associated with higher FA in the right frontal projection fibers in children between the ages of 12 and 14 who were exposed *in utero* to cocaine (Warner et al., 2006). Finally, a recent DTI study using an animal model of cocaine exposure, thereby permitting causal relationships to be concluded, has shown that rats infused with cocaine for a four-week period exhibit reduced FA in the splenium of the CC (Narayana et al., 2009).

Gene expression studies have also provided evidence that cocaine use may be responsible for deficits in WM integrity. An investigation of myelin-related gene expression in postmortem striatal tissue of CD users revealed decreased levels of proteolipid protein (PLP1), claudin 11 (CLDN11) and transferrin (TFN) in every region examined except the NAc (Kristiansen et al., 2009). PLP1, CLDN11 and TFN are involved in creating and maintaining the structural integrity of myelin (Kursula, 2008; Campagnoni, 1988). However, another postmortem gene expression study that was conducted specifically on the NAc found decreased levels of myelin basic protein (MBP), PLP1 and myelin-associated oligodendrocyte basic protein (MOBP) in CD users (Albertson et al., 2004). MBP, along with PLP1, is responsible for about 80% of CNS

myelin protein (Albertson et al., 2004). Reduced gene expression of MBP has also been shown in the splenium of rodents infused with cocaine (Narayana et al., 2009).

To date, there has been one published investigation of WM differences in CD patients at different stages of abstinence, see Xu et al., 2010 mentioned above (also see preliminary results published in abstract form in Nierenberg, et al., 2005). Given the evidence for WM deficits in current cocaine users, and evidence of early recovery of WM in abstinent cocaine users, the present study assessed WM over longer periods of abstinence. Using a cross-sectional design, we examined a cohort of abstinent cocaine patients who varied in the duration of their abstinence. Comparisons between a non-using control population and abstinent patients and within the abstinent patient group (split into three groups based on the duration of abstinence) allowed us to test for WM integrity differences related to cocaine use and to assess if these differences changed with abstinence duration. Although the present study used a between-subject cross-sectional design rather than a within-subject longitudinal design, the observation of WM differences as a function of abstinence duration would nonetheless identify neurobiological characteristics associated with successful abstinence: these may be of therapeutic importance (i.e., they may facilitate ongoing abstinence) and may provide useful biomarkers for other longitudinal investigations.

2. METHODS

2.1. Subjects

Forty-three abstinent cocaine patients were recruited from in-patient and out-patient addiction treatment centers located in New York State. The 43 controls were recruited through

the Volunteer Recruitment Pool at the Nathan S. Kline Institute for Psychiatric Research. All 43 patients received a primary Axis I diagnosis of Cocaine Dependence and from the onset of treatment were closely monitored for continued abstinence with random urine toxicology testing for multiple substances at least two times a week. Patients would also meet at least once a week with a personal counselor who was accredited through the state of New York as an alcoholism and substance abuse counselor. Duration of abstinence, as assessed through negative biweekly random urine screens for the durations noted, was confirmed by the counselors at the addiction treatment centers. Exclusion criteria were as follows: 1) Any DSM IV, Axis 1 diagnosis excluding dependence or a past diagnosis of depression caused by CD based on the Structured Clinical Interview for the DSM IV (SCID); 2) Head trauma resulting in loss of consciousness for longer than 30 minutes; 3) Presence of any past or current brain pathology; 4) A diagnosis of HIV: 5) The presence of any contradictions to an MRI; 6) Over the age of 55 years; 7) Under the age of 19 years; 8) Presence of WM hyperintensities (only one patient was excluded from the analysis because of clinically significant WM hyperintensities). Because of the high rates of comorbidity of alcohol and drug abuse among this population patients were not excluded if they had abused other drugs or alcohol prior to the onset of their cocaine abstinence (3 individuals had comorbid alcohol dependence and 7 individuals had comorbid heroin dependence). None of the patients were currently using any amount of alcohol or drugs. Years of drug use were recorded during the initial SCID interviews. Controls were excluded if they had any major Axis 1 disorder or alcohol/drug dependence diagnosis based upon a SCID for the DSM IV. The study received Institutional Review Board approval at the Nathan S. Kline Institute for Psychiatric Research. All participants were screened for any contradictions to an MRI and signed an informed consent document administered by HIPAA-certified staff.

The sample consisted of 43 patients (2 women) and 43 controls (7 women) (see table 1). The patients and controls did not differ in age (37.5 ± 8.0, 38.8 ± 10.8, respectively; p =.55) but did differ in years of education (12.3 ± 2.0, 14.6 ± 2.2, respectively; p =.001). Consequently, education was included as a covariate in the patient-control group comparisons. The patients were split by abstinence duration into three categories consisting of 13 short term (ST) abstainers (0.7-5.1 weeks), 14 mid-term (MT) abstainers (10-40.3 weeks) and 16 long-term (LT) abstainers (44-102 weeks). The three patient groups did not differ on age at time of testing (F (2, 40) =.83, p=.44) or years of use prior to the most recent period of abstinence (F (2, 40) =2.03, p =.15) but did differ on years of education (F (2, 40) =3.44, p=.04; pairwise contrasts revealed a significant difference between the MT and LT group) and therefore years of education was included as a covariate in the between-patient group analyses. Finally, the ST group was compared to an age and education-matched subset of the control group. The ST group consisted of 13 men and the controls consisted of 11 men and 2 women. Neither the mean age of short-term patients (36.7 ± 8.2) and controls (41.1 ± 11.2) nor the mean years of education of short-term patients (12.5 ± 1.6) and controls (12.7 ± .95) were significantly different ($p \leq .26$ for age, $p \leq .66$ for education).

2.2. Image Acquisition

MRI scans were performed on a 1.5T Siemens Vision system (Erlangen, Germany) at the Center for Advanced Brain Imaging (CABI) at the Nathan S. Kline Institute. Image sequences acquired included: magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE=11.6/4.9 ms, flip angle = 8%, 172 slices, 1.20mm slice thickness, 307 mm FOV, 256 x 256 matrix, pixel size = 1.20 x 1.20mm^2, no gap). For 27 of the controls the sequence had 190 slices, 1mm slice thickness, 300mm FOV, 256 x 256 matrix, pixel size 1 x 1mm^2, no gap. T2 (TR=5000 ms, TE =

22/90 ms, 26 slices, 5 mm slice thickness, no gap, 192 x 256 matrix, flip angle = 90%, 224 mm FOV, pixel size = .88 x .88 mm^2) and diffusion-tensor images (TR=6000 ms, TE=100 ms, 128 x 128 matrix, 320 mm FOV, b-value=1000 s/mm^2, 8 non-collinear gradient orientations, NEX=7, 19 slices, 5 mm slice thickness, no gap, pixel size = 2.5 x 2.5 mm^2. A double spin echo, pulsed-gradient echo planar acquisition was employed to minimize distortion due to eddy currents (Reese et al., 2003).

2.3. Image Processing

FA was calculated using a C++ program created by Babak Ardekani at the Center for Advanced Brain Imaging (CABI) at the Nathan S. Kline Institute and has been used in previous DTI studies (Hoptman et al., 2008). The MPRAGE images were skull striped using Freesurfer Version 1.3 (Segonne et al., 2004) and registered to the original MPRAGE volume and saved as a binary mask using the Automated Registration Toolbox (ART) (Ardekani et al., 1995; Klein et al., 2009). The binary mask was then applied to the original MPRAGE images. The resulting volumes were then spatially transformed into MNI space using ART. The skull stripped MPRAGE volume and b=0 volumes were also registered to the raw T2 images using a rigid body linear transformation. The b=0 image was then corrected for susceptibility-induced distortion by matching it to the raw T2 image using a 2-D nonlinear registration in ART. Finally, the transformations performed above were combined in one step and were applied to the native FA image to obtain a distortion- corrected and spatially normalized FA volume.

A WM mask was created using the normalized FA volumes from all of the participants employed in each analysis. The threshold for this image was obtained using Otsu's (1979) nonparametric method. The images also were masked so that only voxels with data present for

all participants were included in the analyses. An exploratory whole-brain voxelwise analysis of covariance (VANCOVA) was performed using the FA maps and WM masks for each analysis. The VANCOVA is in-house software that uses a general linear model to evaluate variance. We conducted three voxelwise analyses: 1) a comparison of 43 abstinent patients vs. 43 non-using controls with years of education as a covariate 2) a comparison of 13 short-term abstinent patients against a control cohort of 13 age and education-matched individuals 3) a comparison in which abstinent group (ST, MT, and LT) was the between-subject variable and years of education was included as a covariate. In the first two of these, we identified clusters of at least 200 contiguous voxels (200mm3) each significant at $p < .005$ with the additional constraint that at least one voxel was significant at $p < .001$. In the last analysis, we used a lower voxelwise threshold of at least 200 contiguous voxels (200 mm^3) each significant at $p < .05$ with the constraint of at least one voxel being significant at $p < .001$. This staged thresholding procedure was based on Baudewig (2003) and has been used in other publications by our group (e.g. Hoptman et al., 2008, 2009). A lower threshold was adopted for the three abstinent groups analysis because of the lower number of participants in this analysis and because any WM differences between patient groups was expected to be smaller than would be expected between patients and controls. For significant clusters from the abstinent group comparison, each participant's mean FA value for that cluster was calculated and then entered into SPSS version 12 (SPSS Inc, Chicago, Illinois). Cluster-level ANCOVA's were then performed which provided cluster-level, education-adjusted summary statistics and pairwise comparisons between groups. The WM areas were identified using the MRI Atlas of Human White Matter (Mori et al., 2005). Talairach coordinates were automatically derived from the MNI coordinates using the "*whereami*" tool available as part of AFNI (Cox, 1996).

3. RESULTS

3.1. Abstinent patients versus controls

The voxelwise comparison between all abstinent patients and all controls identified lower FA in the WM of CD individuals in seven regions and higher FA in the WM of CD individuals in two regions (see table 2). Abstinent patients exhibited lower FA in the left anterior callosal fibers, left genu of the CC, right superior longitudinal fasciculus, right callosal fibers and the superior corona radiata bilaterally. Abstinent patients expressed higher FA in the splenium of the CC and right superior longitudinal fasciculus (see Figure 2).

3.2. Short-term abstinent patients vs. controls

The previous analysis comparing all abstinent patients and all controls is likely to be most sensitive to differences in FA that hold for the duration of cocaine abstinence. In contrast, the comparison between ST abstinent patients and controls should be most sensitive to differences associated with recent use and should, therefore, be most similar to previous comparisons of current users and controls. The voxelwise *t*-test between short-term abstinent patients and an age and education matched control cohort showed lower FA in the CD group in seven WM regions (see table 3). Regions included the right anterior limb of the internal capsule, right genu of the CC, left anterior portion of the cingulum, superior corona radiata bilaterally, right cingulum superior to the isthmus of the CC and the right precentral gyrus WM. There were no regions with higher FA in the ST patients.

3.3. ANCOVA results for abstinent patients

Significant differences between the ST, MT, and LT abstinent groups were observed in a number of WM areas (see table 4). Groups differed bilaterally in the inferior longitudinal fasciculus, right anterior thalamic radiation, right ventral posterolateral nucleus (VPL) of the thalamus, left superior corona radiata, superior longitudinal fasciculus bilaterally, right cingulum and the WM of the right precentral gyrus. A number of different patterns of pairwise effects were observed across these ten areas (see Figure 3).

Higher FA with longer abstinence was observed in the right anterior thalamic radiation (higher FA from ST to MT and stable FA between MT and LT) and the right cingulum (higher FA from ST to MT and a trend [$p \leq .055$] towards higher FA from MT to LT). The WM of the right precentral gyrus showed stable FA between ST and MT and lower FA between MT and LT. Lower FA with longer abstinence was also observed. The left superior longitudinal fasciculus showed lower FA at two different locations from ST to MT and stable FA between MT and LT. The left inferior longitudinal fasciculus, the right inferior longitudinal fasciculus and the right superior longitudinal fasciculus all exhibited stable FA from ST to MT and lower FA from MT to LT.

Finally, two areas showed a nonmonotonic pattern. The left superior corona radiata showed higher FA from ST to MT and then lower FA from MT to LT. The right VPL nucleus of the thalamus showed an opposite pattern with lower FA from ST to MT and then higher FA from MT to LT.

4. DISCUSSION

Our results provide evidence of significant brain structural differences between abstinent patients and non-using controls. These differences were present in a group of recently-abstinent

patients (up to five weeks since last cocaine use) and also in a larger group of 43 patients who were abstinent from 0.7 weeks to almost two years. While the locations of the differences were not identical in the two contrasts, the results provide evidence of WM differences that persist for former users through all three periods of abstinence assessed. That said, a more specific test of WM changes with abstinence did show that there are differences between users who vary in abstinence duration and that these are regionally distinct from the ones showing persistent impairment. Thus, the results suggest that abstinence of up to two years duration is characterized by one set of structural brain differences relative to the recently abstinent and a second set of differences relative to the healthy controls. While the former unique features may give insight into brain changes that arise from or perhaps enable long-term abstinence, the latter may reflect deficits that either arose from cocaine use and persisted or preceded cocaine use and may even have predisposed towards such use.

The comparison between ST patients and age and education - matched controls showed lower FA in seven WM tracts. Because of the short period of abstinence in the ST group (0.7-5.1 weeks), one might expect their WM structures to be the most similar to current users. Indeed, previous studies have identified lower FA in current users, some of which (the internal capsule and the genu of the CC) are consistent with the present results (Lim et al., 2008; Moeller et al., 2005). The administration of cocaine is known to have adverse vascular effects. In an MRI study, Bartzokis et al., (1999) found that 28% of CD patients compared to 7% of non-using controls displayed severe WM hyperintensities that are thought to be the result of cerebrovascular toxicity. Individuals who abuse cocaine can suffer from vascular toxicity leading to stroke that is not accounted for by other risk factors (Fessler et al., 1997; Nolte et al., 1996; Levine and Welch, 1996). In a study of depressed geriatric patients, Hoptman et al., (2009) showed that increased

blood pressure, a cerebrovascular risk factor, was associated with lower FA in frontostriatal regions. Thus, the net effect of such cerebrovascular toxicity associated with cocaine use could be responsible for the lower FA values that were observed.

The contrast between all patients and all controls could reflect WM differences that persist despite varying lengths of abstinence. A possible reason for the overall lower FA values in the patient group could be cerebrovascular toxicity resulting from cocaine use as described above. Former CD users have exhibited deficits in attention and motor skills even after one year of abstinence (Toomey et al., 2003). Indeed, we saw that our patient group had lower FA bilaterally in the superior corona radiata through which corticospinal and corticobulbar motor tracts as well as sensory tracts descend (Blumenfield, 2002). It has been shown that damage to the corona radiata can lead to sensory deficits (Shinoura et al., 2009). Sensorimotor deficits have been observed in CD users and include an increase in choreoathetoid movements (Bartzokis et al., 1999), dystonia and tremors (Cardoso and Jankovic, 1993). Additionally, an fMRI study found that current CD users exhibited less efficient activation of the dorsal striatum during a motor task than a control cohort (Hanlon et al., 2009). The dorsal striatum is believed to be involved in sensorimotor integration (Balleine et al., 2007). It seems plausible that these sensorimotor deficits persist into abstinence. Additionally, in the patient group, multiple callosal regions displayed lower FA. Existing literature on current CD individuals shows lower FA in the CC (Moeller et al., 2005; Ma et al., 2009; Lim et al., 2008) and higher impulsivity scores have been correlated with lower FA in the anterior CC (Moeller et al., 2005; Lim et al., 2008). Therefore, the lower FA values of the CC in our patient group could explain why deficits in executive functioning are still evident even after six months of abstinence (Sclafani et al., 2002). It may be that the CC is disrupted before the onset of CD and thus leads to CD, or that prolonged

cocaine use causes either irreparable damage to the CC or damage that takes more than two years to fully repair. Whichever situation pertains, we see that there are clear differences that cannot be attributed to current cocaine use between individuals who were addicted to cocaine and individuals who have no history of CD.

The analysis of the abstinent patient groups revealed FA differences, almost all of which were regionally distinct from the FA differences stated above. The differences were varied, including both higher and lower FA as a function of the length of abstinence. As stated above, current cocaine use is associated with lowered FA that is believed to account for decreased cognitive functioning. Therefore, higher FA values with longer abstinence would be consistent with a restoration of WM integrity. Higher FA was associated with longer duration of abstinence in the right superior longitudinal fasciculus, right body of the CC, right posterior limb of the internal capsule and in the left cerebellum (Xu et al., 2010). Increased FA has been shown in a longitudinal study assessing patients suffering from severe traumatic brain injury; notably, the increase over time followed an initial decrease in FA that was observed immediately after the injury suggesting that the pattern of FA changes accompanying brain recovery from insult may be complex (Sidaros et al., 2008).

Moreover, lower values of FA with longer abstinence may also be consistent with a normalization of white matter. Since extended cocaine use is associated with various changes in neural functioning, it may be that certain WM tracts of current CD individuals are utilized more, either to compensate for the loss of function in other affected areas or because they are associated strongly with specific addictive behavior. For example, higher FA has been observed in current CD users when compared to non-using controls in the WM of the anterior cingulate (Romero et al., 2010), an area shown to be hyperactive in current CD individuals when viewing

cocaine stimuli (Garavan et al., 2000). A possible reason for lower values of FA with continued abstinence could be that once an individual is recovering from his or her addiction, these tracts are no longer over-utilized resulting in lower FA. However, this explanation would predict higher FA in these areas in the ST group relative to the controls which was not observed, albeit possibly due to the smaller sample sizes of this contrast or WM changes that may have already occurred within the five weeks of abstinence in the ST group.

Alternatively, lower FA with ongoing abstinence may signify a reparative process in which damaged areas exhibit an increase in astrocytes during early abstinence that would result in higher FA values. Glial fibrillary acidic protein (GFAP) is a protein that is upregulated by astrocytes after chemical or physical insult (Aronica et al., 2000) and changes in GFAP levels can be used to assess neuronal insult or injury (Eng et al., 2000). A study assessing the levels of GFAP three weeks after mice were given cocaine intravenously once a day for one week found significantly increased GFAP levels in the NAc shell, NAc core and prefrontal cortex (Bowers and Kalivas, 2003). In addition, vimentin, a marker for immature or reactive astrocytes showed an increase in the PFC after a three week withdrawal period (Bowers and Kalivas, 2003). A study measuring regional cerebral blood flow (rCBF) in abstinent patients (mean duration of abstinence = 49.02 ± 64.07 weeks) found increased rCBF in the globus pallidus and frontal white matter in abstinent users (Ernst et al., 2000) which these authors postulated could be due to the high energy requirements of astrocytes. Therefore, higher FA in WM tracts between patients could be explained by the increased preponderance of astrocytes that are evident after neuronal injury caused by repeated cocaine administration. The timing of this increase in FA could be a result of the specific tract that is affected, the amount of neuronal injury that was incurred and how long it takes to recover. Higher FA earlier in abstinence that then reduces with continued

abstinence may thus reflect an early proliferation of astrocytes in the WM tracts that are responding to the neuronal injury caused by cocaine administration.

The right cingulum showed higher FA in those with the longest abstinence. The cingulum is one of the primary WM tracts involved with limbic system functioning. This tract has been shown to connect the anterior thalamus with the hippocampus (Burgel et al., 2006) and carries afferent connections from the cingulate gyrus to the entorhinal cortex (Mori et al., 2005). fMRI studies in current CD individuals using response inhibition paradigms consistently show hypoactivation in the cingulate gyrus when compared to controls (Li et al., 2007; Kaufman et al., 2003) and co-activation of both the anterior cingulate and the hippocampus has been shown for tasks that require learning from one's errors (Hester et al., 2008). Chronic cocaine use is frequently associated with deficits in cognitive functioning including decision making, judgment, attention, planning and mental flexibility (e.g. Bolla et al., 1998; Kubler et al., 2005), and abstinent cocaine users still show deficits in executive functioning six months after abstinence (Sclafani et al., 2002). It is tempting to speculate that lower FA in the cingulum may underlie some of these cognitive and executive deficits including compromised learning of the negative consequences of one's behavior. Given that the ST group exhibited lower FA in two areas of the cingulum when compared to non-using controls, it is notable that higher FA in the cingulum was observed for the LT group relative to the ST group indicating that heightened integrity in this pathway may be related to longer abstinence.

Another tract exhibiting higher FA over time between the abstinent groups was the right anterior thalamic radiation. The anterior thalamic radiation connects the dorsomedial and anterior thalamic nuclei with the prefrontal cortex (Sprooten et al., 2009) and lower FA values within it has previously been linked to the abnormal prefrontal function of those with

schizophrenia and bipolar disorder (McIntosh et al., 2008; Sprotten et al., 2009). Increased prefrontal functioning with abstinence may be related to the higher FA of the anterior thalamic radiation and may also be related to the observed higher FA in the vicinity of the right precentral gyrus.

It is notable that all areas showing lower FA with increasing abstinence fell on either the inferior or superior longitudinal fasciculus. The superior longitudinal fasciculus II showed higher FA bilaterally in the ST group relative to the MT or LT groups. In a longitudinal study, Xu et al., (2010) found that higher FA in the superior longitudinal fasciculus at the onset of treatment predicted a longer duration of abstinence. The superior longitudinal fasciculus II has been characterized as a WM tract that links the prefrontal and parietal cortices (Makris et al., 2005). It may play an important role in coordinating prefrontal-parietal processes involved in working memory, visuospatial perception and attention (Makris et al., 2005). A meta-analysis of studies examining subcortical lesions that resulted in visuospatial neglect found the lesions to be located at or near the superior longitudinal fasciculus (Bartolomeo et al., 2007). Utilizing fMRI and a verbal working memory task, recently abstinent users showed hyperactivation in the prefrontal and parietal cortices and prefrontal hyperactivation on a visuospatial attention task when compared to control subjects (Tomasi et al., 2007). The authors postulated that this hyperactivation could be due to increased attention and control processes to compensate for a decrease in executive functioning that is associated with cocaine use. Though speculative, the lower FA in the MT and LT groups might reflect diminishing reliance on a prefrontal-parietal compensatory mechanism through recovery of executive functions.

The inferior longitudinal fasciculus is an association tract that connects the parietal and temporal cortices and the occipital and temporal cortices with very strong connections to

temporal polar cortex (Hua et al., 2009). The temporal polar cortex is located at the junction of higher-order visual, auditory, and olfactory/insular association cortices (Ding et al., 2009) and is hypothesized to be responsible for binding processed perceptual inputs to visceral emotional responses (Olson et al., 2007). The higher FA observed bilaterally in this tract in the ST group relative to the MT and LT groups may reflect increased utilization of this tract during addiction, perhaps related to a role in drug craving (Garavan et al., 2000; Bonson et al., 2002). Conceivably, with continued abstinence this tract exhibits lower FA mirroring a reduction in strong cue-induced visceral emotional responses that are associated with CD.

There are specific limitations in the present study that need to be acknowledged. First, when between-groups analyses were conducted on the three sub-groupings of abstinent patients, the sample sizes were relatively small with the attendant reductions in power that this imposes. Also, images in the present study were collected using a 1.5T scanner with 5 mm slice thickness and just 8 gradient orientations. It is now possible to collect thinner slices and more orientations at higher field strength. Nonetheless, because of the slice thickness and the fact that seven excitations were collected for each direction, excellent signal-to-noise ratios were achieved here. We also did not collect any health-related information on study participants and it is known that factors such as cardiovascular disease or diabetes can influence the development of white matter and therefore cannot be ruled out as factors in the observed differences in white matter between abstinent groups. Another potential issue was raised by a reviewer of this manuscript who pointed out that although not statistically significant, there is a numerical difference between the short- and long-term abstinence groups in terms of overall years of cocaine use. Long-term patients, on average, had shorter durations of use than short-term patients and it is possible that the relative success these long-term patients have had in resisting relapse might arise because of

shorter original exposure periods to the drug of abuse. In turn, this may have been reflected in differences in WM integrity. However, the long-term group in this study used cocaine for an average of 7 or more years, and to our minds, it seems highly unlikely that such a protracted period of use could result in significantly less impairment in this group. Lastly, it also needs to be pointed out that this study was conducted predominantly in male participants and that in view of this; appropriate care should be taken in generalizing these results to abstinent female CD patients.

Because of this study's cross-sectional design, it is impossible to determine if the observed FA differences between patients at different stages of abstinence were due to dynamic intra-individual changes that perhaps reflect recovery of function, or if they reflect pre-existing differences between patients. Whichever situation pertains, these cross-sectional results suggest that although WM deficits exist in the abstinent users as a whole, there may also be additional differences in brain structure in those who have attained a relatively long period of abstinence compared to those who are more recently abstinent. The regions showing these differences include white matter tracts thought to be involved in motor, cognitive and emotional processes but without precise assessments of psychological changes occurring with abstinence, the interpretations offered for the functional changes that accompany WM differences between the groups must remain speculative. The caveats notwithstanding, the patterns of FA differences across abstinence durations may reflect dynamic patterns of changing reliance on different psychological processes as drug users escape their drug dependence.

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Figure Legends

Figure 2.

Brain areas that show differences between all patients and all controls. Blue signifies lower FA and red signifies higher FA in the patient group. Number refers to region (see Table 2). Images are in radiological orientation with left hemisphere shown on the right side of the image.

Figure 3.

Brain areas that show differences between abstinence groups. Letter A refers to higher FA with abstinence. Letter B refers to lower FA with abstinence. Letter C refers to higher and then lower FA with abstinence. Letter D refers to lower and then higher FA with abstinence. Number refers to region (see Table 4). Scatterplots show education-adjusted FA values (y-axis) plotted against abstinence duration (x-axis). FA values are scaled from 0-1000. Images are in radiological orientation.

Figure 2.

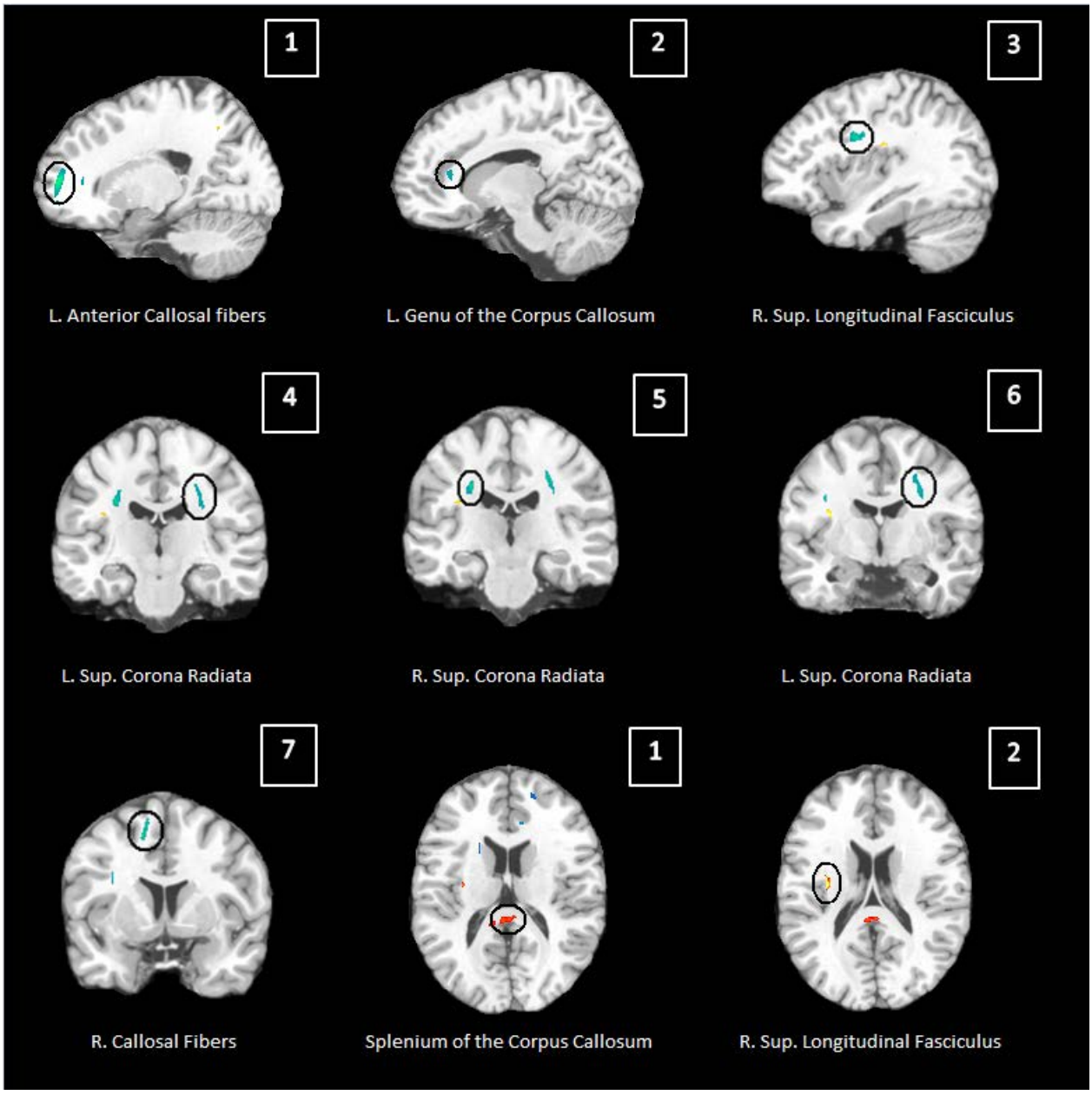
1
L. Anterior Callosal fibers
2
L. Genu of the Corpus Callosum
3
R. Sup. Longitudinal Fasciculus
4
L. Sup. Corona Radiata
5
R. Sup. Corona Radiata
6
L. Sup. Corona Radiata
7
R. Callosal Fibers
1
Splenium of the Corpus Callosum
2
R. Sup. Longitudinal Fasciculus

Figure 3.

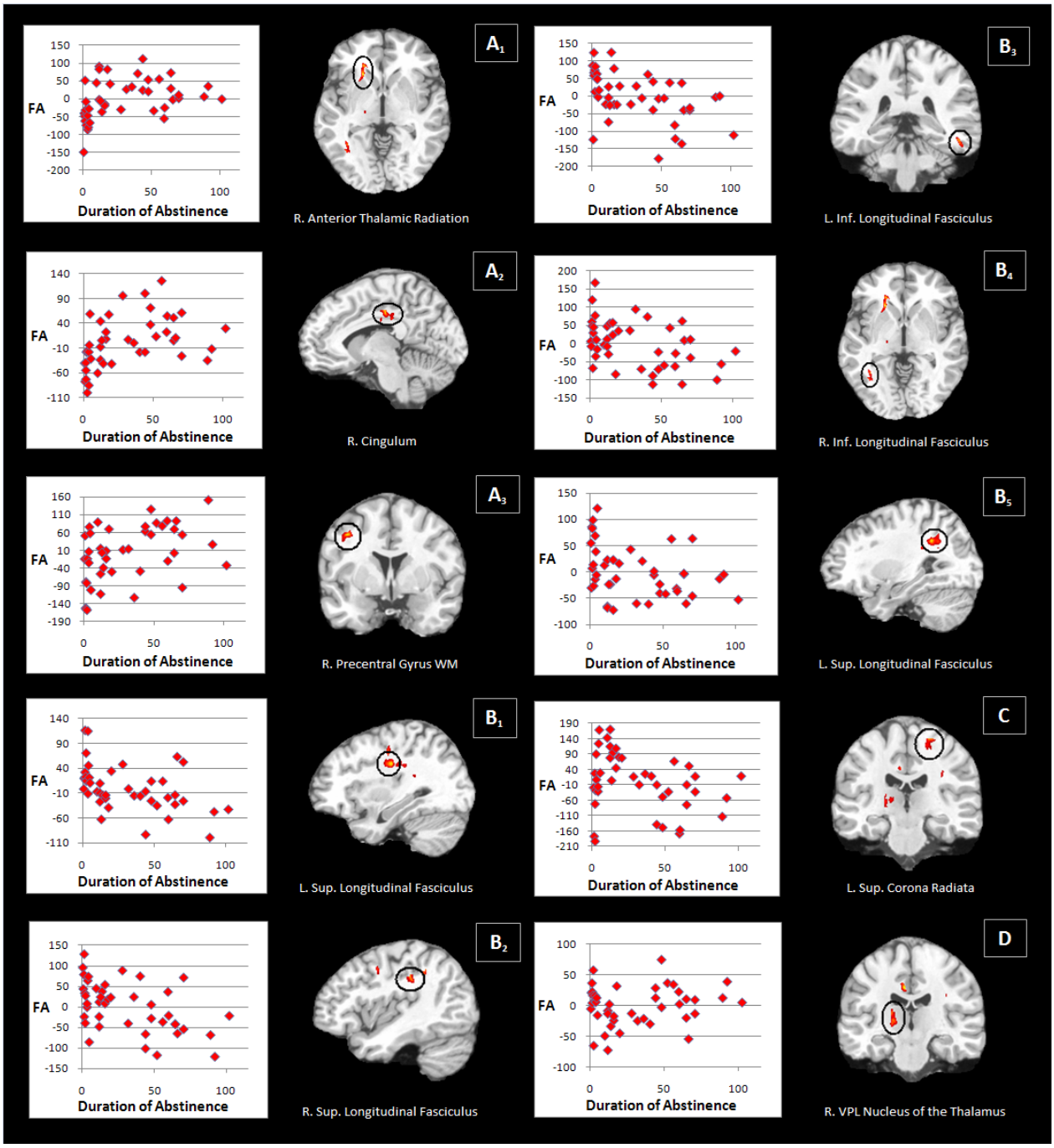
A1
R. Anterior Thalamic Radiation
B3
L. Inf. Longitudinal Fasciculus
A2
R. Cingulum
B4
R. Inf. Longitudinal Fasciculus
A3
R. Precentral Gyrus WM
B5
L. Sup. Longitudinal Fasciculus
B1
L. Sup. Longitudinal Fasciculus
C
L. Sup. Corona Radiata
B2
R. Sup. Longitudinal Fasciculus
D
R. VPL Nucleus of the Thalamus
FA
Duration of Abstinence

Table 1.

Participant Demographics

All patients	Group			*F*	*p*
	Short-term (N=13)	Mid-term (N=14)	Long-term (N=16)		
Length of abstinence (weeks)	0.7-5.1	10-40.3	44-102	-	-
Age (years)	36.7 (8.2)	39.8 (9.4)	36.2 (6.5)	0.83	0.42
Years of education	12.5 (1.6)	13.2 (1.4)	11.4 (2.3)	3.44	0.01[a]
Years of use	11.9 (6.0)	8.8 (5.5)	7.14 (7.1)	2.03	0.15
Comorbid (Alcohol/Heroin)	0/1	2/4	1/2	-	-
Sex (Male/Female)	13/0	14/0	14/2	-	0.17[b]
All patients vs. All controls	Group		*p*		
	CD (N=43)	Controls (N=43)			
Age (years)	37.4 (8.0)	38.8 (10.8)	0.55		
Years of education	12.3 (2.0)	14.6 (2.2)	0.01		
Sex (Male/Female)	41/2	36/7	0.08[b]		
Short-term patients vs. controls	Group		*p*		
	ST (N=13)	Controls (N=13)			
Age (years)	36.7 (8.2)	41.1 (11.2)	0.26		
Years of education	12.5 (1.6)	12.7 (.95)	0.66		
Sex (Male/Female)	13/0	11/2	0.14[b]		

Note: [a] Significant between MT and LT groups
[b] Chi-Square significance level

Table 2.

Talairach coordinates of FA differences between all patients and all controls

Anatomical region	Talairach coordinate			Cluster size	*t*- value
Decreased FA in patients	X	Y	Z		
1. L. anterior callosal fibers	-19	50	5	440	-3.54
2. L. genu of the corpus callosum	-12	31	10	251	-3.18
3. R. superior longitudinal fasciculus	34	-3	26	205	-3.30
4. L. superior corona radiata	-26	-20	32	282	-3.14
5. R. superior corona radiata	26	-22	30	501	-3.45
6. L. superior corona radiata	-25	-9	34	310	-3.24
7. R. callosal fibers	11	1	49	205	-3.33
Increased FA in patients					
1. Splenium of the corpus callosum	2	-36	15	286	3.10
2. R. superior longitudinal fasciculus	31	-14	19	217	3.42

Table 3.

Talairach coordinates of FA differences between short-term abstinent patients and matched controls

Anatomical region	Talairach coordinate			Cluster size	*t*-value
	X	Y	Z		
R. anterior limb of the internal capsule	16	6	10	393	-3.42
R. genu of the corpus callosum	8	25	13	301	-3.37
L. anterior portion of the cingulum	-8	26	15	228	-3.56
L. superior corona radiata	-26	-20	30	817	-3.89
R. superior corona radiata	26	-23	29	567	-3.91
R. cingulum superior to isthmus of CC[a]	14	5	32	529	-3.95
R. precentral gyrus WM	39	-2	35	303	-4.14

Note: [a] CC stands for corpus callosum

a negative *t*-value denotes a decrease in patients

Table 4.

Talairach coordinates of FA differences between abstinent patient groups

Anatomical region	Talairach coordinate			Cluster size	*F*	Pairwise *p*- values[a]		
	X	Y	Z			ST vs. MT	MT vs. LT	ST vs. LT
A. Increase in FA with abstinence								
1. R. anterior thalamic radiation	20	23	0	754	5.01	0.0001	-	0.0001
2. R. cingulum	7	-20	32	433	5.11	0.028	-	0.0001
3. R. precentral gyrus WM	36	-3	38	215	4.88	-	0.004	0.0003
B. Decrease in FA with abstinence								
1. L. superior longitudinal fasciculus	-32	-15	33	595	4.64	0.005	-	0.0001
2. R. superior longitudinal fasciculus	39	-28	30	321	5.18	-	0.0001	0.0001
3. L. inferior longitudinal fasciculus	-47	-36	-12	214	4.61	-	0.011	.0001
4. R. inferior longitudinal fasciculus	34	-58	0	349	4.34	-	0.003	0.0001
5. L. superior longitudinal fasciculus	-28	-47	27	500	4.49	0.002	-	0.003
C. Increase and then decrease in FA with abstinence								
L. superior corona radiata	-19	-23	54	266	4.80	0.008	0.0001	-
D. Decrease and then increase in FA with abstinence								
R. VPL[b] nucleus of the thalamus	17	-20	5	561	4.54	0.003	0.0001	-

Notes: [a]p-values for groups that showed significant differences in FA
[b]ventral posterolateral

CHAPTER 2

Intact inhibitory control processes in abstinent drug abusers (I): A functional neuroimaging study in former cocaine addicts.

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ABSTRACT

Neuroimaging studies in current cocaine dependent (CD) individuals consistently reveal cortical hypoactivity across regions of the response inhibition circuit (RIC). Dysregulation of this critical executive network is hypothesized to account for the lack of inhibitory control that is a hallmark of the addictive phenotype, and chronic abuse is believed to compound the issue. A crucial question is whether deficits in this circuit persist after drug cessation, and whether recovery of this system will be seen after extended periods of abstinence, a question with implications for treatment course and outcome. Utilizing functional magnetic resonance imaging (fMRI), we examined activation in nodes of the RIC in abstinent CD individuals (n=27) and non-using controls (n=45) while they performed a motor response inhibition task. In contrast to current users, these abstinent individuals, despite extended histories of chronic cocaine-abuse (average duration of use = 8.2 years), performed the task just as efficiently as non-users. In line with these behavioral findings, no evidence for between-group differences in activation of the RIC was found and instead, robust activations were apparent in both groups within the well-characterized nodes of the RIC. Similarly, our complementary Electroencephalography (EEG) investigation also showed an absence of behavioral and electrophysiological deficits in abstinent drug abusers. These results are consistent with an amelioration of neurobiological deficits in inhibitory circuitry following drug cessation, and could help explain how long-term abstinence is maintained. Finally, regression analyses revealed a significant association between level of activation in the right insula with inhibition success and increased abstinence duration in the CD cohort suggesting that this region may be integral to successful recovery from cocaine addiction.

1. INTRODUCTION

Current theories of addiction posit that deficits in inhibitory control play a major role in the development of addiction and the propensity to relapse (Everitt et al., 2008). The inability to inhibit an undesired behavior is one of the more significant facets of drug dependence (Lyvers, 2000) and diagnostic evaluations of drug addiction typically contain questions pertaining to the ability to inhibit behaviors with known negative consequences (DSM-IV). Although inhibitory control is considered a multi-faceted construct (Evenden, 1999), cocaine addicts display deficits on various measures of inhibitory control including impaired response inhibition (Fillmore and Rush, 2002; Verdejo-Garcia et al., 2007), impulsive choice (Coffey et al., 2003) and poor decision making (Monterosso et al., 2001). Most tasks measuring inhibitory control fall into paradigms that are broadly measuring either impulsive choice or impulsive responding. Measures of both constructs suggest that inhibitory control is involved in the acquisition and escalation/dysregulation phases of drug use (Perry and Carroll, 2008).

Neuroimaging studies conducted on current cocaine dependent (CD) users have shown that reduced inhibitory control is associated with neurobiological deficits in both prefrontal inhibitory control and insular regions. Kaufman et al. (2003), utilizing a Go/No-Go task, found that on successful inhibitions of a prepotent response, current cocaine users displayed hypoactivity in the right anterior cingulate and right insula, suggesting that these regions may be responsible for the weakened inhibitory control associated with cocaine dependence. These results were replicated in a study utilizing the same task with additional cortical hypoactivations observed in the right inferior parietal lobule and right middle frontal gyrus of current CD individuals (Garavan et al., 2008). Hester and Garavan (2004) examined current CD users on a

Go/No-Go task with increased working memory demands and found that current users had poorer inhibitory performance compared to non-using controls that were associated with reduced activation in the anterior cingulate cortex and right prefrontal cortex. Supporting evidence for inhibitory control deficits comes from other paradigms and other modalities. For example, using a "Counting" Stroop task, Barros-Loscertales et al. (2011) showed decreased activation of the right inferior frontal gyrus in current CD users compared to non-using controls when responding to incongruent stimuli. Utilizing diffusion tensor imaging in current CD individuals, Moeller et al. (2005) found that white matter integrity in the anterior corpus callosum was reduced in CD individuals and negatively correlated with behavioral measures of inhibitory control. Finally, Ersche et al. (2011b) found that gray matter volumes in the insulae of current CD individuals were reduced compared to non-using controls and that reduced GM in the insulae of current users was correlated with greater impairments in behavioral measures of inattention as measured by the Stop Signal and Rapid Visual Information Processing Task. Although there is some uncertainty in specifying the exact cognitive process that underlies the cocaine users inhibitory control deficits (Li et al., 2008; Li et al., 2006b), collectively, these results provide strong evidence that reduced inhibitory control in current users can be characterized by neurobiological deficits in prefrontal regions.

There is a clear imperative to determine whether deficits of inhibitory control ameliorate after the discontinuation of cocaine use. Improvement in inhibitory control accompanying continued abstinence could suggest that successful recovery from cocaine addiction is facilitated by increased inhibitory control. An investigation of two groups of recently abstinent CD patients (1 vs. 4 weeks) showed no differences on the "Impulse" subset of questions from the Difficulties in Emotion Regulation Scale. However, both abstinence groups showed poorer inhibitory

control relative to non-using controls (Fox et al., 2007). Another study utilizing the Behavioral Assessment of the Dysexecutive Syndrome scale found that abstinent CD patients (mean abstinence of 25 weeks) exhibited inhibitory control deficits when compared to non-using controls (Verdejo-Garcia et al., 2007). These results suggest that deficits in inhibitory control may persist after the cessation of cocaine use. However, self-report measures of impulse control have limitations (Perry and Carroll, 2008) and consequently, neurobiological investigations of inhibitory control might be valuable in providing an objective measure of inhibitory deficits and their potential amelioration in abstinent CD individuals.

To date, only two neuroimaging studies have examined motor response inhibition in abstinent CD individuals. Li et al. (2008) looked at response inhibition in abstinent CD males (n=15) utilizing a stop-signal task and examined activity patterns in the rostral anterior cingulate cortex and the dorsal medial frontal cortex. The authors found decreased activity in the rostral anterior cingulate in the CD group and theorized that this effect was responsible for inhibitory control deficits in CD individuals. The specific duration of abstinence was not reported in this study (although participants were at least 2 weeks post cessation), so one outstanding question is the length of abstinence that is required for the amelioration of cortical hypoactivity. Connolly et al. (2012) utilized a Go/No-Go motor response inhibition task to examine cortical activations in abstinent CD individuals who had attained either shorter (n=9; average duration = 2.4 weeks) or longer (n=9; average duration = 69 weeks) periods of abstinence. This investigation found that both the short- and long-term abstinence groups displayed greater cortical activity than drug naïve controls when performing a successful motor response inhibition in multiple nodes of the canonical response inhibition circuit (RIC). The RIC has been identified as including the right middle and inferior frontal gyri, right inferior parietal lobule, bilateral insula and the midline

cingulate and pre-SMA (Chen et al., 2009; Chevrier et al., 2007; Dodds et al., 2010; Fassbender et al., 2009; Fassbender et al., 2004; Garavan et al., 2006; Garavan et al., 2008; Garavan et al., 1999; Hampshire et al., 2010; Hester and Garavan, 2004; Kaufman et al., 2003; Konishi et al., 1999; Leung and Cai, 2007; Li et al., 2006a; Xue et al., 2008). These findings were paralleled by the absence of behavioral differences between the abstinent groups and the non-using controls, a finding suggestive of recovery of function. Thus, the finding of normalized inhibitory performance in tandem with increased cortical activity in inhibitory control areas in this study would appear to point to a period of major recovery within the RIC after drug cessation.

Because of the contradictory results from investigations of motor response inhibition in abstinent CD individuals, it remains unresolved whether there are enduring deficits in inhibitory control after extended cessation of drug use. These contradictory results may be due to the different motor response inhibition tasks that were used (Swick et al., 2011) or the relatively small sample sizes in both studies. Here, using a cross-sectional design, we examined a larger cohort of abstinent CD individuals with large variation in their durations of abstinence. As part of a multi-methodological approach to this issue, we also performed a parallel event-related potential (ERP) investigation in a second cohort of abstinent drug abusers and non-using controls (Morie et al., 2013). Comparisons between a non-using control population and abstinent patients, as well as within the abstinent patient group allowed us to test for cortical activation differences related to previous cocaine use and to assess if these differences changed with abstinence duration.

2. METHODS

2.1. Subjects

Twenty-seven abstinent cocaine patients were recruited from in-patient addiction treatment centers located in New York State and 45 controls were recruited through the Volunteer Recruitment Pool at the Nathan S. Kline Institute for Psychiatric Research. It should be noted that the participants in our complementary EEG study constituted an almost completely separate cohort with only two patients and six controls participating in both EEG and fMRI studies. All 27 patients received a primary Axis I diagnosis of Cocaine Dependence and underwent random urine toxicology testing for cocaine and other abusable substances (alcohol, opiates, amphetamines, cannabinoids, phencyclidine, barbiturates, and benzodiazepines) at least twice a week to monitor continued abstinence. Abstinence was also confirmed by a New York State accredited substance abuse counselor with whom the patient met on a weekly basis. Abstinent patients were clean for an average of 32.3 weeks (Minimum = 0.87 weeks, Maximum = 100 weeks; SD = 23.9). It should be noted that the minimum duration of abstinence was only found in one participant and that the 14 patients with the shortest duration of abstinence had an average of 13.4 weeks of cocaine cessation. Exclusion criteria for patients and controls were as follows: 1) Any DSM-IV, Axis 1 diagnosis (excluding dependence or a past diagnosis of depression caused by CD for patients) based on the Structured Clinical Interview for the DSM-IV (SCID); 2) Head trauma resulting in loss of consciousness for longer than 30 minutes; 3) Presence of any past or current brain pathology; 4) A diagnosis of HIV; 5) The presence of any contraindications to an MRI; 6) Age above 55 years and below 19 years; 7) Presence of WM hyperintensities (only one patient was excluded from the analysis because of clinically significant WM hyperintensities). Because of the high rates of comorbidity of alcohol and drug abuse among the patient population, patients were not excluded if they had abused other drugs or

alcohol prior to the onset of their cocaine abstinence (5 individuals had comorbid alcohol dependence and 8 individuals had comorbid heroin dependence). None of the patients were currently using any amount of alcohol or drugs and through self-report all but two individuals reported having a previous relapse. Years of drug use were recorded during the initial SCID interviews. Controls were excluded if they had any major Axis 1 disorder and/or current or past alcohol/drug dependence diagnosis based on a SCID for the DSM-IV. The study received Institutional Review Board approval at the Nathan S. Kline Institute for Psychiatric Research. All participants were screened for contraindications for MRI and signed an informed consent document administered by HIPAA-certified staff.

The comparison samples of patients and controls consisted of 27 patients (3 women) and 45 controls (10 women) (see Table 5). The patients and controls did not differ in age (37.8 ± 7.8, 38.1 ± 10.6, $t(70) = -0.10$; $p = .92$) but patients had fewer years of education (12.9 ± 1.4, 13.7 ± 1.7, $t(70) = -2.01$; $p = .05$).

2.2. Stimuli and Tasks

All participants completed a Go/No-Go motor response inhibition task, while being scanned, that consisted of a series of pictures depicting neutral scenes from the International Affective Picture System (IAPS) (Lang PJ, 1997). This same task was also employed in our EEG investigation. The IAPS is a large set of standardized photographs that are rated with regard to their tendency to evoke an emotional response in the viewer. From this set, 158 neutral pictures were chosen with a mean emotional valence and arousal of 5.2 and 3.5 respectively, on a scale from 1 to 9. All stimuli subtended 8.6˚ horizontally x 6.5˚ vertically of visual angle. Stimuli were delivered to a monitor in the magnet for a duration of 800 ms and were separated by a

blank screen presented for 200 ms. Participants were instructed to quickly press a button at the onset of each stimulus (Go trials) and to withhold a response in instances when a stimulus was repeated (No-Go trials). Stimuli were presented pseudorandomly in three blocks with each block containing 180 trials. Within each block, 22 trials (12%) were No-Go trials. The high proportion of Go trials renders the quick button press to the occurrence of a stimulus to be the prepotent response. The withholding of a button press to stimulus repetition therefore required the recruitment of inhibitory neural mechanisms.

2.3. Image Acquisition

MRI scans were performed in a 1.5T Siemens Vision system (Erlangen, Germany) at the Center for Advanced Brain Imaging (CABI) at the Nathan S. Kline Institute. Functional scans were acquired in three runs of 103 volumes utilizing a T2-weighted echo-planar sequence (TR/TE= 2000/50 ms, flip angle = 85°, 5 mm slice thickness, 224 mm FOV, 64 x 64 matrix, pixel size = 3.5 x 3.5 mm^2, no gap). Twenty-two axial slices were obtained parallel to the AC-PC plane. Structural images were acquired utilizing a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE=11.6/4.9 ms, flip angle = 8°, 172 slices, 1.2mm slice thickness, 307 mm FOV, 256 x 256 matrix, pixel size = 1.2 x 1.2mm^2, no gap).

2.4. Image Processing

The functional and anatomical data were pre-processed and analyzed using Brain Voyager (QX 2.3, Maastricht, The Netherlands) running in Windows XP environment. Functional scans were preprocessed by performing a slice scan time correction, 3D motion correction and high pass temporal filtering. Functional scans were excluded if they displayed > 2

mm of motion in a given plane. For the patients, one participant was excluded from the analyses because of too much motion while one participant had two runs excluded and two participants each had one run excluded. For the controls, one participant was excluded because of too much motion. One participant had two runs excluded while four participants each had one run excluded. The T1-weighted anatomical slices were normalized into Talairach space and coregistered with the functional timecourses. The resulting volumetric time courses were then spatially smoothed using a 6 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.5. Analysis Strategy

In this event-related design, successful inhibitions to No-Go trials (STOPS) and unsuccessful inhibitions (ERRORS) served as regressors of interest. These regressors were convolved with a two-gamma-variate hemodynamic response function and subjected to a first-level analysis using a fixed effects general linear model (GLM). For our analyses, we chose to only examine STOPS activation as the task did not result in sufficient numbers of ERRORS to provide for a meaningful comparison between STOPS and ERRORS.

Because we were most interested in examining cortical activations associated with inhibitory control, we first identified regions-of-interest (ROI) previously implicated as part of the RIC network within the task-defined map. This procedure consisted of identifying centers of mass based upon peak voxel activations and then confirming that the centers of mass fell within the canonical RIC. A review of the imaging literature on response inhibition processes utilizing similar motor response inhibition tasks identified the right middle and inferior frontal gyri, right inferior parietal lobule, bilateral insula and the midline cingulate and pre-SMA as canonical nodes of the RIC (Chen et al., 2009; Chevrier et al., 2007; Dodds et al., 2010; Fassbender et al.,

2009; Fassbender et al., 2004; Garavan et al., 2006; Garavan et al., 2008; Garavan et al., 1999; Hampshire et al., 2010; Hester and Garavan, 2004; Kaufman et al., 2003; Konishi et al., 1999; Leung and Cai, 2007; Li et al., 2006a; Xue et al., 2008). The peak activations within each of these regions were identified and then served as the center of a 13 mm^3 (2,197 voxels) cubic ROI (see Figure 4).

For each ROI, *t*-tests were performed between all patients and all controls utilizing the average ROI activation for each participant. This analysis was performed within BrainVoyager and utilized a contrast of STOPS > 0 (0 = Baseline activation levels). Because this analysis utilized the average ROI activation for each individual as the independent variable and was not a voxelwise comparison, there was no correction for multiple comparisons. Additionally, we did not perform an ROI-level correction as this would have resulted in a more stringent alpha-level and made a null-result more likely.

Next, we conducted a whole-brain voxelwise comparison between patients and controls to investigate whether there were any activation differences between the two groups in any regions of the brain. A voxelwise *t*-test was performed between groups (False Discovery Rate (FDR); q = 0.05) utilizing a *t*-test contrast of STOPS>0 and a cluster threshold of at least four contiguous voxels. In addition, a more liberal uncorrected voxelwise *t*-test ($p \leq 0.001$; 4 voxel threshold) was also inspected.

To ensure that any failure to find between-group differences from the previous whole-brain analysis was not due to the requirement to correct for multiple tests, we next restricted the group difference analysis to a mask of task-activated areas. This mask was created by collapsing all patients and control into one group and thresholding the contrast of STOPS> 0 (FDR; q = 0.05) (anatomical resolution) (see Figure 4). A voxelwise *t*-test on STOP activation was then

performed between groups (FDR; q = 0.05; cluster threshold of at least four contiguous voxels) within this mask.

Finally, a linear regression approach was utilized to investigate whether duration of abstinence was predictive of brain responses within the RIC. For this analysis, we extracted the mean beta-weights for each of the ROIs. These beta-weights are the mean activation value of the contrast STOPS > 0 within the ROI for each individual that were utilized in our between groups ROI analyses. These values were then entered into PASW Statistics Version 20 (SPSS, Inc., 2009, Chicago, IL) as a dependent variable in a linear regression with duration of abstinence, years of cocaine use, age and total number of STOPS as independent variables. A similar linear regression was conducted only on non-using controls utilizing total number of STOPS and age as the independent variables if they were found to be a significant predictor of ROI activation in a patient only regression.

3. RESULTS

3.1. Behavioral results

Overall, abstinent patients did not display any significant behavioral differences from controls in terms of task performance (see Table 5). Patients did not differ from controls in the percentage of correct STOPS (0.75 ± 0.19, 0.76 ± 0.19, respectively, $t(70) = -0.35$; p =0.72), total number of STOPS (48.8 ± 12.0, 50.4 ± 12.5, respectively, $t(70) = -0.56$; p = 0.58) and total number of ERRORS (13.3 ± 8.7, 11.2 ± 9.6, respectively, $t(70) = .97$; p = 0.34) committed. Patients also did not differ from controls in reaction time for correct responses (HITS) (386 ± 57, 399 ± 60.8, respectively, $t(70) = -0.90$; p =0.37) or ERRORS (355.6 ± 116, 347.8 ± 66.3, respectively, $t(68) = 0.36$; p =0.72). We also conducted a signal detection analysis to better

examine individual differences in response patterns. Utilizing the *d'* values from the signal detection analysis, there were no significant differences between patients and controls in *d'* values (3.52 ± 1, 3.58 ± 1.1, respectively, $t(70) = -0.22$; $p = 0.83$). *d'* is computed by taking into account the probability of correctly responding to targets when a target is present and the probability of incorrectly initiating a response in the absence of a target (Green and Swets, 1966). For the patients, a linear regression was performed with total STOPS as the dependent variable and duration of abstinence, years of cocaine use and age as the independent variables. None of the independent variables were significant predictors of total number of correct STOPS.

3.2. Abstinent patients vs. controls

The main focus of this study was to investigate if individuals who were abstaining from cocaine use would display cortical hypoactivations in the RIC when compared to non-using controls. For the ROI analysis, abstinent patients did not differ from controls within any of the seven ROIs utilizing a threshold of $p < 0.05$ (see Table 6). Abstinent patients did not differ from controls in the right insula ($t(70)=-0.17$; $p=0.86$), right inferior frontal gyrus/middle frontal gyrus ($t(70)=0.28$; $p=0.78$), right inferior parietal lobule/precuneus ($t(70)=-0.85$; $p=0.40$), right inferior frontal gyrus ($t(70)=-0.13$; $p=0.89$), left pre-supplementary motor area/cingulate ($t(70)=0.42$; $p=0.68$), left precentral gyrus ($t(70)=-1.17$; $p=0.24$) and left insula ($t(70)=0.51$; $p=0.61$).

In the whole-brain analysis, no regions differed between patients and controls at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method. For the analysis of abstinent patients vs. controls, restricted to a mask of regions activated by the contrast of Stops > 0, no regions differed between groups at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method. The uncorrected whole-brain voxelwise analysis

between groups showed that patients displayed higher activation than controls in the right superior temporal gyrus ($p<0.001$; cluster threshold of at least four contiguous voxels).

3.3. Duration of abstinence

To examine if cortical activations within the RIC were predictive of duration of abstinence, response success, age or years of cocaine use a linear regression was conducted utilizing the beta-weights from each of the predefined ROIs as the dependent variables. The regressions included total number of STOPS, duration of abstinence, years of cocaine use and age as independent variables in the linear regression and found that greater activation of the right insula was predicted by both greater duration of abstinence ($p=0.01$) and total number of STOPS ($p=0.0001$) (see Figure 5). We repeated this analysis excluding the participant with the shortest duration of abstinence (0.87 weeks) and found that greater duration of abstinence and total number of STOPS continued to be predictive of greater right insula activation. A similar regression was conducted in the controls using total number of STOPS and age as independent variables. For the controls, right insula activation was not predicted by total number of STOPS ($p=0.12$).

4. DISCUSSION

Our current investigation of inhibitory control in abstinent CD individuals revealed an absence of cortical activation differences in the RIC as compared to non-using controls. Additionally, duration of abstinence did not appear to be a major contributing factor to the present results since response success was not a significant predictor of length of abstinence and the patients performed the task just as successfully as the healthy controls. Participants in our

complementary EEG study also completed the same Go/No-Go task and similarly displayed no differences in behavioral or electrophysiological activity relating to inhibitory control (Morie et al., 2013). Both of these studies contradict previous investigations of motor response inhibition in current CD individuals showing cortical hypoactivations in the RIC when compared to non-using controls (Garavan et al., 2008; Kaufman et al., 2003), monitoring and inhibitory deficits in current drug abusers, evidenced by N2 and P3 amplitude reductions (Sokhadze et al., 2008; Yang et al., 2009), and deficits in monitoring ability (Franken et al., 2007). Utilizing two different methodologies and two virtually discrete cohorts (with an overlap of only two patients and six controls) both studies independently provide evidence suggestive of a recovery of inhibitory control within this population occurring over a time frame of weeks to months rather than years. Supporting this hypothesis, we have also observed evidence of recovery within white matter tracts of abstinent CD individuals utilizing diffusion tensor imaging (Bell et al., 2011). Similarly, Hanlon et al. 2011 observed reduced gray and white matter in current CD individuals when compared to both non-using control and abstinent CD individuals. However, because of this study's cross-sectional design, it is impossible to determine whether the abstinent patients' similarity of cortical activations in the RIC to non-using controls is definitively a result of recovery of function. It could be that this specific cohort was unique in that they did not display cortical hypoactivations in the RIC during cocaine dependence.

Our findings were not fully in line with prior investigations of abstinent CD individuals which have shown both hypo and hyperactivations in the RIC circuit when compared to non-using controls. Li et al. (2008) found that abstinent CD individuals showed cortical hypoactivations in the rostral anterior cingulate cortex when performing a motor response inhibition task. The authors do not list the abstinence duration of their cohort so it is possible

that the participants in the study were only very recently abstinent in contrast to our cohort where our 14 abstinent users with the shortest time clean had an average duration of abstinence of 13.4 weeks. Therefore, our patient group may be further along in terms of abstinence duration which could be indicative of a strengthening of the RIC so that continued abstinence is possible. It is also possible that these two different outcomes were a result of the different types of motor response inhibition tasks that were used in each investigation. While Li et al. (2008) used a stop-signal task, the investigation we conducted utilized a Go/No-Go motor response inhibition task. A recent quantitative meta-analysis has shown that while these two tasks have significant overlap in the cortical regions they activate, Go/No-Go tasks produced greater activation in the frontoparietal control network than stop-signal tasks (Swick et al., 2011). Results from our investigation also differed somewhat from those of Connolly et al. (2012) in which both short (2.4 weeks) and long (69 weeks) duration abstinent patients displayed hyperactivations in the RIC relative to non-using controls. It is not clear why our cohort also did not display cortical hyperactivations, however, both studies are consistent in that they do not show the cortical hypoactivity of the RIC that is typical of current users.

The absence of performance and activation differences in abstinent CD abusers is especially notable given the robust evidence of inhibitory control deficits in cocaine addiction. These deficits are hypothesized to be partly responsible for the switch from single to daily drug usage (acquisition stage), and the switch from controlled to compulsive drug intake (Perry and Carroll, 2008). Evidence supporting this model comes from Ersche et al. (2012) who showed that siblings of stimulant dependent individuals exhibited significantly decreased levels of inhibitory control when compared to non-using controls suggesting that deficits in inhibitory control precede substance dependence. Furthermore, rats that are rated as low in inhibitory

control are more likely to escalate their initial drug-taking (Dalley et al., 2007) and develop compulsive drug-taking despite punishment (Belin et al., 2008) than rats rated as high in inhibitory control. It is also hypothesized that chronic drug use may result in structural and functional changes in cortical control areas which may then result in decreased inhibitory control (Dalley et al., 2011; Perry and Carroll, 2008). Regardless of the mechanism, there is general agreement that deficits in inhibitory control constitute a significant facet of drug dependence and that continued problems with inhibitory control could constitute a risk factor for relapse if not addressed. Based upon this, a goal of drug addiction treatment could be to increase the levels of inhibitory control in CD individuals. It has been shown that reduced inhibitory skills are associated with worse cocaine treatment outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Streeter et al., 2008). Specifically, Moeller et al. (2001) showed that CD individuals who scored low on measures of inhibitory control were more likely to drop out of drug treatment and relapse to cocaine use. The abstinent users who participated in our study were all recruited from in-patient addiction treatment centers and were required to attend meetings with counselors at least 3 times a week. Additionally, most of the patients included in the study had achieved relatively long periods of abstinence during which they were receiving constant counseling on how to deal with their urges to use drugs again. Therefore, it is possible that because the cohort of former users in the current investigation was receiving intensive treatment that involved counseling on restraining urges, they possessed strengthened cognitive control mechanisms. These strengthened cognitive control mechanisms could explain why they do not display the typical hypoactivations associated with current cocaine dependence. One interpretation of these results is that increased duration of cocaine abstinence results in dynamic neurobiological changes that enable extended abstinence. Therefore, the period of abstinence in this cohort

coupled with environmental seclusion may have resulted in an increased ability to inhibit behaviors which was then represented by a normalization of cortical activations in the RIC.

Although the results showed no differences between abstinent patients and controls in cortical activation of the RIC, we did find evidence of individual differences in cortical functioning within the right anterior insula of abstinent patients specifically relating to duration of abstinence and response success. It was observed that when STOPS occurred, increased cortical activation of the right anterior insula was predictive of increased response success and increased duration of abstinence. Interestingly, right insula activation in controls was not predicted by response success suggesting that this effect may be specific to recovering cocaine addicts. Evidence suggests that the anterior insular cortex plays an important role in maintaining drug use. Naqvi et al. (2007) showed that lesions of the anterior insulae were associated with the abrupt cessation of nicotine intake in dependent individuals. The authors speculated that this relationship was due to an association between this region and the urge to smoke cigarettes, consistent with this region's role in interoceptive processes (Craig, 2009). This would suggest that continued drug use, despite aversive consequences, may be related to subjective drug urges and cravings mediated by anterior insular function. Our observation of inhibition-related increases in right anterior insula activation that correlate positively with the duration of abstinence might therefore provide a window into the restoration of functions that are unrelated to drug use. It will be interesting to determine in future research if the normal cognitive functioning of this brain region might provide a biomarker of recovery from addiction. It has been proposed that the anterior insular cortex is a critical component of a cognitive control system called the salience network. This network is theorized to consist of both the anterior cingulate cortex and the anterior insulae, with the primary function being to choose between

competing external and/or internal stimuli in order to guide behavior (Seeley et al., 2007). It is hypothesized that within the salience network, the anterior insular cortex functions to first identify relevant stimuli from a wide array of choices. Once the stimulus is identified, the anterior insulae is then responsible for engaging higher-order processes that are related to processing the task at hand, and at the same time attenuating cognitive networks that are not conducive to task-related processing (Menon and Uddin, 2010). It is possible that greater engagement of the right anterior insula during motor response inhibition signifies a more active cognitive control system in that individual. We can speculate then that greater right insula activation is related to an increased ability to identify relevant stimuli that then need to be inhibited and that this effect could be responsible for longer durations of abstinence. However, whether this insula effect is responsible for, or is a result of, increased abstinence cannot be determined by this experimental design. Future investigations should be conducted to clarify the precise role this region plays in maintaining cocaine abstinence.

There are specific limitations in the present study that need to be acknowledged. Because of this study's cross-sectional design, it is impossible to determine if the absence of cortical deficits in abstinent CD individuals are due to a recovery of inhibitory deficits, or if they reflect pre-existing differences between patients. As stated previously, Ersche et al. (2012) showed that non-using individuals displayed similar cognitive deficits as their drug-dependent siblings. Unfortunately, we did not collect family history information in this study. Therefore, it is possible that the absence of cortical activation differences between the groups may be due to similar family backgrounds. Additionally, this study employed a 1.5T magnet which is not as powerful as a 3T magnet. However, multiple studies examining response inhibition in current and abstinent cocaine addicts have also employed 1.5T magnets (Connolly et al., 2012; Garavan

et al., 2008; Kaufman et al., 2003). It also needs to be pointed out that this study was conducted predominantly in male participants and that in view of this; appropriate care should be taken in generalizing these results to abstinent female CD patients.

4.1 Conclusions

Our relatively large sample of abstinent CD individuals and non-using controls provides evidence that individuals receiving intensive in-patient treatment for their addiction do not display the cortical hypoactivations in the RIC observed in current CD individuals. Furthermore, the right anterior insula was identified as a potentially important node of the RIC for response success and maintaining abstinence, a region that is hypothesized to be crucial for initiating cognitive control processes. Complementing these findings, we also observed similar electrophysiological and behavioral results in a separate cohort of abstinent drug abusers (Morie et al., 2013). Although speculative, these results seem to provide evidence that intensive in-patient treatment may result in cortical normalization within the RIC and that right anterior insula activation reflects a continued strengthening of the cognitive control mechanisms that then helps the user to maintain abstinence.

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Figure Legends

Figure 4.

Brain regions that were activated utilizing a *t*-test contrast of Stops > 0 (false discovery rate corrected; q = 0.05) (anatomical resolution) in patients and controls (N=72). Images are in radiological orientation. Figure only shows positive activations. These activations were utilized to perform a between groups analysis restricted to a mask of task-activated regions. Black boxes show the size of the cubic ROIs within the brain activation map in each respective plane with the white lines intersecting at the peak activation which served as the center of each ROI.

Figure 5.

Scatterplots showing the relationships between right insula activation and duration of abstinence (r^2=0.66; p=0.01) (1) and the total number of STOPS (r^2=0.66; p=0.0001) (2) for patients only. Duration of abstinence is in weeks.

Figure 4.

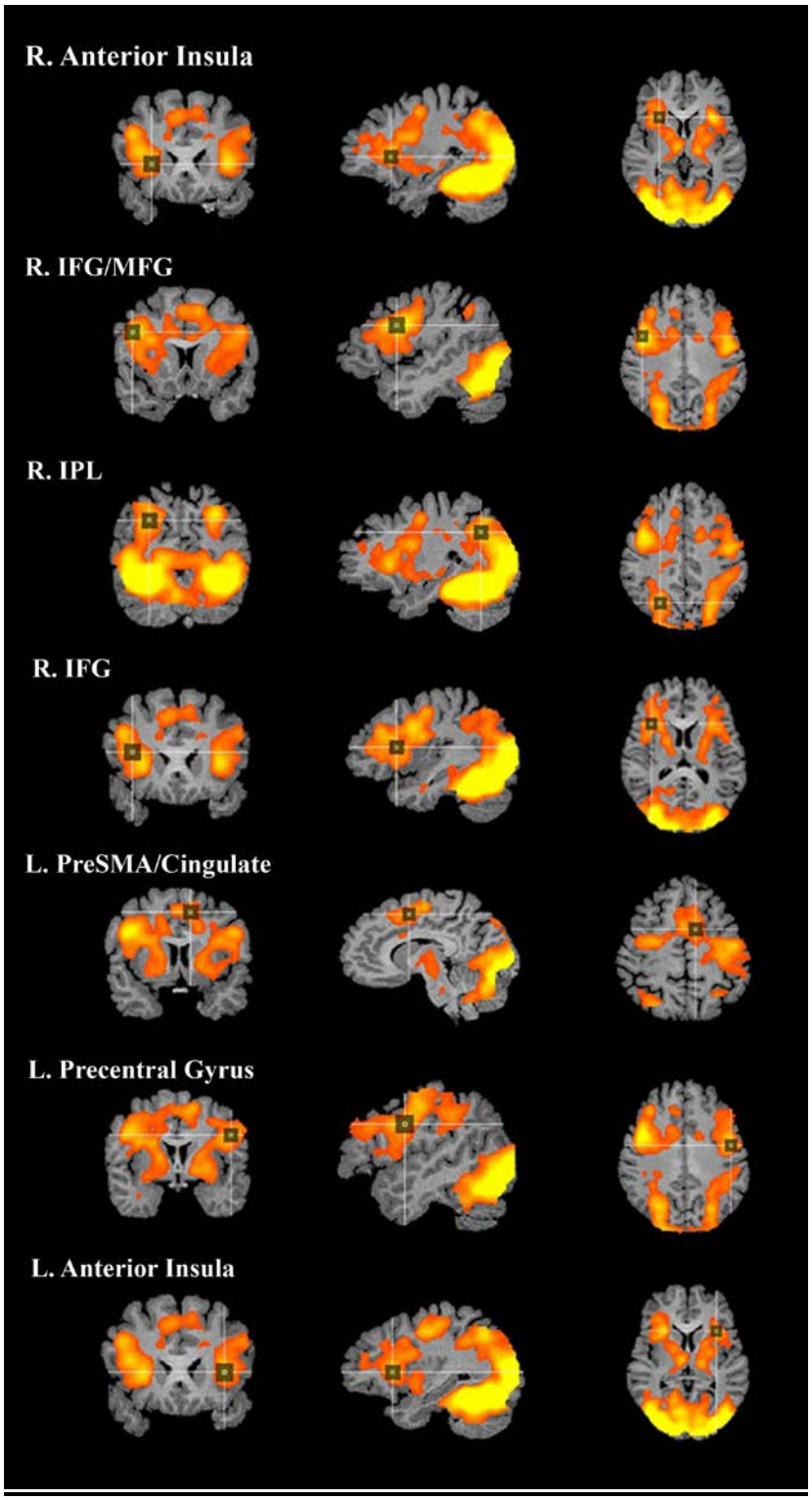
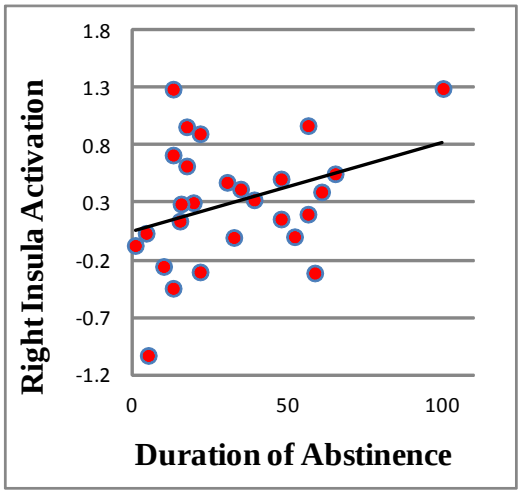

R. Anterior Insula
R. IFG/MFG
R. IPL
R. IFG
L. PreSMA/Cingulate
L. Precentral Gyrus
L. Anterior Insula

Figure 5.

1.


Right Insula Activation
1.8
1.3
0.8
0.3
-0.2
-0.7
-1.2
0
50
100
Duration of Abstinence

2.

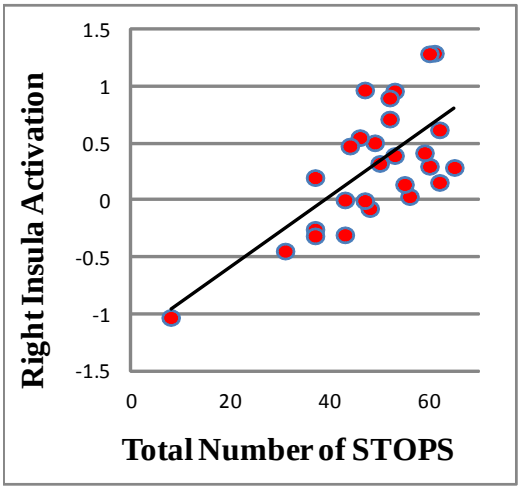

Right Insula Activation
1.5
1
0.5
0
-0.5
-1
-1.5
0
20
40
60
Total Number of STOPS

Table 5
Participant Demographics

All patients vs. All controls	Group		*p*
	CD (N=27)	Controls (N=45)	
Age (years)	37.8 (7.8)	38.1 (10.6)	0.92
Years of education	12.9 (1.4)	13.7 (1.7)	0.05[a]
Sex (Male/Female)	24/3	35/10	0.24[b]
% Correct STOPS	75% (19%)	76% (19%)	0.72
Total STOPS	48.1 (12.0)	50.4 (12.5)	0.58
Total ERRORS	13.3 (8.7)	11.2 (9.6)	0.34
HITS RT[c]	386 (57)	399 (61)	0.37
ERRORS RT[c]	356 (116)	348 (66)	0.72
d'	3.5 (1.0)	3.6 (1.1)	0.83

Note: [a] Significant between patients and controls
[b] Pearson's chi-square significance level
[c] RT = Reaction Time in milliseconds

Table 6
Talairach coordinates of ROIs

Cluster	Anatomical region	Talaraich coordinate			Cluster size	*t*-value	P vs C[a] *p*-value[b]
		X	Y	Z			
1	R. anterior insula	27	19	6	2,197	4.90	0.86
2	R inferior/middle frontal gyrus	44	9	30	2,197	5.97	0.78
3	R. inferior parietal lobule	25	-61	34	2,197	5.75	0.40
4	R. inferior frontal gyrus	35	19	15	2,197	4.92	0.89
5	L. preSMA/cingulate	-9	4	48	2,197	4.54	0.68
6	L. precentral gyrus	-46	-2	30	2,197	5.08	0.24
7	L. anterior insula	-31	19	7	2,197	5.30	0.61

Note: [a]P vs C refers to Patients vs. Controls
[b]*p*-values are results from *t*-tests between patients and controls in each ROI

CHAPTER 3

Recovering from Addiction: Dorsal Striatal Reactivity to Cocaine Cues is Associated with Persistent Craving in Abstinent Cocaine Addicts.

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ABSTRACT

A significant problem with treating cocaine dependence is the difficulty in objectively determining who is most likely to relapse. Cocaine addiction has been characterized by both deficits in inhibitory control and an increased reactivity to cocaine cues, both of which are hypothesized to play an integral role in the development of addiction and the propensity to relapse. Because of the significance of these factors to dependence, we hypothesized that a reduction in both impulsivity and cocaine craving would result in a reduced risk of cocaine relapse. Using functional magnetic resonance imaging (fMRI), we examined activations in nodes of the response inhibition circuit (RIC) in abstinent cocaine dependent (CD) individuals (n=20) and non-using controls (n=19) while they performed a response inhibition task. We also examined neural activation patterns in both the dorsal and ventral striatum in the CD individuals and non-using controls while they performed a cocaine craving task. In contrast to current CD users, there were no between-group differences in activation of the RIC and striatum. However, at the subject-level, CD individuals displayed a positive correlation between cocaine cue-related neural activation in the dorsal striatum and cocaine craving scores. Furthermore, CD individuals also displayed a negative correlation between impulsivity scores and response inhibition-related activation in the right inferior parietal lobule and right inferior/middle frontal gyrus. Therefore, while there were no group-level differences between CD individuals and non-using controls, the CD individuals displayed subject-level differences that we suggest may be indicative of relapse risk.

1. INTRODUCTION

One in four people entering treatment for cocaine addiction will still be using on a weekly basis 5 years after treatment (Simpson et al., 2002). However, it is not well understood why the majority of abstainers show protracted resistance to relapse while a significant minority will continue to be at high-risk of recidivism over extended periods of time. A common refrain of treatment providers concerns the profound difficulties they face in identifying those individuals most likely to relapse. Understanding individual differences in recovering cocaine addicts that may contribute to relapse risk is a significant public health issue. Current theories of addiction posit that deficits in inhibitory control allied with increased compulsion to seek and take cocaine play an integral role in the development of addiction and the propensity to relapse (Everitt et al., 2008). Indeed, both the inability to inhibit behaviors with known negative consequences and the compulsion to seek and take drugs are represented in multiple diagnostic criteria for cocaine dependence (Association, 2000).

Numerous behavioral studies have identified impulse control deficits in cocaine dependent (CD) individuals (Coffey et al., 2003; Fillmore and Rush, 2002; Monterosso et al., 2001; Verdejo-Garcia et al., 2007), but do not provide information on the neurobiological substrates of these deficits. Neuroimaging studies using classic Go/No-Go motor response inhibition tasks have consistently shown hypoactivity in the so-called cortical response inhibition circuit (RIC) when currently using cocaine addicts are compared to non-using controls. This hypoactivity is mainly seen in the right anterior cingulate cortex, right insula, right inferior parietal lobule and right middle frontal gyrus (Garavan et al., 2008; Hester and Garavan, 2004; Kaufman et al., 2003). It is thought that RIC hypoactivity may be related to the weakened

impulse control associated with cocaine dependence, and it has been hypothesized that this decreased impulse control is partly responsible for the switch from single to daily drug usage (the acquisition stage) and the switch from controlled to habitual drug intake (Perry and Carroll, 2008). Indeed, Ersche et al. (2012) have shown that siblings of stimulant-dependent individuals also exhibit significantly decreased levels of inhibitory control compared to non-using controls, suggesting that deficits in inhibitory control may in fact be endophenotypic and predispose to substance dependence. Evidence supporting this view also comes from animal models of cocaine addiction which have shown that rats that score lower on measures of impulse control are more likely to escalate their initial drug-taking (Dalley et al., 2007) and ultimately to engage in compulsive drug intake (Belin and Everitt, 2008).

Along with deficits in inhibitory control, the compulsivity associated with drug-seeking is another defining characteristic of severe addiction. This compulsivity can be understood as perseverant actions that are inappropriate to the situation at hand, have no obvious relationship to the overall goals of the individual and which often result in undesirable consequences (Dalley et al., 2011). Everitt and Robbins (2005) forwarded the thesis that drug addiction is comprised of a switch from voluntary drug use to compulsive drug intake. The voluntary acquisition stage is initially driven by the rewarding effects of the drug (Campbell and Carroll, 2000), but this initial use escalates to compulsive/habitual drug-taking due to an interaction between Pavlovian and instrumental learning processes (Everitt et al., 2008). This occurs when previously neutral environmental stimuli become associated with drug use and become conditioned stimuli (drug cues). When these cues are combined with the reinforcing effects of drugs, the presentation of drug cues alone can act as a reinforcer and produce automatic drug-seeking or drug-taking behavior (Pavlovian instrumental transfer). A proposed neurobiological mechanism for this

transition is that striatal reactivity to drug cues switches from a predominantly ventral to a predominantly dorsal activation pattern and that this switch is mediated by dopaminergic innervation (Everitt et al., 2008; Everitt and Robbins, 2005; Pierce and Vanderschuren, 2010). This switch is thought to occur through ventral striatal "spiraling" connections between midbrain dopamine neurons and the dorsal striatum (Haber et al., 2000; Ikemoto, 2007). Multiple animal studies have demonstrated that while the ventral striatum is involved with the acquisition of cue-controlled cocaine seeking, the appearance of habit-driven cocaine intake is dependent upon dorsal striatal control (Belin and Everitt, 2008; Ito et al., 2004; Murray et al., 2012; Vanderschuren et al., 2005). Thus, ventral striatal activity to drug cues is associated with the early rewarding stage of drug-taking while dorsal striatal activity to drug cues accompanies the later stages of compulsive/habitual drug use. Positron emission tomography (PET) studies have also revealed increased dopamine levels in the dorsal striatum when human participants viewed cocaine cues (Volkow et al., 2006, 2008; Wong et al., 2006), findings that have been replicated using functional MRI (fMRI) (Garavan et al., 2000). Activations in the dorsal striatum have been correlated positively with subjective ratings of craving (Risinger et al., 2005). Further, fMRI studies have also shown dorsal striatal activity to the presentation of nicotine drug cues (McClernon et al., 2009) and implicated dorsal striatal activation as a marker of addiction (Vollstadt-Klein et al., 2010) and relapse (Grusser et al., 2004). Therefore, hypoactivation of the RIC during inhibitory control and drug-cue related hyperactivation of the dorsal striatum both appear to be important biomarkers of cocaine addiction.

Although both these processes have been relatively well-characterized in current cocaine users, much less is known about how they function after cocaine cessation. In the only functional imaging study of craving in abstinence that we are aware of, Potenza et al. (2012)

utilized imagined situations of drug intake and saw correlations between subjective levels of craving and neural activations in the hippocampus, insula, and anterior and posterior cingulate in response to drug cues in recently abstinent CD individuals (mean = 22.3 weeks; SD=3.0). Additionally, they saw increased neural activation in the dorsal striatum and multiple cortical and subcortical regions in patients during the drug imagery session when compared to non-using controls. These results suggest that the cue-induced dorsal striatum activation patterns seen in current cocaine users persist at least until the first few weeks of abstinence.

In contrast to the relative paucity of investigations looking at the neural correlates of craving in abstinence, a number of studies have assessed the functioning of the RIC during cocaine abstinence. To date, three neuroimaging studies have examined motor response inhibition in abstinent CD individuals. Li et al. (2008) assessed response inhibition in abstinent CD males (n=15) using a stop-signal task, expressly looking at activity patterns in the rostral anterior cingulate cortex and the dorso-medial frontal cortex. They found decreased activity in the rostral anterior cingulate in the abstinent CD group and theorized that this effect was responsible for inhibitory control deficits in CD individuals. The specific duration of abstinence was not reported in this study (although participants were at least 2 weeks post cessation), so one outstanding question is the length of abstinence that is required for the amelioration of cortical hypoactivity in the RIC. In Connolly et al. (2012), our research group employed a Go/No-Go motor response inhibition task to examine cortical activations in abstinent CD individuals who had attained either shorter (n=9; average duration = 2.4 weeks) or longer (n=9; average duration = 69 weeks) periods of abstinence. We found that both the short- and long- term abstinence groups displayed greater cortical activity than drug naïve controls when performing a successful motor response inhibition in multiple nodes of the canonical RIC. These findings were

paralleled by the absence of behavioral differences between the abstinent groups and the non-using controls, a finding suggestive of a relatively substantial recovery of inhibitory function. In a recent follow-up study in a larger abstinent CD cohort (n=27), we again examined activation in nodes of the RIC, comparing both performance and activation patterns to those of non-using controls (n=45), while a motor response inhibition task was performed (Bell et al., 2013). In contrast to current users, these abstinent individuals, despite extended histories of chronic cocaine-abuse (average duration of use = 8.2 years), performed the task just as efficiently as non-users. In addition to these behavioral findings, we found no evidence for between-group differences in activation of the RIC and instead, robust activations were apparent in both groups within the well-characterized nodes of the RIC. We also conducted a complementary event-related potential (ERP) study which showed an absence of behavioral and electrophysiological deficits in a separate cohort (n=21) of abstinent drug abusers (Morie et al., 2013). Thus, the finding of normalized inhibitory performance in tandem with increased cortical activity in inhibitory control areas in our work may reflect either a period of major recovery within the RIC after drug cessation or preexisting differences that facilitate abstinence.

However, while it appears that, at the group-level, individuals who are receiving treatment for cocaine dependence do not display the cortical hypoactivations in the RIC that have been identified in current CD individuals, it is unclear if there are more specific subject-level differences in RIC activation. Furthermore, it is unknown whether dorsal striatal hyperactivation to cocaine cues persists through more extended periods of abstinence and also whether there are subject-level differences in striatal activation to cocaine cues. Because persistent dysfunction within the neural circuitry underlying these two functions is theorized to disproportionately account for continued drug use, we believe that understanding the functioning of these regions

after cocaine cessation at the subject-level is crucial to understanding relapse resistance. Indeed, supporting evidence shows that decreases in subjective levels of craving (Da Silveira et al., 2006; Heinz et al., 2006; Paliwal et al., 2008) and impulsivity (Aharonovich et al., 2006; Brewer et al., 2008; Moeller et al., 2001; Schmitz et al., 2009; Streeter et al., 2008; Winhusen et al., 2013) correlate with better drug treatment outcomes. Therefore, although at the group-level, recovering cocaine addicts may not display the neural activation deficits observed in current users, it could be that these deficits persist in certain individuals.

Here, we conducted a cross-sectional examination of CD individuals at varying durations of abstinence to investigate neural activation associated with inhibition and craving. We employed a multi-dimensional craving questionnaire to measure individual craving levels to the visual presentation of cocaine stimuli and a multi-dimensional impulsivity questionnaire. We hypothesized that a reduction in both subjective levels of craving and impulsivity would be associated with decreased dorsal striatal activation to cocaine cues as well as normalized RIC activation. In line with our previous work, we fully expected that the cocaine abstinent group would not display the neural activation deficits observed in current cocaine users (Bell et al., 2011; Bell et al., 2013; Morie et al., 2013) . However, we postulated that a subset of the abstinent CD individuals would continue to display neural activation deficits related to cocaine-cue reactivity and inhibitory control that are independent of duration of abstinence. We hypothesized that a persistence of these neural activation deficits despite cocaine abstinence could indicate an increased risk of relapse.

2. METHODS

2.1. Subjects

Twenty male abstinent CD patients were recruited from in-patient and out-patient addiction treatment centers located in New York City (Bronx County) and 19 male controls were recruited through internet advertisements. All 20 patients received a primary Axis I diagnosis of Cocaine Dependence. Fourteen of the patients were in-patients without access to drugs and alcohol and under constant supervision and mandatory drug-testing. Four of the patients were using out-patient facilities and were legally required to undergo random urine toxicology testing to monitor continued abstinence. Abstinence was also confirmed by a New York State accredited substance abuse counselor with whom the patient met on at least a weekly basis. Two of the patients were under no direct supervision but visited out-patient facilities for group-meetings or support. Individuals did not have an incentive to be dishonest about being abstinent as we were also conducting a study on current cocaine users and therefore possible recruits could enter either study without one study being more beneficial than the other. Patients were abstinent for an average of 44.9 weeks (Minimum = 1.9 weeks, Maximum = 574.2 weeks; SD = 127.1). Exclusion criteria for patients and controls were as follows: 1) Any major psychiatric illness; 2) Head trauma resulting in loss of consciousness for longer than 30 minutes; 3) Presence of any past or current brain pathology (two patients displayed clinically significant brain pathology and were not included in the cohort of 20 patients); 4) A diagnosis of HIV; 5) The presence of any contraindications to an MRI; 6) Age above 65 years and below 19 years; 7) Presence of WM hyperintensities (one patient displayed clinically significant WM hyperintensities and was not included in the cohort of 20 patients). Because of the high rates of comorbidity of alcohol and other drug abuse among the patient population, patients were not excluded if they had abused

other drugs or alcohol prior to the onset of their cocaine abstinence (10 individuals had at least comorbid alcohol abuse and 5 individuals had comorbid heroin dependence). However, all 20 patients listed cocaine as their primary drug of choice. None of the patients were currently using any amount of alcohol or drugs. Years of self-reported drug use were recorded during the initial interviews. Controls were excluded if they had any history of drug or alcohol dependence and/or history of psychiatric illness. The study received Institutional Review Board approval at the Albert Einstein College of Medicine. All participants were screened for contraindications for MRI and signed an informed consent document administered by HIPAA-certified staff. Participants received a gift card worth $60 for successful completion of the experimental protocol.

The comparison sample consisted of 19 controls (see Table 7). The patients and controls did not differ in age (47.8 ± 8.5, 42.2 ± 12.1, respectively, $t(37) = 1.7$, $p = .10$), but patients had fewer years of education (12.1 ± 1.9, 13.7 ± 1.9, respectively, $t(37) = -2.66$; $p = .01$).

2.2. Stimuli and Tasks

2.2.1. Craving Measurement

To measure the level of craving in response to drug cues, we used a subjective, self-report measure called the Cocaine Craving Questionnaire-Now (CCQ-N). The CCQ-N is a 45-question multifactorial self-report instrument that measures various aspects of craving in the present tense (Tiffany et al., 1993). The CCQ-N breaks down into four first-order factors that have been described as measuring the following; Factor 1=Desire, Factor 2=Lack of Self-Efficacy, Factor 3=Compulsivity, Factor 4=Relief (Heinz et al., 2006). Scores from the CCQ-N have been correlated with neurophysiological processes that may underlie compulsive cocaine

craving. For example, it has been demonstrated that higher craving levels on the CCQ-N are correlated with increased dopamine levels (Volkow et al., 2006, 2008) and increased brain glucose metabolism (Volkow et al., 2010) in the dorsal striatum.

The CCQ-N was administered to all patients and controls in a private room before they performed any tasks in the scanner. The participants viewed 112 cocaine-related images on a computer monitor at least 24 hours before completing the fMRI portion of the experiment to protect against habituation effects. The cocaine images consisted of individuals engaged in cocaine use, paraphernalia for cocaine administration and pictures of cocaine itself. These images were collected from an extensive internet search and reflected normal and idealized interpretations of everyday cocaine use that would be experienced by the typical user. That is, these pictures did not depict a harsh environment containing negative imagery such as violence or unhealthy looking individuals or paraphernalia that might be seen in typical anti-drug advertisements. Each image was presented for a duration of 1800 ms and was separated by a blank screen presented for 200 ms. The total task time was 3.7 minutes. To ensure that participants were attending to the task, stimuli had a 12% chance of repeating for each block. Participants were instructed to press the spacebar only when they saw a stimulus repeat. As soon as all of the pictures were presented, participants were then instructed to fill out the CCQ-N. These same pictures were used in the subsequent fMRI experiment.

2.2.2. Impulsivity Measurement

Impulsivity was assessed through the self-administration of the Barratt Impulsiveness Scale (BIS-11) (Patton et al., 1995). This measure consists of 30 questions that have been used in multiple studies to assess personality traits associated with impulsivity in CD individuals

(Coffey et al., 2003; Ersche et al., 2011; Moeller et al., 2005). There are three second-order factors in the BIS-11 consisting of Attentional impulsiveness, Motor impulsiveness and Non-planning impulsiveness. The BIS-11 has been correlated with cortical thickness (Schilling et al., 2012), structural integrity (Moeller et al., 2005) and neural functioning (Wittmann et al., 2011) of RIC regions and is therefore capable of capturing the neurophysiological characteristics of impulsivity. Participants filled out the BIS-11 after the successful completion of the MRI scanning session.

2.2.3. Cocaine Cue Task

To invoke cocaine craving while in the MRI, participants were shown the same cocaine-related pictures as described above. Stimuli were presented via VisuaStim digital goggles (Resonance Technology, Northridge, CA). A block design was utilized for this cocaine cue task with alternating blocks consisting of cocaine cues, positive images, neutral images and rest periods. The neutral images were taken from the International Affective Picture System (IAPS) (Lang, 2008) and were similar in complexity and color to the cocaine cue pictures. The IAPS is a large set of standardized photographs that are rated with regard to their tendency to evoke an emotional response in the viewer. A majority of the positive images were also obtained from the IAPS. However, due to the limited number of positive images in the IAPS set that were rated by men as high in both positive valence and arousal, we obtained additional images from outside the IAPS consisting of similar imagery. Positive images are included in the study design as a control for the cocaine images which are rated by CD men as high in positive valence and arousal (Moeller et al., 2009). Neither the neutral or positive pictures had any images that could be construed to be related to drugs or drug use (e.g. there were no pictures containing cups which

could be interpreted as containing alcohol). There were four separate runs for this task. Each run consisted of 12 stimuli blocks, 4 REST blocks and 12 distractor task blocks presented in a pseudorandom order (see Figure 6.). The stimuli blocks were comprised of four blocks each of cocaine cues and positive and neutrally valenced pictures. Each of the blocks contained seven distinct pictures for a total of 112 distinct pictures for each cue category. Each picture was presented for 1800 ms and followed by a blank screen presented for 200 ms. Pictures were preceded by a screen stating "Picture Task" for 2000 ms for the purpose of informing the participant that a cue category was about to begin. Total block length was 16 seconds. The order of category blocks and all of the pictures within the blocks were pseudorandomized within each run. To ensure that participants were attending to the task, pictures had a 12% chance of repeating within each block presentation. Participants were instructed to press a button only when they saw a picture repeat. After each presentation of a cocaine, positive or neutral stimuli block, the participants completed either a Go/No-Go distracter task called the "XY" task (Fassbender et al., 2009; Hester et al., 2004), or encountered a REST block. The XY task consisted of a serial stream of alternating presentations of the letters X and Y. The stimuli were 5.08 and 6.35 cm in height for X and Y, respectively. Each letter presentation was 600 ms long and was separated by a blank screen presented for 400 ms. The participants were instructed to press a response button for each letter presentation but were to withhold their response if there was a back-to-back repeat presentation of a letter. There was a 12% chance of any of the letters repeating for each presentation of the XY task and the total task length was 14 seconds. The distracter task was meant to disrupt cognitive processes related to the preceding block of stimuli and help return participants to a neutral baseline prior to the next set of stimuli. Finally, there were four REST blocks presented pseudorandomly throughout each run that were 14 seconds in

duration. These blocks consisted of the word “Rest” in white letters against a black background. REST blocks were presented so that they were not the first or last block shown to the participant. The total duration of the task was 29.44 minutes.

2.2.4. Response Inhibition Task

All participants also completed a Go/No-Go motor response inhibition task that consisted of a series of pictures depicting neutral scenes from the IAPS (Bell et al., 2013). From this set, 158 new, neutral pictures were chosen with a mean emotional valence and arousal of 5.2 and 3.5 respectively, on a scale from 1 to 9 based on normative ratings from the IAPS dataset (Lang, 2008). All stimuli subtended 8.6 degrees horizontally x 6.5 degrees vertically of visual angle. Stimuli were presented for 800 ms and were separated by a blank screen presented for 200 ms. Participants were instructed to quickly press a button at the onset of each stimulus (Go trials) and to withhold a response in instances when a stimulus was repeated (No-Go trials). Stimuli were presented pseudorandomly in three blocks with each block containing 180 trials. Within each block, 22 trials (12%) were No-Go trials. The high proportion of Go trials renders the quick button press to the occurrence of a stimulus to be the prepotent response. The withholding of a button press to stimulus repetition proves quite difficult for most individuals and therefore requires the recruitment of inhibitory control mechanisms.

2.3 Image Acquisition

MRI scans were performed in a 3.0T Philips Achieva Quasar TX (Netherlands) at the Gruss Magnetic Resonance Research Center (MRRC) at the Albert Einstein College of Medicine. Functional scans for the cocaine cue task were acquired in four runs of 219 volumes

utilizing a T2-weighted echo-planar sequence (TR/TE= 2000/20 ms, flip angle = 90°, 3 mm slice thickness, 240 mm FOV, 80 x 80 matrix, pixel size = 3.0 x 3.0 mm^2, no gap). Forty-three axial slices were obtained parallel to the AC-PC plane. Functional scans for the inhibitory control task were acquired in three runs of 101 volumes utilizing a T2-weighted echo-planar sequence (TR/TE= 2000/20 ms, flip angle = 90°, 3 mm slice thickness, 240 mm FOV, 80 x 80 matrix, pixel size = 3.0 x 3.0 mm^2, no gap). Forty-four axial slices were obtained parallel to the AC-PC plane. Structural images were acquired utilizing a T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) (TR/TE=8.3/3.8 ms, flip angle = 8˚, 220 slices, 1mm slice thickness, 240 mm FOV, 240 x 187 matrix, pixel size = 1.0 x 1.0 mm^2, no gap).

2.4. Image Processing

The functional and anatomical data for both experiments were pre-processed and analyzed using Brain Voyager (QX 2.4, Maastricht, The Netherlands) running in Windows XP environment. Functional scans were preprocessed by performing a 3D motion correction. Functional scans were excluded on a run-by-run basis if they displayed > 3 mm of motion in a given plane. The T1-weighted anatomical slices were normalized into Talairach space and coregistered with the functional timecourses. The resulting volumetric time courses were then spatially smoothed using an 8 mm full-width at half-maximum (FWHM) Gaussian kernel.

2.5. Analysis Strategy

2.5.1. Cocaine Cue Task

In this block design, cocaine (COC), positive (POS), neutral (NEU) and XY task blocks served as regressors of interest. The REST blocks were not modeled and served as the baseline

measure. These regressors were convolved with a two-gamma-variate hemodynamic response function and subjected to a first-level analysis using a random effects general linear model (GLM).

Because it has been hypothesized that an interaction between the dorsal and ventral striatum are responsible for cocaine dependence (Everitt et al., 2008; Everitt and Robbins, 2005; Pierce and Vanderschuren, 2010), we created six regions of interest (ROIs) consisting of the caudate, putamen and ventral striatum specific to either the left or right hemisphere (See Figure 7.) The anatomically defined ROIs were created in BrainVoyager by using the "Draw with mouse" option on a standardized brain in Talairach space using a brain atlas for reference (Haines, 2007). The ventral striatum was defined as being inferior to the internal capsule and anterior to the anterior commisure while the dorsal striatum consisted of the remaining caudate and putamen (MacDonald et al., 2011).

To examine if there were any differences in cocaine-cue related activation between patients and controls in the dorsal and ventral striatum, the activation for each ROI for each participant was calculated and compared with a Group (Patients vs Controls) x ROI (Left Caudate, Right Caudate, Left Putamen, Right Putamen, Left Ventral Striatum and Right Ventral Striatum) analysis of variance (ANOVA) . This analysis was performed within IBM SPSS Statistics Version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) and utilized a contrast of COC > REST.

To identify cocaine-cue related activation differences between patients and controls in any other regions of the brain, we conducted a whole-brain voxelwise between groups analysis (False Discovery Rate (FDR); q = 0.05) utilizing a *t*-test contrast of COC > REST activation and a cluster threshold of at least four contiguous voxels.

A linear regression was utilized to investigate whether ROI activation in response to cocaine-cues was predictive of CCQ-N scores in patients. For this analysis, we extracted the mean beta-weights for each of the ROIs from each individual. Our activation measure was the contrast of COC > REST. These values were entered into IBM SPSS Statistics Version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) as the dependent variable in a linear regression with CCQ-N Factor 1 (Desire), CCQ-N Factor 2 (Lack of Self-Efficacy), CCQ-N Factor 3 (Compulsivity), CCQ-N Factor 4 (Relief) and duration of abstinence as our independent variables.

This regression was conducted for each of the six basal ganglia ROIs in all 20 patients. Additionally, for any ROIs found to be a significant predictor of craving scores, we then conducted another linear regression utilizing scores from a contrast of POS > REST as the dependent variable and included all of the same independent variables. This was conducted to determine if the results were specific to cocaine-related stimuli and not just a response to stimuli that are generally positively valenced and arousing. A similar linear regression was conducted for the non-using controls if striatal activation in the patients was found to be a significant predictor of CCQ-N scores.

2.5.2. Response Inhibition Task

In this event-related design, successful responses to Go trials (HITS), successful inhibitions to No-Go trials (STOPS) and unsuccessful inhibitions (ERRORS) served as regressors of interest. These regressors were convolved with a two-gamma-variate hemodynamic response function and subjected to a first-level analysis using a random effects

general linear model (GLM). One control and one patient were dropped from the analysis because they did not complete the task properly.

The ROIs for this task were obtained from a previous examination of response inhibition in 27 abstinent CD individuals and 45 non-using controls utilizing the same Go/No-Go task (Bell et al., 2013) The ROIs were identified within a task-defined map based on a contrast of STOPS > Baseline. This procedure first involved identifying centers of mass based upon peak voxel activations and then confirming that the centers of mass fell within the canonical RIC. A review of the imaging literature on response inhibition processes utilizing similar motor response inhibition tasks identified the right middle and inferior frontal gyri, right inferior parietal lobule, bilateral insula and the midline cingulate and pre-SMA as canonical nodes of the RIC (Chen et al., 2009; Chevrier et al., 2007; Dodds et al., 2010; Fassbender et al., 2009; Fassbender et al., 2004; Garavan et al., 2006; Garavan et al., 2008; Garavan et al., 1999; Hampshire et al., 2010; Hester and Garavan, 2004; Kaufman et al., 2003; Konishi et al., 1999; Leung and Cai, 2007; Li et al., 2006; Xue et al., 2008). The peak activations within each of these regions were identified and then served as the centers of 13 mm^3 (2,197 voxels) cubic ROIs.

To examine if there were any differences in cortical activation between patients and controls in the RIC the activation for each ROI for each participant was calculated and compared with a Group (Patients vs Controls) x ROI (Left Insula, Right Insula, Right Inferior Frontal Gyrus, Right Inferior Frontal Gyrus/Middle Frontal Gyrus, Right Inferior Parietal Lobule, Left Pre-Supplementary Motor Area/Cingulate, and Left Precentral Gyrus.) ANOVA. This analysis was performed within IBM SPSS Statistics Version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) and utilized a contrast of STOPS > HITS.

Next, we conducted a whole-brain voxelwise comparison between patients and controls to investigate whether there were any activation differences between the two groups in any regions of the brain. A voxelwise *t*-test was performed between groups (False Discovery Rate (FDR); q = 0.05) utilizing a *t*-test contrast of STOPS > HITS and a cluster threshold of at least four contiguous voxels.

A linear regression investigated whether BIS-11 factor scores were predictive of RIC activations in patients. For this analysis, we extracted the mean beta-weights for each of the ROIs based on the contrast of STOPS > HITS. These values were then entered into IBM SPSS Statistics Version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) as the dependent variables in separate linear regressions with BIS-11 Attentional impulsiveness, BIS-11 Motor impulsiveness, BIS-11 Non-planning impulsiveness, duration of abstinence and total number of STOPS as independent variables. This regression was conducted for each of the seven ROIs. .If impulsivity scores were found to be a significant predictor of ROI activation in the patient regression we then tested for a similar effect with similar regressors, excluding duration of abstinence, in the controls.

3. RESULTS

3.1. Behavioral results

3.1.1. Craving Scores (CCQ-N)

Patients had higher scores than controls on the Total Score (119.95 ± 41.3, 78.6 ± 24.3, respectively, $t(37) = 3.8$; $p \leq .001$), Factor 1 (Desire) (1.8 ± 0.91, 1.2 ± 0.37, respectively, $t(37) = 2.9$; $p \leq .007$), Factor 2 (Lack of Self-Efficacy) (2.7 ± 1.5, 1.4 ± 0.80, respectively, $t(37) = 3.2$; p

≤.003), and Factor 3 (Compulsivity) (3.6 ± 1.5, 1.8 ± 0.68, respectively, $t(37) = 4.8$; p ≤.001) of the CCQ-N. Patients did not differ from controls on Factor 4 (Relief) of the CCQ-N (2.8 ± 1.1, 2.2 ± 0.92, respectively, $t(37) = 1.7$; p ≤.09) although there was a trend towards significance (see Table 7.).

3.1.2. Impulsivity Scores (BIS-11)

Patients had higher scores than controls on the Total Score of the BIS-11(63.70 ± 13.1, 53.5 ± 7.7, respectively, $t(37) = 2.9$; p ≤.006) and the Attentional impulsiveness (15.30 ± 4.6, 12.50 ± 2.7, respectively, $t(37) = 2.3$; p ≤.03) and Non-Planning impulsiveness (25.60 ± 6.6, 21.0 ± 4.2, respectively, $t(37) = 2.6$; p ≤.01) factors of the BIS-11. Patients did not differ from controls on the Motor impulsiveness factor of the BIS-11 (22.8 ± 5.4, 20.1 ± 3.4, respectively, $t(37) = 1.9$; p ≤.07) although there was a trend towards significance (see Table 7.).

3.1.3. Response inhibition task

Patients did not differ from controls in the percentage of correct STOPS (0.69 ± 0.15, 0.78 ± 0.14, respectively, $t(35) = -1.72$; p ≤ .09), total number of STOPS (42.3 ± 13.0, 48.8 ± 13.1, respectively, $t(35) = -1.51$; p ≤ 0.14) or total number of ERRORS (19.1 ± 10.9, 13.6 ± 9.8, respectively, $t(35) = 1.62$; p ≤ 0.11) committed. Patients also did not differ from controls in reaction time for HITS (439.7 ± 54.9, 399.1 ± 69.8, respectively, $t(35) = 1.97$; p ≤.06) or ERRORS (366.9 ± 91.5, 319.5 ± 97.3, respectively, $t(35) = 1.52$; p ≤.14) (see Table 7.).

3.2. Neuroimaging results

3.2.1. Abstinent patients vs. controls

In the ROI analysis for cocaine cue reactivity, abstinent patients did not differ from controls within any of the six pre-defined ROIs utilizing a threshold of $p < 0.05$ and a contrast of COC > REST. There was no difference in the main effect of Group, $F(1,37) = 0.59$, $p \leq 0.44$. In the whole-brain analysis for cocaine cue reactivity, no regions differed between patients and controls at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method utilizing a contrast of COC > REST.

In the ROI analysis for inhibitory control, abstinent patients did not differ from controls within any of the seven pre-defined ROIs utilizing a threshold of $p < 0.05$ and a contrast of STOPS > HITS. There was no difference in the main effect of Group, $F(1,35) = 1.48$, $p \leq 0.23$. In the whole-brain analysis for inhibitory control, no regions differed between patients and controls at a threshold of $p < 0.05$, corrected for multiple comparisons using the FDR method and utilizing a contrast of STOPS > HITS.

3.2.2. Abstinent patients

To examine if activations within the dorsal and ventral striatum were associated with cocaine craving or duration of abstinence, linear regressions were conducted utilizing the beta-weights from each of the predefined ROIs as the dependent variables. We found that increased activation of the right putamen when viewing cocaine stimuli was significantly associated with increased scores on Factor 4 (Relief) of the CCQ-N (β=0.67, p=0.02) (see Table 8). The controls did not exhibit the same relationship between right putamen activation and CCQ-N Factor 4 scores (β=-0.01, p=0.99). Similarly, utilizing a contrast of POS > REST, patient's right putamen activation was not associated with CCQ-N Factor 4 scores (β=0.33, p=0.29).

We also examined whether decreased scores on the BIS-11 were predictive of increased activation during correct inhibitions. We found that increased activation of the right inferior parietal lobule when inhibiting a response was predictive of decreased scores on the Motor factor of the BIS-11 (β=-0.93, p=0.004) in abstinent patients (see Table 8). Controls did not exhibit the same relationship between right inferior parietal lobule activation and BIS-11 Motor scores (β=-0.12, p=0.71). We also found that for patients, increased activation of the right inferior /middle frontal gyrus when inhibiting a response was predictive of decreased scores on the Motor factor of the BIS-11 (β=-0.66, p=0.05) (see Table 8). Controls did not show a relationship between right inferior /middle frontal gyrus activation and scores on the Motor factor of the BIS-11 (β=-0.19, p=0.56).

4. DISCUSSION

Multiple studies have provided evidence that decreased RIC activation and increased dorsal striatal activation to drug cues are both neuromarkers of cocaine dependence. This project sought to explore whether abstinent cocaine dependent individuals show individual differences in neural activations associated with cocaine craving and impulsivity. While at the group-level we did not see any differences in neural activation patterns between patients and controls, we did observe subject-level differences that were exclusive to the abstinent CD group. We saw that increased activation of the right putamen when viewing cocaine cues was positively correlated with scores on the CCQ-N related to relief and that decreased activation of the right IPL and IFG/MFG when inhibiting a response were each negatively correlated with scores on the BIS-11 related to motor impulsivity. Because of the evidence that increased craving in response to drug

cues (Da Silveira et al., 2006; Heinz et al., 2006; Paliwal et al., 2008) and increased impulsivity (Aharonovich et al., 2006; Moeller et al., 2001) are both behaviors indicative of cocaine dependence and relapse potential ,we postulate that activations in these regions could prove to be useful predictors for increased relapse risk.

Our first significant finding was that increased activation of the right dorsal striatum in response to drug cues was positively correlated with Factor 4 (Relief) of the CCQ-N. To understand the role of the dorsal striatum in habit formation, it is first necessary to introduce the concept of instrumental behaviors which are behaviors where the result is completely dependent upon an action. It is theorized that instrumental behaviors are controlled by two separate and distinct systems referred to as the action-outcome (A-O) and stimulus-response (S-R) systems. The A-O system deals with behavior that is conducted with outcome-expectancy, that is, behavior that is based upon an awareness of the outcome. In contrast, the S-R system refers to behavior that is initiated by environmental stimuli with little regard to the actual outcome. To put it more clearly, S-R behavior refers to actions that are commonly thought of as habits, that is, behavior that is conducted with little or no conscious processing. One of the most common ways to test if a behavior has become habitual is through devaluation. That is, if a behavior is goal-directed, then responding should decrease if the outcome is devalued is some fashion. If a behavior is not goal-directed, then responding should stay the same even if the outcome is devalued (S-R behavior). The dorsal striatum is hypothesized to have a major role in habit formation and studies have shown the contribution of this structure to S-R behavior. The role of the dorsal striatum in habit formation was explored through a study which showed that rats with a dorsolateral striatum lesion did not develop S-R behaviors and instead continued to engage in A-O behavior while rats with an intact dorsolateral striatum developed S-R behaviors (Yin et al.,

2006). Thorn et al. (2010) further elucidated the role of this region by showing that activity in dorsolateral striatal neurons in rats was positively correlated with increased habitual learning on a T-maze task. Importantly, a human study examining habitual behavior also found the dorsal striatum to be associated with habit formation. Tricomi et al. (2009) utilized a free-operant task that was initially rewarded on a VI 10-s schedule and then devalued. This study showed that greater right putamen activation was associated with the appearance of habitual behavior (responding after devaluation). It should be noted that the dorsolateral striatum in rats is hypothesized to be a homologue of the human putamen (Balleine and O'Doherty, 2010). Because of the evidence implicating the putamen in habit formation, our results showing that right putamen activation at the subject-level being associated with cocaine craving provides evidence that habit-driven cocaine craving can persist even after cocaine abstinence. Furthermore, the existence of this subcortical neural activation in abstinent individuals could provide an important biomarker for relapse risk as it may illustrate that the individual still suffers from habit-driven cocaine seeking. A S-R rather than A-O reaction to cocaine-cues could make it harder for an individual to refrain from drug use.

These results also show the utility in utilizing a multi-dimensional measure of craving as only Factor 4 (Relief) of the CCQ-N was correlated with increased right putamen activation. Examples of some of the questions related to the Factor of Relief on the CCQ-N ask whether if the user was taking cocaine they “could think more clearly”, “feel more powerful”, and “could control things better”. A study of treatment-seeking CD individuals showed a negative correlation between scores on this factor and percentage of negative urine screens (Heinz et al., 2006). It is tempting to speculate that questions from Factor 4 are specifically representative of relapse risk because they capture the habit-driven aspects of cocaine dependence that when

persisting in to abstinence, are most likely to cause relapse. Therefore, we have evidence that putamen activation is associated with habit-driven behavior and that the Factor of Relief is predictive of treatment success. By demonstrating that right putamen activation in response to cocaine stimuli is correlated with the Factor of Relief (which has been shown to be correlated with cocaine relapse) leads us to speculate that greater right putamen activation in response to cocaine-cues may be a biomarker for relapse risk.

Our second significant finding is that patients who had higher scores on the Motor Impulsiveness factor of the BIS-11 showed less activation in the right inferior parietal lobule and middle /inferior frontal gyrus. The Motor Impulsiveness factor on the BIS-11 has been described as measuring the amount of spontaneous actions that an individual undertakes (Ersche et al., 2011). Higher scores on this factor indicate greater levels of motor impulsiveness. Examples of questions on this subscale ask, “I do things without thinking”, “I act on the spur of the moment” and “I can only think about one thing at a time”. Most strikingly, this factor has been shown to be negatively correlated with treatment dropout in a cohort of abstinent stimulant dependent users (Winhusen et al., 2013). We hypothesize that our finding of greater right inferior parietal lobule and middle /inferior frontal gyrus activation being correlated with less motor impulsiveness indicates a role for these two regions in relapse risk. Multiple studies have provided evidence implicating the inferior parietal lobule in inhibitory control. Using a stop signal task, Hu and Li (2012) showed that in the time period before a successful inhibition, the inferior parietal lobule was activated and this was taken by the authors to mean that this region is involved in preparatory motor inhibition. In a cued attention task, it was shown that the inferior parietal lobule was activated in response to the cue but not the task target providing more evidence for the role of this region in attentional control (Hopfinger et al., 2000). Similarly, the

right middle/inferior frontal gyrus has been implicated in multiple studies examining inhibitory control (Garavan et al., 1999; Simmonds et al., 2008). What is interesting is that both of these regions have been hypothesized to form part of what is called the fronto-parietal control network. This network is theorized to be responsible for initiating and adjusting control based on the circumstances of the situation (Dosenbach et al., 2008). It is possible then that individuals who exhibit deficits in the functioning of this control system have a more difficult time recognizing what needs to be inhibited and adjusting their behavior accordingly. In conclusion, previous studies have shown that both right inferior parietal lobule and middle/inferior frontal gyrus activations are associated with impulsivity and that the Motor Impulsiveness factor is correlated with treatment success. These results demonstrated that these two nodes of the RIC are associated with the Motor Impulsiveness factor (which is correlated with treatment drop-out) which leads us to postulate that reduced activation in these regions may be useful as a biomarker for relapse risk.

The aim of this paper was to identify whether abstinent cocaine dependent individuals show individual differences in neural activations related to cocaine craving and impulsivity. We found three significant findings where neural activations were predictive of both higher cocaine craving and impulsivity. Behavioral research has shown that higher craving and impulsivity scores are both correlated with worse treatment outcomes, including relapse (Aharonovich et al., 2006; Heinz et al., 2006; Moeller et al., 2001; Paliwal et al., 2008). Our own hypothesis is that a combination of these processes is responsible for an increased propensity to relapse. Most strikingly, the first-order factors that these cortical and subcortical regions correlate with have both been shown to be predictive of treatment success. It could be that individuals who display both neural control of craving by the dorsal striatum and deficits in the RIC leading to higher

impulsivity are most susceptible to relapse and therefore might require more intensive treatment measures. An interesting finding is that the scores of the Relief and Motor impulsiveness factors were not found to be significantly different between abstinent CD and non-using control participants, although there was a trend towards significance for both factors. However, non-using control factor scores were not found to be significant predictors of neural activation patterns. It could be that questions for these factors pertaining to craving and impulsiveness capture a very specific relapse risk phenotype associated with neural activation patterns that is not evident in abstinent CD individuals that are less susceptible to relapse. Since we hypothesize that a majority of our cohort is not as susceptible to relapse, and that these two factors are indicative of relapse risk, it would stand to reason that the scores for a majority of our abstinent CD group would not differ from non-using controls.

In contrast to current CD users, there were no between-group differences in activation of the RIC and striatum. However, at the subject-level, CD individuals displayed a positive correlation between neural activation in the right putamen and cocaine craving scores. Furthermore, CD individuals also displayed a negative correlation between impulsivity scores and neural activations in the right inferior parietal lobule and right inferior/middle frontal gyrus. Importantly, these findings occurred independently of duration of cocaine abstinence. We hypothesize that these results may be indicative of a recovery of the neural activation deficits observed in current CD individuals in most of the former users while also illustrating how some persons continue to display neural activation deficits associated with cocaine-cue reactivity and impulsivity. We hypothesize that this unique pattern of deficient neural activation corresponding to cocaine cue reactivity and impulsivity after cocaine cessation represents a significant relapse risk phenotype.

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Figure Legends.

Figure 6. Below is an example sequence of block order for one run of the cocaine cue task. There are 12 stimuli blocks (4 each of cocaine, positive and neutral pictures), 12 XY Task blocks and 4 REST blocks in one run. Stimuli blocks are always followed by either an XY Task block or a REST block. There are four runs in total.

Figure 7. The six ROIs utilized for the cocaine craving task are shown below. Regions shown in red are right lateralized while regions in orange are left lateralized. 1) Left and right caudate 2) Left and right putamen and 3) Left and right ventral striatum.

Figure 6.

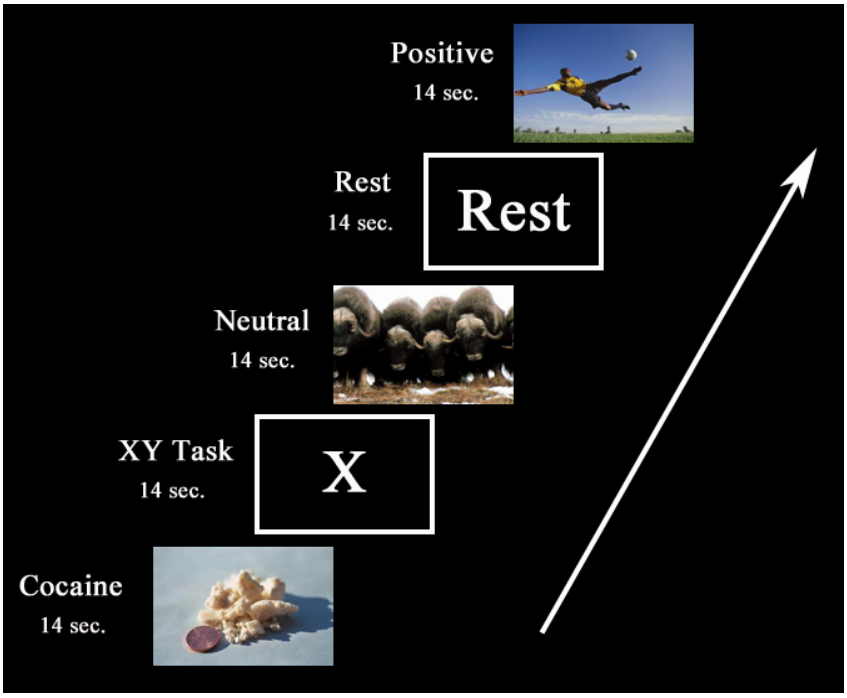
Positive
14 sec.
Rest
14 sec.
Rest
Neutral
14 sec.
XY Task
14 sec.
X
Cocaine
14 sec.

Figure 7.

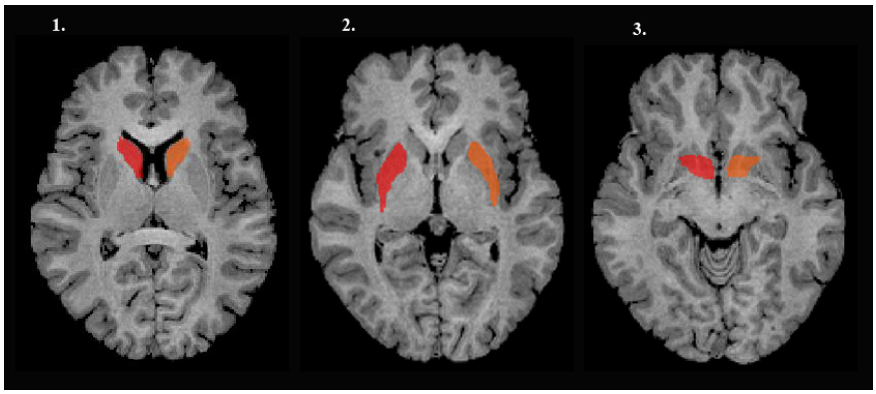

Table 7.
Behavioral data

All patients vs. All controls			
	Group		*p*
Demographics	CD (N=20)	Controls (N=19)	
Age (years)	47.8 (8.5)	42.2 (12.1)	0.10
Years of education	12.1 (1.9)	13.7 (1.9)	0.01[a]
WRAT	30.2 (5.0)	38.4 (5.6)	0.000[a]
Race (Black/Hispanic/White)	9/8/3	8/4/7	0.23[b]
Cocaine Cue Task	CD (N=20)	Controls (N=19)	
CCQ-Total	119.9 (41.3)	78.6 (24.3)	0.001[a]
CCQ-F1	1.8 (0.9)	1.2 (0.4)	0.007[a]
CCQ-F2	2.7 (1.5)	1.4 (0.8)	0.003[a]
CCQ-F3	3.6 (1.5)	1.8 (0.7)	0.000[a]
CCQ-F4	2.8 (1.1)	2.2 (0.9)	0.09
Response Inhibition Task	CD (N=19)	Controls (N=18)	
% Correct STOPS	0.7 (0.2)	0.8 (0.1)	0.09
Total STOPS	42.3 (13.0)	48.8 (13.1)	0.14
Total ERRORS	19.1 (10.9)	13.6 (9.8)	0.11
HITS RT	439.7 (54.9)	399.1 (69.8)	0.06
ERRORS RT	366.9 (91.5)	319.5 (97.3)	0.14
BRI-Total	63.7 (13.1)	53.5 (7.7)	0.006[a]
BRI-Attention	15.3 (4.6)	12.5 (2.7)	0.03[a]
BRI-Motor	22.8 (5.4)	20.1 (3.4)	0.07
BRI-NP	25.6 (6.6)	21.0 (4.2)	0.01[a]

Note: [a] Significant between patients and controls
[b] Pearson's chi-square significance level
[c] RT= Reaction Time

Table 8.
Neuroimaging data

All Patients			
Anatomical Region	Predictor	β	*p*
1. R.Putamen	CCQ-N F4	0.67	0.02
3. R. IPL/precuneus	BIS-11 Motor	-0.93	0.004
4. R. IFG/MFG	BIS-11 Motor	-0.66	0.05

GENERAL DISCUSSION

After describing the specific neurobiological deficits associated with cocaine dependence, a pressing question is whether substantial and sustainable neural recovery occurs in individuals who have abstained from cocaine use. Throughout the studies conducted, we have provided evidence that we continuously refer to as suggestive of a recovery of neurobiological function. However, it is necessary to understand what exactly we mean by the term "recovery". Cocaine dependence, as diagnosed by the DSM-IV, is contingent upon positive answers to multiple questions assessing the ability to control cocaine intake and the extent to which an individual's life is based around the act of obtaining and consuming the desired substance (DSM-IV). These questions can be understood as measuring both an individual's compulsivity to take drugs, and the inability to abstain or control the drug use. Multiple studies have examined how increased compulsivity and decreased inhibitory control contribute to severe cocaine dependence and identified the grey and white matter regions associated with these cognitive processes (Ersche et al., 2011a; Everitt et al., 2008; Moeller et al., 2005). One of the primary indicators of cocaine dependence is that the presentation of drug-associated cues can trigger craving for the substance which then leads to compulsive drug use (Everitt and Robbins, 2005; Koob and Le Moal, 2008; Pierce and Vanderschuren, 2010; Robinson and Berridge, 2008). When we refer to craving, we understand it as a cognitive process that is separate from "wanting" a drug and is better understood as a "must have" subjective state that is more intense and usually brought on by the presentation of drug-related stimuli (Everitt et al., 2008). Multiple studies have identified a relationship between level of craving and successful abstinence with lower craving levels being associated with greater treatment success (Da Silveira et al., 2006; Heinz et al., 2006; Paliwal et

al., 2008). Because of the relationship between craving and cocaine addiction, we consider the absence of severe craving in response to drug-related stimuli to be a critical component of recovery. Specifically, we posit that recovery consists of a time when drug use cannot be triggered by drug-associated cues as the behavior of the individual is no longer controlled by Stimulus-Response (S-R) actions. Instead, the individual should exhibit Action-Outcome (A-O) behavior which would mean that the person no longer has to make the choice to not use drugs because the act of using is no longer a viable or desirable option. This is nicely illustrated by a quote from Bob Savino, the director at Open Arms, Inc., a halfway house that we collaborated with on multiple projects,: "lots of medium term recovery people, say in the 2 - 5 yr range, still talk about '*How I loved getting high', or say things like 'recovery is so hard'. When I hear those statements, I usually challenge their basis, and ask why that is so. A recovered person would be able to see the connection between getting high and criminal activity, separation from family, loss of job, etc. and be able to associate that pain with the initial remembrance of euphoria, and eventually replace the euphoric recall with its reality.*" In addition to the absence of cue-induced craving, we hypothesize that recovery is also contingent on the amelioration of the inhibitory control deficits that are observed in current CD individuals (Barros-Loscertales et al., 2011; Fillmore and Rush, 2002; Kaufman et al., 2003; Verdejo-Garcia et al., 2007). These inhibitory control deficits are believed to play a part in predisposing individuals towards cocaine addiction and to make relapse more likely (Broos et al., 2012; Economidou et al., 2009; Ersche et al., 2012; Everitt et al., 2008). Multiple studies have shown that increased deficits in inhibitory control are associated with worse treatment outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Moeller et al., 2001; Streeter et al., 2008). Based upon the substantial evidence implicating drug-cue reactivity and inhibitory control deficits in the development and

maintenance of cocaine addiction, we hypothesize that recovery is a neurobiological process that occurs through an amelioration of the cortical and sub-cortical deficits related to both inhibitory control and drug-cue reactivity that are observed in current CD individuals (Ersche et al., 2011a; Garavan et al., 2008; Hester and Garavan, 2004; Kaufman et al., 2003; Moeller et al., 2005; Volkow et al., 2006, 2008). The three studies that we conducted were specifically designed to elucidate how these cognitive processes and the white matter (WM) associated with them present after the cessation of cocaine use.

Our investigations utilizing both fMRI and DTI methodologies identified multiple differences and similarities at the group-level between abstinent CD individuals and non-using controls. Specifically, our group-level fMRI investigations in **Chapters 2 and 3** of abstinent CD individuals showed an absence of the neural and behavioral deficits in inhibitory control and cue-induced craving that have been identified in current CD individuals. Additionally, our DTI investigation in **Chapter 1** showed multiple similarities and differences between abstinent users and non-users relating to WM structural integrity in regions associated with inhibitory control and attention. From these examinations we have hypothesized that at the group-level, cocaine cessation appears to be associated with an absence of the WM and neural activation deficits that have been observed in current CD groups. These results lead us to postulate that cocaine abstinence after long-term use is characterized by a state of cognitive functioning that appears to be different from that which has been reported in current CD users, but which also has both similarities and differences to non-using controls. Therefore, at the group-level, abstinence after long-term cocaine abuse appears to reflect a distinct state of cognitive functioning that we hypothesize to be possibly more important than the neural functioning associated with current

drug dependence. This hypothesis stems from the logic that cognitive functioning during this time period would have a dramatic impact on successful versus unsuccessful abstinence.

In **Chapter 1** we utilized DTI at the group-level to explore how measures of WM integrity were associated with the status and duration of abstinence. We saw that individuals who were abstinent from cocaine use exhibited multiple differences in FA values as compared to non-using controls. Additionally, we also found differences in FA values between groups of individuals who differed in duration of cocaine abstinence. Specifically, as a group, abstinent CD individuals exhibited lower FA in seven regions and expressed higher FA in two regions. Abstinent patients who were identified as short-term (ST) abstinent (0.7-5.1 weeks of abstinence) displayed lower FA in multiple regions when compared to a matched cohort of non-using controls. There were no regions with higher FA in the ST patients. Finally, the abstinent patients were classified as ST, medium-term (MT) (10-40.3 weeks) or long-term (LT) abstinent (44-102 weeks) and these groups were compared. The groups differed bilaterally in ten different regions. A number of different patterns of pairwise effects were observed between groups across these ten areas. It should be noted that these results were not always indicative of a constant increase or decrease in FA values across all three groups, in some instances only the ST and LT groups differed from one another or only the ST and MT groups differed from one another. These results provided evidence of differences in WM integrity as a function of duration of abstinence. We hypothesized that these findings could result from various neurobiological processes including cerebrovascular toxicity, restoration of WM integrity, increased presence of astrocytes, or overutilization of WM tracts that occur separately or in tandem with one another. Although there are multiple interpretations for the presence of increased or decreased WM integrity, it is possible to speculate that at the group-level, cocaine abstinence is characterized by

a distinct WM profile dependent on duration of abstinence that differs in significant ways from that of current CD individuals. For example, current CD individuals have displayed lower FA than non-using controls in the WM of the inferior prefrontal cortex (Lim et al., 2002; Romero et al., 2010), internal capsule (Lim et al., 2008), genu of the CC (Moeller et al., 2005), and the isthmus, body and splenium of the CC (Lim et al., 2008; Ma et al., 2009). The group identified as ST abstinent in our study displayed lower FA in the right anterior limb of the internal capsule, right genu of the CC, left anterior portion of the cingulum and the right cingulum superior to the isthmus of the CC than non-using controls, all regions found to have WM deficits in current CD groups relative to non-using controls. These results suggest that our recently abstinent CD group (≤5.1 weeks of abstinence) express similar WM profiles to those seen in current users. One possible explanation for this finding is that for most abstinent CD individuals, the first few weeks of cocaine cessation are a particularly sensitive time period where a distinct neurocognitive abstinent state has not yet emerged. It can also be argued that these results suggest that neurobiological changes that may reflect recovery do not even begin to take place for most individuals until at least after a few weeks of cocaine cessation, a finding that has significant implications for the treatment of cocaine dependence. When examining abstinent groups at more extended periods of abstinence (≥10 weeks), we saw that there were various differences in WM integrity that included both increases and decreases in FA between groups at varying durations of abstinence. Significantly, three regions that displayed WM deficits in the ST group relative to non-using controls showed increased WM integrity in the more extended abstinence groups. It appears then that at durations of abstinence beginning at about 10 weeks of abstinence, we see specific differences in WM integrity relative to the ST abstinent group. We hypothesize that these differences may be reflecting a distinct neurocognitive state of functioning to that of

current CD individuals. Additional evidence for substantial neurobiological changes occurring after 10 weeks of abstinence comes from Connolly et al. (2013) who by utilizing voxel-based morphometry, showed that abstinent CD individuals exhibited higher grey matter volumes than non-using controls only after 35 weeks of abstinence. Additionally, also utilizing voxel-based morphometry, Hanlon et al. (2011) showed that CD individuals with ≥1 month of abstinence showed greater WM tissue density than current users providing further evidence of distinct neurobiological profiles in abstinent versus current cocaine users. Despite the limitations of the cross-sectional experimental design, it is possible that these results could also be evidence of WM recovery as a function of duration of abstinence. To summarize, we saw decreases in WM integrity in the ST abstinent group relative to non-using controls that are very similar to what have been reported in current CD individuals. In groups with more significant durations of abstinence, we saw increased levels of WM integrity in three regions relative to the ST abstinent group. At the group level, increased duration of abstinence appears to be associated with specific WM integrity levels that are separate from those observed after relatively short periods of abstinence. Specifically, this information could result in treatment providers tailoring their programs to reflect the differences in neurobiological functioning that exist between the first few weeks of abstinence versus the first few months of abstinence.

In **Chapter 2** we examined whether there were any cortical activation differences in the response inhibition circuit (RIC) between patients and non-using controls. Even though activation differences have been observed in the RIC between current cocaine users and non-using controls (Barros-Loscertales et al., 2011; Hester and Garavan, 2004; Kaufman et al., 2003), our examination of abstinent CD individuals did not provide evidence of significant differences between groups in the RIC. Additionally, we did not find any behavioral differences between

groups in terms of d' values (a measure of both stimuli sensitivity and response bias), percentage of correct STOPS and number of correct STOPS. Of particular importance is that these neurobiological and behavioral null results were all replicated in **Chapter 3** utilizing the same task but with a completely different cohort of patients and a more powerful magnet (3T vs. 1.5T). These results suggest that at the group level, recovering CD individuals do not show the same behavioral and neural activation deficits related to inhibitory control that have been observed in current CD individuals. Furthermore, because the average duration of abstinence was 32.3 weeks in **Chapter 2** and 44.9 weeks in **Chapter 3**, it is possible that the absence of deficits is related to the more extended length of cocaine abstinence. Additionally, to further investigate the variable of duration of abstinence, we separated out 15 of the individuals in **Chapter 2** who had the shortest duration of abstinence (average = 14.6 weeks) and compared RIC activation in this group to the non-using control group. This analysis, which was not reported in our main results, also showed that there were no neural activation deficits in the RIC relative to non-using controls. What we can postulate from this analysis is that as early as 14.6 weeks, the RIC deficits in current CD individuals are absent after a combination of cocaine cessation and treatment services. These results are significant in light of the findings from **Chapter 1** which showed that the ST abstinent group ($\leq$ 5.1 weeks) displayed similar deficits to current CD individuals while groups with more prolonged abstinence displayed either increased WM integrity in regions found to be reduced in the ST group or WM profiles that were spatially distinct. Therefore, utilizing two separate methodologies and three relatively distinct cohorts of patients, we obtained evidence at the group-level that CD individuals who have obtained several months of abstinence do not display the deficits in WM and RIC cortical activation that are present in current CD individuals. We can postulate then that as a group, abstinence $\geq$ 10 weeks

may result in a unique neurocognitive state that is represented by levels of WM integrity and RIC cortical activations that are distinct from that of current CD users and appear to reflect substantial recovery. It is possible that ≥ 10 weeks of abstinence is a critical period for most individuals recovering from cocaine addiction and that treatment should take into account the fact that the neurobiological deficits that are seen in current users appear to no longer present at this stage. It is important to stress that our hypothesis is that these results may be indicative of recovery at the group-level. Therefore, they are not able to address whether certain individuals continue to display neurobiological deficits despite extended periods of abstinence. What these results do suggest is a possible time-frame when recovery is possible for a majority of individuals. However, perhaps most importantly, these results provide promising evidence that recovery (as measured by an absence of WM integrity and RIC activation deficits) is a possibility within a population of treatment-seeking, formerly CD individuals. Although it could be argued that these results represent neural states that existed before treatment, these three studies included a relatively large cohort of treatment-seeking individuals from multiple treatment centers located throughout the New York metropolitan area. Our population included individuals from very diverse socio-economic strata who had little in common besides an extended history of cocaine dependence. Although it is possible that all of these individuals possessed pre-existing differences that explain why they do not display the same neurobiological deficits observed in current users, it seems more plausible that these results occurred as a result of drug-taking cessation and competent treatment services. Regardless of the plausibility of these outcomes, our investigations all employed a cross-sectional experimental design which makes it impossible to confirm whether these results are truly representative of neurobiological change. The next logical step to confirming the temporal progression of these findings is to

perform a longitudinal examination that could track over time any changes in WM integrity and RIC neural activation.

Two of the more interesting findings from **Chapters 1 and 2** were an increase in right insula activation and right cingulum WM integrity with increased duration of abstinence. It is hypothesized that the anterior insulae are responsible for awareness, and more specifically, that these regions are responsible for representing the present situation and constantly updating how one understands his or her external and internal environment based on changing conditions (Craig, 2010). It has also been proposed that the anterior insulae are critical components of a cognitive control system called the salience network. The salience network is theorized to consist of both the anterior cingulate cortex and the anterior insula and the primary function of this network is to choose between competing external and/or internal stimuli in order to guide behavior (Seeley et al., 2007). It is hypothesized that within the salience network, the anterior insula functions to first identify relevant stimuli from a wide array of choices. Once the stimulus is identified, the anterior insula is then responsible for engaging higher-order processes that are related to processing the task at hand, and at the same time attenuating cognitive networks that are not conducive to task-related processing (Menon and Uddin, 2010). Evidence exists for lateralized activation of the anterior insula with the right anterior insula playing a specific role in engaging cognitive networks. An fMRI study showed that the right anterior insula and anterior cingulate cortex both play a critical role in switching between two major brain networks (the central executive network and the default mode network) that are each respectively activated and deactivated together when performing a cognitive task (Sridharan et al., 2008). The authors postulated that the right anterior insula may be responsible for generating signals that trigger hierarchical cognitive control mechanisms in the anterior cingulate cortex. Evidence for the role

of the right anterior insula in engaging cognitive control networks comes from a lesion study where it was shown that individuals with right anterior insula lesions were impaired in altering their behavior in response to the changing rules of a task (Hodgson et al., 2007). Based on the above arguments, it is suggested that the right anterior insula has a role in first identifying the salient stimuli and then second, engaging the proper brain networks to process the salient stimuli. In **Chapter 2** we observed that in the patients, increased right anterior insula activation during the salient stimuli was predicted by greater response success. Additionally, greater right anterior insula activation was predicted by greater duration of abstinence in the abstinent CD group. It is possible that greater engagement of the right anterior insula during motor response inhibition and greater WM integrity in the cingulum signify a more active cognitive control system in that individual. A more active cognitive control system could allow for a greater ability to inhibit drug use urges and result in more extended durations of abstinence. It should be noted that the cingulum connects the different subregions of the cingulate and does not appear to directly connect the cingulate to the anterior insula (Craig, 2009). However, these two regions do share a type of neuron referred to as "von Economo neurons" which are only found within the cingulate and the insula and possess very distinct anatomical and functional features (Watson et al., 2006). It has been proposed that it is through these specialized neurons that the anterior cingulate cortex and anterior insula are able to communicate and form the salience network (Craig, 2009). Therefore, it is possible that increased WM integrity of the cingulum may influence the functioning of the insula. That is, greater WM integrity of the cingulum could possibly be correlated with increased efficiency of the insula and that both of these structures show increased efficiency with greater duration of cocaine abstinence. Future studies could be conducted to

elucidate how the cingulum WM integrity and right insula activation interact to influence the duration of cocaine abstinence.

In **Chapter 3** we examined cocaine-cue reactivity in a group of abstinent CD individuals. At the group level, we did not see any neural activation differences in any regions of the brain between the abstinent CD group and the non-using control group when viewing cocaine-related stimuli. Previous examinations have shown that current CD individuals typically display increased cortical and subcortical neural activation when viewing cocaine-related stimuli (Garavan et al., 2000; Goldstein et al., 2009; Wilcox et al., 2011) compared to non-using controls. More specifically, it has been shown that dorsal striatal activation in response to cocaine cues is positively correlated with subjective craving levels in current CD individuals (Volkow et al., 2006, 2008; Volkow et al., 2010; Wong et al., 2006) indicating a special role for this region in cocaine craving. As discussed in **Chapter 3**, striatal activation to drug cues in cocaine addicts is hypothesized to represent habit-driven cocaine intake rather than reward-based consumption. Habit-driven cocaine intake would appear to be particularly dangerous as the individual is not in control of their cocaine use and would therefore find it harder to terminate drug use. We theorized that continued striatal activation to drug cues after cocaine cessation would be indicative of increased relapse risk. Our results are interesting as it would seem that individuals who have stopped using cocaine for a relatively short period of time show neural activations in response to cocaine stimuli that are indistinguishable from non-using controls with no history of cocaine dependence. Our cohort of abstinent CD individuals for this investigation were drug-free for an average of 44.9 weeks which is in line with the two previously discussed studies showing that recovery, as defined by an absence of the deficits seen in current CD groups, is evident in groups with $\geq$ 10 weeks of abstinence. Because we found that these deficits

do not occur in our cohort of abstinent users, a future step would be to examine the temporal progression of neural activation patterns in response to cocaine-cues. By performing a longitudinal investigation that begins at treatment onset, we could provide more definitive evidence of whether these deficits ameliorate as a result of cocaine abstinence or if they were not present at the beginning of treatment. It is possible that treatment-seeking users do not display the same neural activation patterns as non-treatment seekers and that the desire to stop cocaine use is accompanied by an absence of the neural activations associated with compulsive drug-seeking that have been identified in current users. Regardless, these studies provide evidence that a diverse cohort of treatment-seeking individuals, when examined as a group, display very similar neurocognitive profiles relating to inhibitory control and cocaine craving as individuals who have had no significant experience with cocaine throughout their entire lives.

After observing that cocaine abstinent groups do not display many of the neurobiological deficits seen in current users, we think it is necessary to postulate a possible explanation for these results. One possibility is that these group-level effects could have resulted from the patients enrollment in either an in-patient or out-patient drug treatment program. Therapy manuals released by the National Institute of Drug Abuse (NIDA) describe drug addiction as a treatable disorder and that the most effective treatment procedures consist of a combination of group and individual therapy (Daley, 2002). Research has also shown that greater participation in treatment services is related to a reduction in drug use (Worley et al., 2008). Almost all of the CD participants from our three studies were recruited from either in-patient or out-patient drug treatment facilities that conducted group and individual therapy. These facilities typically administered treatment programs that consisted of recovering addicts receiving intensive support from certified staff members who gave the impression that they were genuinely dedicated to

improving the lives of those who were enrolled in the programs they were employed by. The directors of the programs we worked with were all personally involved in everyday operations and expressed a sincere desire to see the patients who were admitted to their programs achieve sobriety. Therefore, it is tempting to postulate that a reason for the absence of neurobiological deficits in the groups we tested was due to the fact that they were enrolled in effective drug treatment programs that were efficiently run by well-intentioned directors and staffed with dedicated counselors. However, we could find no evidence on whether drug treatment results in more pronounced neurobiological recovery when compared to no treatment at all. Because we did not examine the effect of treatment on neural integrity or functioning, it is impossible to state with any certainty whether the absence of deficits is due to the receipt of addiction recovery services. A possible future study could address this issue by examining the effects of in-patient and out-patient treatment on the neurobiological functioning of recovering cocaine addicts. That is, whether active treatment versus no-treatment produces differences in WM integrity and neural activations relating to both inhibitory control and cocaine cue reactivity which could ascertain whether treatment plays a significant role in the neurobiological recovery from cocaine addiction. Furthermore, future studies could investigate which therapies or combination of therapies produce the most significant results so that limited funds could have the greatest impact on relapse prevention.

So far, this discussion has focused on the absence of neurobiological deficits at the group-level in treatment-seeking abstinent CD individuals. However, it is well known that many individuals who receive treatment for cocaine addiction will unfortunately still relapse back to drug use (Simpson et al., 2002). We, as well as others (Everitt et al., 2008), posit that this relapse is partly due to continued neurobiological deficits in both cocaine-cue reactivity and inhibitory

control. Therefore, although at the group-level we observed what we hypothesized to be neurobiological recovery, it must also be the case that some individuals continue to display these deficits either as 1) a function of abstinence duration or 2) through a decreased neurobiological resistance to relapse that occurs relatively independently of duration of abstinence. What our group-level investigations did not provide was more specific subject-level information that could be used to identify individuals who are most likely to relapse from those that are more resistant to relapse. In both **Chapters 2 and 3**, we observed more specific subject-level neurobiological differences within recovering cocaine addicts that were both dependent and independent of length of abstinence. Specifically, we saw that when abstinent CD individuals were inhibiting a prepotent response, right insula activation was positively correlated with the total amount of correctly inhibited responses and that non-using controls did not show this relationship. These results were replicated in both of our examinations of RIC activation in **Chapters 2 and 3** which utilized completely separate cohorts and different magnet strengths but maintained the same paradigm. Because controls did not express the same relationship, it is tempting to speculate that right insula activation in recovering CD individuals plays a more important role in inhibitory control than for non-users. It is possible that either as a result of drug use or as a preexisting condition, the right insula has acquired a unique role related to inhibiting motor responses. Garavan et al. (2008) showed that in current CD users, the intravenous injection of cocaine lead to improved performance on a response inhibition task that was associated with increased activation of the right insula. We speculate that hypoactivation of the right insula is related to the increased impulsivity that is observed in current users. Recent studies have suggested that increased impulsivity precedes cocaine addiction and may play a role in predisposing an individual towards cocaine use and addiction (Belin et al., 2008; Ersche et al., 2012). However,

it is not known whether hypoactivation of the right insula predates cocaine addiction. Interestingly, we also found that right insula activation when inhibiting a response was predictive of increased duration of abstinence in **Chapter 2** which examined RIC activation patterns. Because reduced inhibitory control is theorized to predate cocaine addiction, our results could be indicative of neurobiological recovery after the discontinuation of cocaine use in certain individuals. It may be that the cessation of cocaine ingestion, coupled with the receipt of addiction treatment services, resulted in a strengthening of right insula function for some patients that is reflected by increased inhibitory control. This increased right insula activation could then make it more likely to obtain lengthier durations of abstinence as there is a greater cognitive ability to inhibit inappropriate actions. Another possible role for the insula in successful cocaine abstinence is not in direct physical inhibition, but rather, in the selection of actions that should be inhibited. As discussed earlier, the anterior insula is hypothesized to be an integral part of an executive control network that identifies and chooses salient stimuli (Seeley et al., 2007; Sridharan et al., 2008). It is possible that individuals with less reactive anterior insula activation are not as likely to recognize external stimuli informing them that they should recruit inhibitory control mechanisms. The result of this less efficient inhibitory control system in some recovering addicts is that they would be less likely to employ the necessary neural networks responsible for inhibitory response and could therefore be more likely to relapse. Regardless of the mechanism, it appears that the right insula has a role in increased inhibitory control in both current and abstinent CD individuals. Because of the evidence suggesting that increased impulsivity leads to worse treatment outcomes (Aharonovich et al., 2006; Brewer et al., 2008; Moeller et al., 2001; Streeter et al., 2008), it is possible that right insula activation when inhibiting a response could help to predict treatment success. Individuals who are found to have

less reactive insula activation may need more intensive treatment measures that help to address greater deficits in inhibitory control. Identifying individuals who are most in need of focused treatment interventions will allow relatively limited funding to be dispersed in a more cost-effective manner to those most in need. However, despite the studies cited above suggesting increased impulsivity as predating cocaine addiction, the cross-sectional nature of the experiment makes it impossible to ascertain whether the relationship between right insula activation and increased inhibitory success was due to prolonged duration of abstinence or is a preexisting condition that allows for more extended periods of abstinence. Therefore, because we have provided evidence for a role of the right insula in inhibitory control and abstinence duration, it would be prudent to examine how right insula activation relates to successful abstinence by conducting a longitudinal study. This longitudinal examination would obtain fMRI measures of inhibitory control at treatment onset and at multiple temporal stages of cocaine abstinence to examine whether insula activation patterns change as a function of duration of abstinence and if they are predictive of both treatment retention and relapse status.

In **Chapter 3** subject-level effects were found in the right putamen, middle/inferior frontal gyrus and inferior parietal gyrus in abstinent CD individuals. We saw that activation patterns in these three regions were associated with behavioral measures of either cocaine-craving or impulsivity. We hypothesized that these results, when combined, provided evidence of an increased propensity to relapse in a subset of our cohort. These findings are an example of the potential utility of performing subject-level investigations in abstinent CD groups. While as a group abstinent CD individuals did not show differences in neural activation in any of these regions when compared to non-using controls, we did see subject-level differences within the abstinent CD group. A subset of individuals who do not display normalized neural activation

patterns relating to inhibitory control and cocaine craving could provide an explanation for why some recovering addicts would find it harder to stay in recovery than others. This is important as individuals seeking treatment for cocaine addiction tend to be a heterogeneous population that has been shown to respond to treatment differently (Stulz et al., 2010). However, due to the cross-sectional nature of our experimental design it is impossible to tell whether an absence of normalized neural function is due to an inadequate amount of cocaine abstinence. It could be that those individuals who continue to show cognitive deficits would display amelioration after more a more extended drug-free period. Because we have established that some patients continue to present with neural deficits, it would be necessary to conduct a longitudinal investigation to elucidate the temporal progression of these neural activation patterns in affected individuals.

It is important to build upon the work described in this thesis by investigating specific populations that are especially affected by cocaine dependence. A future direction for this work is to explore the role of HIV status on recovery from cocaine dependence. It has been shown that individuals with HIV (HIV+) display HIV-associated neurocognitive disorders (HAND) even after receiving antiretroviral treatment (Woods et al., 2009). Deficits in inhibitory control have been identified as a prominent sequela of HAND (Hardy et al., 2006; Hinkin et al., 1999; Martin et al., 2004). HAND have been associated with deficits in neurobiological functioning including decreased white matter (WM) integrity (Stubbe-Drager et al., 2012) and decreased cortical activation when engaged in inhibitory control (Meade et al., 2011). Cocaine is the most commonly abused illicit substance other than marijuana in individuals diagnosed with HIV (Korthuis et al., 2008). CD individuals who were diagnosed with HIV (CHIV+) have been shown to display more pronounced deficits in inhibitory control than CD individuals without a diagnosis of HIV (CHIV-) (Gonzalez et al., 2005; Martin et al., 2004; Meade et al., 2011).

Deficits in inhibitory control are of significant importance because they relate to an HIV+ individual's ability to maintain a strict schedule of medication-taking and engage in responsible sexual behavior (Martin et al., 2004). It is postulated that the co-occurrence of cocaine use and HIV infection are responsible for more severe HAND and even the progression of HIV to AIDS (Buch et al., 2011). Not only does cocaine dependence appear to coincide with increased HAND, it has also been shown that HIV+ status is associated with an increased probability of cocaine relapse (Shah et al., 2006). Understanding how positive HIV status affects both the neural mechanisms related to inhibitory control and relapse potential after cocaine cessation is therefore of great public health interest. The results could be used to identify neuromarkers specific to CHIV+ individuals that are associated with these two processes. Our group has examined both relapse potential and inhibitory control in abstinent CHIV- individuals and identified several cortical and subcortical regions that appear to be associated with the two cognitive processes. Therefore, we intend to examine neural activations related to inhibitory control and relapse potential in abstinent CHIV+ individuals and see how they compare to both abstinent CHIV- individuals and HIV- non-using controls.

In conclusion, our experiments suggest that the previously identified neurobiological deficits in WM integrity and neural activations related to inhibitory control and cocaine-cue reactivity are not present at the group-level in treatment-seeking CD individuals with at least a few months of abstinence. Importantly, we investigated specific regions that have been identified in multiple studies of current cocaine users as expressing neurobiological deficits utilizing very similar inhibitory control and cocaine-cue reactivity paradigms. Of particular importance is that we were able to replicate our behavioral and neurobiological null results relating to inhibitory control in two separate cohorts of individuals at two different magnet

strengths. We theorized that the absence of these deficits could be indicative of recovery resulting from both cocaine cessation and the patients being enrolled in effective cocaine treatment programs. Additionally, we also observed more specific subject-level differences within the recovering CD group that we speculated to be representative of individual levels of both relapse risk and neurobiological recovery as a function of duration of abstinence. These results were predominantly located in regions that have previously been implicated by multiple studies as being integral to cognitive control and cocaine craving. We postulated that some of these subject-level differences may be evidence of variable rates of recovery within the abstinent cocaine population and could help explain why approximately 25% of this population will go on to relapse. Both our group and subject-level results appear to support the hypothesis that recovery of the neurobiological deficits observed in current users is possible after cessation of drug use and enrollment in drug treatment programs. Although we have provided evidence that abstinent CD individuals do not display the same neurobiological deficits as current users, because of the cross-sectional nature of these experiments it is impossible to know with any certainty whether these results are due to changes that occur as a result of cocaine abstinence or were present before cocaine cessation. Therefore, to elucidate the temporal progression of any neurobiological changes that occur as a result of abstinence, we propose longitudinal investigations to examine both WM structural integrity and neural activations associated with cocaine craving and inhibitory control. These longitudinal investigations would explore not only neural changes over the course of abstinence but would also examine whether these changes can help to predict relapse potential. The work described in this thesis provides an important step in providing information on the neurobiological functioning of recovering cocaine dependent individuals. Furthermore, it provides evidence that some of the neurobiological deficits that

have been hypothesized as being responsible for initiating cocaine use or resulting from extended cocaine use are not apparent after a combination of drug cessation and treatment. This information provides hope that the neurobiological damage caused by cocaine addiction may not be permanent or that brain function can adapt to the damage. Many individuals dependent on cocaine express a sense of hopelessness about their condition and doubt that they could ever lead a normal life again. Providing evidence of brain normalization even after many years of cocaine use could provide hope to millions of recovering cocaine addicts and the individuals responsible for treating them that clinical recovery is possible and that it is never too late to start over and lead a normal life free from drugs.

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