WORKING MEMORY NETWORK CONNECTIVITY AND INHIBITORY CONTROL IN COCAINE USE

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ABSTRACT

Jennifer Y. Yi: Working Memory Network Connectivity and Inhibitory Control in Cocaine Use
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Support exists for inhibitory control and working memory deficits among cocaine users. Existing literature suggests that working memory is central in successful inhibitory control, and that working memory processes may be best captured by examining network connectivity. This study examined whether working memory network connectivity mediates the relationship between group (cocaine users versus controls) and working memory performance, and group and inhibitory control performance. Participants completed working memory and inhibitory control tasks during functional magnetic resonance imaging. Cocaine users demonstrated poorer inhibitory control performance and reduced activation during the working memory task compared to controls. Working memory network connectivity did not account for group differences in working memory or inhibitory control performance. Specific connectivity between the right insula and inferior frontal gyrus and the right precuneus and inferior parietal lobule were significantly related to working memory and inhibitory performance, respectively, suggesting the role of attention and default mode network regulation.

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CI	Confidence interval
CU	Cocaine user
DLPFC	Dorsolateral prefrontal cortex
DMN	Default mode network
DV	Dependent variable
FMRI	Functional magnetic resonance imaging
FP	Frontal pole
GIMME	Group Iterative Multiple Model Estimation
HC	Healthy control
IFG	Inferior frontal gyrus
INS	Insula
IPL	Inferior parietal lobule
IQ	Intelligence quotient
IV	Independent variable
MFG	Middle frontal gyrus
MRI	Magnetic resonance imaging
PFC	Prefrontal cortex
PREC	Precuneus
ROI	Region-of-interest

INTRODUCTION

Cocaine use continues to be a large public health concern, as cocaine is one of the most commonly abused illicit drugs in the United States. In 2014, over 14% of the U.S. population was estimated to have used cocaine sometime in their life (SAMHSA, 2015). Furthermore, in 2011, there were over 500,000 emergency department visits related to cocaine use (SAMHSA, 2013). Consequently, cocaine use places a large economic burden on society as a result of numerous costs including healthcare, drug enforcement, incarceration, and work productivity loss. Furthermore, cocaine use is associated with a multitude of negative experiences including trauma (Freeman, Collier, & Parillo, 2002; Hyman et al., 2008; Thompson, Lown, & Fullilove, 1992; Wasserman, Havassy, & Boles, 1997), risky sexual behaviors (Campsmith, Nakashima, & Jones, 2000; Hudgins, McCusker, & Stoddard, 1995; Joe & Simpson, 1995), mental disorders (e.g., depression, attention deficit hyperactivity disorder) (Brown et al., 1998; Kleinman et al., 1990; Luthar & Rounsaville, 1993; Rounsaville et al., 1991), serious medical conditions (e.g., cardiovascular events), and death (Cregler & Mark, 1986). Appropriately, there have been considerable efforts to investigate the mechanisms underlying cocaine use in order to better understand its etiology and maintenance and ideally inform prevention and treatment.

Current theories propose that the development and maintenance of substance use disorders, as well as vulnerability to relapse, can be conceptualized as a series of transitions from voluntary and casual substance-seeking and –taking behaviors to compulsive drug use involving cognitive processes such as learning, attention, and memory (Everitt et al., 2008b; Everitt & Robbins, 2005; Volkow, Fowler, & Wang, 2004). More specifically, initial substance use is

understood to be largely voluntary and primarily motivated by the reinforcing and rewarding effects of substances; however, after repeated use, various environmental and internal stimuli become associated with substance-seeking and -taking behaviors and subsequently gain saliency, procuring greater substance use (Volkow et al., 2004; Volkow & Li, 2004). Eventually, these behaviors become habitual and then inflexible and compulsive, ultimately resulting in the loss of impulse control (Everitt et al., 2008a).

Research has suggested that cognitive processes involved in executive control, namely processes responsible for the coordination and implementation of goal-directed and more complex decision-making (Royall et al., 2002; Tranel, Anderson, & Benton, 1994) may contribute significantly to these transitions and vulnerability to relapse (Norman & Shallice, 2000; Perner & Lang, 1999; Verdejo-García & Pérez-García, 2007). In particular, inhibitory control, the ability to inhibit a pre-potent cognitive or motor response (Carlson, Moses, & Breton, 2002; Luijten et al., 2014; Roberts, Fillmore, & Milich, 2011; Smith, Mattick, Jamadar, & Iredale, 2014) and working memory, the temporary storage, processing, integration, and manipulation of gained information (Engle, Tuholski, Laughlin, & Conway, 1999; Kane, Bleckley, Conway, & Engle, 2001; Kane & Engle, 2003; Owen, McMillan, Laird, & Bullmore, 2005) may be two especially important executive control processes related to compulsive cocaine use.

Inhibitory Control

One important component of executive control is inhibitory control. As a core element of behavior, this ability is necessary to implement adaptive control over everyday cognitions and behaviors, particularly to maintain appropriately efficient responses to changes in the environment (López-Caneda, Holguín, Cadaveira, Corral, & Doallo, 2014; Schachar, Tannock,

Marriott, & Logan, 1995). Difficulties with inhibitory control can manifest in several ways including increased susceptibility to irrelevant information, initiation of responses before the availability of sufficient information, or failure to correct inappropriate or incorrect responses (Schachar & Logan, 1990). In everyday behavior, such difficulties can manifest as an inability to persist at a task, engagement in behaviors without thoroughly considering potential negative consequences, a short attention span, or a tendency to engage in risky behaviors or seek out novel situations (Mitchell, Fields, D'Esposito, & Boettiger, 2005). Poor inhibitory control is a common symptom shared by a number of clinical disorders characterized by impulsivity, including attention deficit hyperactivity disorder (ADHD) (Crosbie et al., 2013; Nigg, 2001; Rubia, Smith, Brammer, Toone, & Taylor, 2014), autism spectrum disorders (ASD) (Chan et al., 2011; Mosconi et al., 2009; Sinzig, Morsch, Bruning, Schmidt, & Lehmkuhl, 2008), obsessive-compulsive disorder (OCD) (Bannon, Gonsalvez, Croft, & Boyce, 2002; Penades et al., 2007; Woolley et al., 2008), and pathological gambling (Goudriaan, Oosterlaan, De Beurs, & Van Den Brink, 2006; Leeman & Potenza, 2012).

Of particular importance, difficulties with inhibitory control are also a prominent characteristic of substance use disorders, such as cocaine use disorder (Everitt et al., 2008; Garavan & Hester, 2007; Perry & Carroll, 2008), as they are hypothesized to play a central role in the development of substance use disorders and propensity to relapse to substance use (Everitt et al., 2008; Garavan & Hester, 2007; Perry & Carroll, 2008). Although inhibitory control is generally understood as a multifaceted construct, behavioral inhibition (Diamond, 2013), a form of effortful inhibition (Nigg, 2001) is arguably most closely tied to inhibitory processes related to substance use disorders. According to Goldstein and Volkow (2011), substance use disorders can be understood as a behavioral syndrome of impaired response inhibition and salience attribution

(iRISA), described by four core symptoms: craving, intoxication, bingeing, and withdrawal. Among these cores symptoms, inhibitory control is hypothesized to play a role in all but withdrawal. Appropriately, regular use of cocaine and relapse can be understood as a failure of inhibitory control or in other words, a failure to inhibit the pre-potent response of cocaine-seeking and –taking behaviors when encountering cocaine triggers, in turn leading to a continuation of associated negative consequences (e.g., financial problems, social isolation, poorer physical health, comorbid psychiatric conditions).

Deficits in inhibitory control may be particularly relevant to the development and maintenance of compulsive cocaine use, as well as relapse given the binge-like nature of cocaine-seeking and -taking behaviors. The psychoactive effects of cocaine are characterized by a relatively short half-life, leading to rapid absorption and delivery to the brain after consumption (Benowitz, 1993). Accordingly, the effect of cocaine is short and intense, with studies reporting self-reported peak "highs" 5 to 30 minutes after administration and returns to baseline ratings after 2 to 4 hours (Fischman, 1984; Van Dyke, Jatlow, Ungerer, Barash, & Byck, 1979; Van Dyke, Ungerer, Jatlow, Barash, & Byck, 1983). As such, cocaine is often described to be taken in "binge episodes," defined as out-of-control consumption of large amounts of cocaine over an extended period time (Mutschler, Covington, & Miczek, 2001), contributing to binge-abstinence cycles, in contrast to the regimented manner that other substances (e.g., heroin, nicotine) are often used (Goldstein & Volkow, 2011; Pace-Schott et al., 2005). In particular, binge behavior may reflect greater deficits in inhibitory control, as evidenced by studies among individuals engaging in alcohol-binge behavior (Banca et al., 2016; Bozkurt, Evren, Yilmaz, Can, & Cetingok, 2013; Moreno et al., 2012; Poulton, Mackenzie, Harrington, Borg, & Hester, 2016)

and binge eating behavior (Claes, Vandereycken, & Vertommen, 2002; Kane, Loxton, Staiger, & Dawe, 2004).

Behavioral deficits in inhibitory control among cocaine users. A commonly used behavioral paradigm to measure the behavioral inhibition component of inhibitory control while attempting to dissociate these processes from other executive control processes (Simmonds, Pekar, & Mostofsky, 2008) is the Go/No-Go task. Although it was primarily designed to assess error awareness (Garavan, 2011), it is also widely utilized to measure motor inhibition. During Go/No-Go tasks, individuals are required to make a motor response to a more frequently presented stimulus and withhold to another, less frequently presented stimulus (Swick, Ashley, & Turken, 2011). Inhibitory control performance can be measured with accuracy, calculated as the number of errors of commission (i.e., failed inhibitions), such that fewer errors indicate greater inhibitory control.

Task conditions in Go/No-Go tasks can be conceptualized as "consistent mappings," as different stimuli are associated with different responses and have the potential to be learned and somewhat automated (Verbruggen & Logan, 2008). Therefore, successful inhibitory control performance requires "action restraint" (Eagle, Bari, & Robbins, 2008; Schachar et al., 2007) or in other words, withholding a pre-potent response that has not yet been initiated (Morein-Zamir & Robbins, 2014; Smith et al., 2014). Such a conceptualization can be appropriately extended to better understand the development of compulsive cocaine use such that when cocaine and cocaine-related stimuli develop consistent mappings with cocaine-seeking and –taking behaviors and become cocaine triggers. Accordingly, in order to remain abstinent, cocaine users must inhibit this pre-potent response by overcoming automatic tendencies to engage in cocaine-seeking and –taking behaviors.

Existing literature supports the existence of deficient inhibitory control among cocaine users as they demonstrate poorer performance on Go/No-Go tasks, such that cocaine users demonstrate a greater number of errors of commission compared to healthy controls (Fernández-Serrano, Perales, Moreno-López, Pérez-García, & Verdejo-García, 2012; Hester & Garavan, 2004; Hester, Simoes-Franklin, & Garavan, 2007; Kaufman, Ross, Stein, & Garavan, 2003; Lane, Moeller, Steinberg, Buzby, & Kosten, 2007; Verdejo-García, Perales, & Pérez-García, 2007; Verdejo-García & Pérez-García, 2007). These findings suggest that cocaine users may have impairments in one or more components of inhibitory control, such as stimulus recognition, maintenance of stimulus and response associations, and response selection (Simmonds et al., 2008). Cocaine dependent individuals and healthy controls also demonstrate differences in neural response to inhibitory control (Hester, Bell, Foxe, & Garavan, 2013; Hester & Garavan, 2004; Kaufman et al., 2003). More specifically, aberrant neural response to inhibitory control among cocaine users may reflect inefficient engagement and recruitment of cognitive resources for central components of inhibitory control such as appropriate utilization of rule- and goal-oriented information to inform response selection and updates of motor planning that ultimately aid in response execution (Chambers, Garavan, & Bellgrove, 2009; Chikazoe, 2010; Corbetta & Shulman, 2002; Dosenbach et al., 2007; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010; Li, Huang, Constable, & Sinha, 2006; Luijten, Littel, & Franken, 2011; Mostofsky & Simmonds, 2008; Simmonds et al., 2008).

Working Memory

In addition to inhibitory control, working memory is an important component of executive control as it is crucial for a wide array of cognitive tasks such as reasoning, comprehension, and learning (Baddeley, 2003; Conway, Kane, & Engle, 2003). Importantly,

working memory, although bearing some similarities to short term and long term memory, refers to information being utilized in order to plan and execute behaviors (Cowan, 2008). Short-term memory primarily refers to storage of a limited capacity of information that is marked by its temporary accessibility and limitations of decay over time. In comparison, long-term memory primarily refers to storage of more permanent skills, knowledge, and information, that is not as markedly limited by capacity, but that needs to be accessed by retrieval processes. Thus, working memory can be understood as providing an interface between more immediate actions and long term memory through which information is maintained and manipulated in a temporarily active state.

Working memory is generally understood to achieve active information storage and manipulation through a multi-component system. In particular, Baddeley and Hitch (1974) propose a tripartite model of working memory involving a phonological loop, visuo-spatial sketchpad, and the central executive. The phonological loop, the first storage component of working memory allows active storage of memory traces that can be retrieved and rearticulated during recall or recycled by means of rehearsal (Baddeley, 2003). The second storage component, the visuo-spatial sketchpad, provides a continuous memory record utilizing feature recognition and grouping information (Wheeler & Treisman, 2002). And lastly, the central executive, although relatively less understood than the storage components of working memory is arguably the most important as it is hypothesized to be involved in the manipulation of information and the creation of new representations, beyond simply activating stored information and representations (Baddeley, 2003). By maintaining and manipulating relevant information, working memory serves the overall function of shielding relevant and significant information

from distraction and interference by engaging attentional processes to maintain or suppress information (Engle, 2002; Kane et al., 2001).

Working memory impairment has been found in a range of clinical disorders including attention deficit hyperactivity disorder (ADHD) (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005; Rapport et al., 2008), autism spectrum disorders (ASD) (Geurts, Verté, Oosterlaan, Roeyers, & Sergeant, 2004; Hill, 2004; Verté, Geurts, Roeyers, Oosterlaan, & Sergeant, 2006), schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999; Lee & Park, 2005), and various types of traumatic brain injury (TBI) (Christodoulou et al., 2001). Of particular interest, deficits in working memory have also been found among substance users (Franken & Wiers, 2013; von der Goltz & Kiefer, 2008) and are associated with more severe cocaine use and poorer treatment outcomes (e.g., relapse) (Moeller et al., 2010; Vonmoos et al., 2014). Individuals with working memory deficits, like cocaine users, may have a decreased ability to discriminate between appropriate/relevant and inappropriate/irrelevant information in their working memory (Kane et al., 2001). Indeed, stronger working memory functioning allows for greater resources for attention-shifting, self-reflection, and reasoning in order to successfully engage in adaptive decision-making, namely choosing to resist cocaine cravings to remain abstinent rather than relinquishing to more immediately rewarding and salient alternatives of using cocaine (Barkley, 1997, 2001; Finn, 2002; Finn & Hall, 2004; Oberauer, 2002; Unsworth & Engle, 2007). According to Engle and colleagues (2002), intact working memory maintains goal-oriented information and behavioral options surrounding this information, such as the goal to maintain abstinence and decisions to abstain from cocaine-seeking and –taking behaviors. However, an individual with working memory deficits is expected to become more susceptible to interference and distractions, such as the presence of automatic associations between cocaine

triggers and cocaine-seeking and –taking behaviors that increase in saliency due to an attentional bias towards cocaine and cocaine-related stimuli. Concurrently, with limited memory storage, non-cocaine-related stimuli or the negative aspects of cocaine use become more difficult to retain in working memory (Finn, 2002), Ultimately, this difficulty in utilizing abstinence-promoting information manifests through problematic response selection and execution that instead favor the immediate reward of intoxication.

Behavioral deficits in working memory among cocaine users. Working memory tasks, such as the widely used N-Back task have been utilized to measure working memory performance. During N-Back tasks, individuals are required to make a response every time a currently presented stimulus (e.g., letter, shape, number) is the same as the stimulus presented "n" trials back with increases in "n" reflecting increases in working memory load and capacity demands placed on individuals. Thus, in order to perform successfully, individuals must have the ability and capacity to engage in continuous monitoring of incoming stimuli, while also updating and manipulating content in their working memory, such as previously presented stimuli to appropriately inform response selection (Owen et al., 2005).

In support of the role of working memory in regular cocaine use, studies utilizing N-Back tasks have shown behavioral evidence for working memory deficits among regular cocaine users. During N-Back tasks, cocaine users demonstrate poorer performance as evidenced by more errors compared to healthy controls (Albein-Urios, Martinez-González, Lozano, Clark, & Verdejo-García, 2012; Hester & Garavan, 2009; Tomasi et al., 2007a); however, some discrepant findings exist as not all studies have found differential behavioral performance on N-Back tasks between regular cocaine users and healthy controls. Bustamente and colleagues (2011) did not find group differences in accuracy between cocaine dependent men and matched healthy

controls. In contrast to studies that found differences in N-Back performance between cocaine users and healthy controls, it is not clear whether some of the cocaine dependent men in the sample had any other substance dependencies beyond self-reported recreational use of alcohol, cannabis, and amphetamine. Comorbid substance dependencies may have contributed to differential findings.

Relationship between Inhibitory Control and Working Memory

Although behavioral and neural paradigms seek to isolate the constructs of inhibitory control and working memory, these executive control processes are well understood to interact with one another in order to give rise to higher-order cognitions and behaviors. In a review article, Barrett and colleagues (2004) propose that working memory capacity is related to self-regulatory processes, such as inhibitory control that engage controlled and reflective processes as opposed to relying on more automatic and impulsive processes. Accordingly, when encountering environmental or internal stimuli that activate automatic associations, such as those between cocaine triggers and cocaine-seeking and -taking behaviors, an individual with intact working memory is expected to engage inhibitory processes while utilizing regulatory goal-oriented information as a standard of reference for action selection and execution (Hofmann, Gschwendner, Friese, Wiers, & Schmitt, 2008). Ultimately, this gives rise to self-regulatory cognitions and behaviors, such as those contributing to the maintenance of abstinence from cocaine use. In contrast, an individual with impaired working memory should have more difficulty engaging in inhibitory processes to impede pre-potent cognitions and behaviors, ultimately leading to relapse.

Building upon this understanding of inhibitory control and working memory, Bechara and Martin (2004) forward a theory of asymmetric dependence in substance use disorders that

proposes that decision-making is dependent on the intactness of working memory, while the reverse does not need to hold true. In particular, disruptions in working memory may result in disruptions in inhibitory control in substance use disorders, resulting in "myopia" for the future, such that individuals are unable to successfully operate on the contents of relevant information to inform their action selection and execution (e.g., failure to learn from repeated mistakes) (Bechara, 2005).

Additional literature more explicitly investigating the relationship between working memory and inhibitory control, as well as impulsivity among healthy controls and individuals with other psychopathology lends support to the proposed relationship between these two executive control processes (Barkley, 1997, 2001; Finn, 2002). In a series of experiments, Hinson and colleagues (2003) utilized a delay discounting task under different working memory load conditions with healthy controls in order to examine the relationship between working memory and impulsive consequences of action. When asked to make hypothetical and monetary-based delay discounting decisions under various working memory loads, individuals displayed more impulsivity, as evidenced by greater discounting of delayed rewards (i.e., preference towards short-term over long-term benefits) with increasing working memory load. Although these findings cannot speak to the relationship between specific components of working memory and inhibitory control, they demonstrate the influence of working memory on impulsivity such that working memory constraints are predictive of more impulsive decision-making.

Similar findings have been demonstrated with more diverse populations of individuals endorsing a range of behavioral disinhibition personality traits (Bogg & Finn, 2010). More specifically, behavioral inhibition and working memory capacity were assessed among two community samples of adolescents and young adults using multiple personality scales and dual

task ability tests. Bogg and Finn (2010) found a negative association between behavioral disinhibition personality traits and working memory capacity, arguing that a decreased capacity to actively store and utilize information leads to less sufficient attentional control in the presence of distractors. In turn, diminished control increases the likelihood of disinhibited decision-making. Although the working memory paradigms used in this study do not reflect the appetitive influences involved in encounters with drug triggers, it reveals the significant relationship between working memory and inhibition.

Most relevantly, Gunn and Finn (2013) examined the relationship between inhibitory processes and working memory by examining whether deficits in working memory underlie impulsivity among individuals with alcohol use disorder. Alcohol problems were assessed by measuring the severity of self-reported physical, psychological, and social problems associated with alcohol dependence, while impulsivity was quantified as a latent variable using three impulsivity scales. Additionally, working memory capacity was computed as a latent variable using two working memory tasks. Utilizing a mediational structural equation model, working memory capacity did not mediate the relationship between impulsivity and alcohol problems. However, working memory was negatively correlated with both impulsivity and alcohol problems. In an alternative model, impulsivity proved to mediate the relationship between working memory capacity and alcohol problems, such that poorer working memory capacity predicted greater alcohol problems as mediated by greater impulsivity, Although working memory capacity did not emerge as a significant mediator, this study suggests that the relationship between inhibitory processes and working memory may underlie substance use. Future studies need to be conducted in order to further investigate the directionality of the

relationship between these constructs, ultimately to better understand increased vulnerability to relapse during substance use.

Neural Deficits in Working Memory among Cocaine Users

Although behavioral deficits in working memory among cocaine users are well supported, evidence indicates the importance of understanding the system-based neural architecture contributing to working memory performance. Studies utilizing fMRI with healthy populations have largely demonstrated the central role of the prefrontal cortex (PFC) in working memory. In a meta-analysis of N-Back studies, Owen and colleagues (2005) argue for distinct working memory functions among more specific divisions of the PFC. The ventrolateral prefrontal cortex (VLPFC), primarily the inferior frontal gyrus (IFG) is thought to receive information after being initially received and inspected by the posterior parietal cortex in order to guide the implementation of current and future plans (D'Esposito, Postle, & Rypma, 2000; Dove, Manly, Epstein, & Owen, 2008; John Jonides et al., 1998; Owen & Evans, 1996; E.E. Smith & Jonides, 1998; Wagner et al., 1998). During this information transfer, the dorsolateral prefrontal cortex (DLPFC), primarily the middle frontal gyrus (MFG) is hypothesized to be involved in the use of organization strategies in order to reduce cognitive load accompanying increasing working memory demands (Bor, Duncan, Wiseman, & Owen, 2003; D'Esposito et al., 2000; Duncan & Owen, 2000; Ericcson, Chase, & Faloon, 1980; Owen, Morris, Sahakian, Polkey, & Robbins, 1996). This is further accomplished by continuous information monitoring and appropriate information manipulation. Additional neural involvement includes the inferior parietal lobule (IPL) which has been implicated in a variety of working memory processes including the encoding and recoding of temporal information, attention switching (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008; Ravizza, Delgado, Chein, Becker, & Fiez, 2004), as well as retrieval and

recollection (Cabeza et al., 2008; Vilberg & Rugg, 2008). In addition, the insula, although more typically associated with cognitive control surrounding emotion, self-awareness, interoception, and motor control has also been hypothesized to be engaged during N-Back tasks (Owen et al., 2005; Wager & Smith, 2003). Working memory processes must work in an integrated fashion with other executive processes, thus the rostral PFC/frontal pole is hypothesized to help coordinate relevant information between working memory processes and related cognitive processes (Owen et al., 2005; Ramnani & Owen, 2004).

During N-Back tasks, regular cocaine users demonstrate aberrant (i.e., both increased and reduced) activation in prefrontal regions, as well as reduced activation in the striatum, thalamus, and parietal regions compared to healthy controls (Bustamante et al., 2011; Moeller et al., 2010; Tomasi et al., 2007a). More specifically, Tomasi and colleagues (2007b) found that cocaine dependent individuals had hypoactivation in the MFG, precuneus, parietal cortex, and putamen and hyperactivation in the cerebellum compared to healthy controls. These findings are in line with behavioral findings for which cocaine dependent individuals had lower accuracy than healthy controls. According to previously discussed studies, these findings suggest that regular cocaine users may have reduced engagement in storage-related working memory functions, as well as decreased utilization of organization strategies to manage working memory demands. Reduced activation in the putamen and increased activation in the cerebellum among cocaine dependent individuals may more specifically reflect reduced ability to engage in numerical sequence learning and memory processes (Rauch et al., 1997), while attempting to compensate with greater motor control engagement (Lotze et al., 1999; Stoodley & Schmahmann, 2010). In another study, Bustamente and colleagues (2011) found that cocaine dependent individuals demonstrated hyperactivation in the right IPL compared to healthy controls despite groups

having equal behavioral performance on the task. Increased activation in the inferior parietal cortex may indicate increased, yet inappropriate engagement in attentional processes in the face of unaffected behavioral working memory performance. Similarly, Moeller and colleagues (2010) found that cocaine dependent individuals had hypoactivation in the IFG, putamen, caudate, and thalamus, and frontal pole compared to healthy controls during a delayed memory task. Like hypoactivation in the putamen, hypoactivation in the caudate may reflect impairment in stimulus-response learning (Grahn, Parkinson, & Owen, 2008). Taken together, these findings suggest that multiple components of working memory may be impaired in regular cocaine users.

Prevailing theories of neural function posit that disruptions to neural circuitry underlying cognitive and behavioral processes may be central in the etiology and maintenance of clinical symptoms (Insel et al., 2010; Price & Drevets, 2012). One method of describing neural circuitry is by examining network connectivity, which refers to contemporaneous information distribution and flow across large-scale networks distributed across the brain (Seeley et al., 2007). More specifically network connectivity allows for the examination of intrinsically organized brain circuit activity and its relation to cognition and behavior, above and beyond isolated mapping of individual neural regions gathered from localization-oriented analytic methods (Van Dijk et al., 2010). Furthermore, such examinations can provide compelling insight about how this neural organization and communication is altered in clinical disorders, such as cocaine use disorder.

Importantly, inter-individual variability network characteristics such as efficiency and connection strengths between neural regions has been found to be associated with various measures of cognitive performance (McIntosh, 2000; Sporns, 2011), most notably working memory performance. Hampson and colleagues (2006) found a positive correlation between the functional connection strength between the posterior cingulate cortex (PCC) and middle frontal

gyrus (MFG)/ventral anterior cingulate cortex (vACC) and working memory performance in healthy controls. In another study, healthy controls demonstrated a positive correlation between greater working memory network connectivity, namely between the dorsolateral prefrontal cortex (DLPFC) and left premotor cortex during a working memory task and working memory performance (Hampson, Driesen, Roth, Gore, & Constable, 2010). In addition, disruptions in functional connectivity during a working memory task have also been demonstrated among clinical populations characterized by inhibitory control deficits, such as attention deficit hyperactivity disorder (ADHD) and autism. Among adults with ADHD, Wolf and colleagues (Wolf et al., 2009) found significantly lower functional connectivity among the bilateral ventrolateral prefrontal cortex (VLPFC), anterior cingulate cortex (ACC), superior parietal lobule (SPL), and cerebellum during a working memory task compared with healthy controls. Adults with ADHD also demonstrated increased functional connectivity in right prefrontal regions, left dorsal cingulate cortex, and left cuneus. Koshino and colleagues (Koshino et al., 2005) found lower functional connectivity between the left inferior parietal lobule (IPL) and right dorsolateral prefrontal cortex (DLPFC) and increased functional connectivity between the left DLPFC and right inferior temporal lobule during a working memory task, compared to healthy controls. Taken together, these studies suggest that functional network connectivity may provide an advantageous method of examining the organization and communication of neural mechanisms contributing to better understanding of behavioral deficits among clinical populations. Despite this evidence, to our knowledge there have been no investigations of working memory network connectivity among substance users generally, and cocaine users specifically, highlighting the need to examine the role working memory network connectivity in

relation to other executive control processes such as inhibitory control in contributing to behavioral deficits.

Summary

Taken together, in order to more fully understand the deficits in inhibitory control among cocaine users that in turn have been shown to predict the frequency of cocaine use and treatment outcomes, it is imperative to consider what processes may be accounting for these deficits. In particular, based on the reviewed theoretical and empirical evidence, working memory network connectivity may play a central role in the maintenance of cocaine use and relapse due to failures to engage in inhibitory control processes.

Current Study

The current study proposes to examine the relationship between working memory and inhibitory control among cocaine users through two aims (**Figure 1)**. Aim 1 is to examine whether working memory network connectivity mediates the relationship between group and working memory task performance. It is hypothesized that greater working memory network efficiency will account for group differences in working memory task performance. Aim 2 is to examine whether working memory network connectivity mediates the relationship between group and inhibitory control task performance. Greater working network efficiency is hypothesized to account for group differences in inhibitory control task performance.

MATERIALS AND METHODS

Participants

A total of 31 cocaine users and 29 healthy controls were recruited from Baltimore and Washington, D.C. metropolitan areas using newspaper flyers, provided verbal and written consent approved by the Institutional Review Board (IRB) of the National Institute on Drug Abuse (NIDA), and participated in study procedures. Of these participants, 13 were excluded from analyses with 4 for excessive head motion (CU *n*=3, HC *n*=1), 5 for poor behavioral performance defined as greater than 2 standard deviations from the group mean (CU *n*=2, HC *n*=3), and 4 for technical problems with the fMRI (CU *n*=3, HC *n*=1). The final sample included 23 cocaine users and 24 healthy controls **(Figure 2)**.

Cocaine users were included if they endorsed regular cocaine (i.e., ≥two times per week) and nicotine (i.e., daily smoker) use during the past year prior to participation and did not meet DSM-IV (Association, 2000) diagnostic criteria for current or past substance dependence for any other substances other than nicotine as assessed by the *Structured Clinical Interview for DSM-IV-TR (SCID-I/NP)* (First, Spitzer, & Gibbon, 2002). Healthy controls were included if they did not meet DSM-IV criteria for any current or past substance abuse or dependence, and did not endorse any use of illicit substances in the past 30 days nor current smoking. Exclusion criteria for all participants included: (1) pregnancy, (2) implanted metallic devices (e.g., cardiac pacemaker, surgical clips) or claustrophobia rendering them unsafe to undergo a fMRI scan, (3) major illnesses (e.g., hypertension, diabetes, HIV), (4) neurological illness (e.g., seizure disorders, migraines, multiple sclerosis), (5) current major psychiatric disorders (e.g., borderline

personality disorder, psychotic disorders, anxiety disorders), (6) regular use of any prescription, over-the-counter, or herbal medications that may alter central nervous system function, cardiovascular function, or neuronal-vascular coupling, (7) cognitive impairment (i.e., IQ<85) as assessed by the *Wechsler Abbreviated Scale of Intelligence (WASI-II)* (David Wechsler & Hsiao-pin, 2011), and (8) acute drug intoxication or positive urinalysis results at the start of the study.

General Procedure

The present study includes data from a larger assessment battery **(Figure 3)**. Following informed consent procedures, a pre-scan assessment was administered to all participants, including a MRI Screening Form to determine a participant's eligibility and safety to undergo an MRI scan, a test for current drug use (Triage®), alcohol use (breathalyzer), and pregnancy, the vocabulary portion of the *Wechsler Abbreviated Scale of Intelligence* (WASI-II VIQ) (D. Wechsler, 2011)*, Fagerström Test for Nicotine Dependence* (FTND) (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), and a questionnaire assessing frequency of substance use across 11 drug classes in the past year prior to participation. All cocaine users smoked a cigarette 60 minutes prior to entering the MRI scanner for structural and functional MRI scans. At the end of the visit, participants were debriefed and compensated.

Measures

Self-report and interview measures.

Demographics Form. A Demographics Form was used to collect basic demographic information such as age, ethnicity/race, and gender.

Fagerström Test for Nicotine Dependence (FTND) (Heatherton et al., 1991). The FTND is a 6-item, self-report questionnaire used to measure severity of nicotine dependence during the past 30 days. The FTND demonstrates good test-retest reliability with correlation coefficients

ranging from 0.49 to 0.97 (all *p*s<0.001) on individual items (Pomerleau, Carton, Lutzke, Flessland, & Pomerleau, 1994). HC were excluded if they reported being a current smoker.

MRI Screening Form. The MRI Screening Form was used to help determine a participant's eligibility and safety to undergo an MRI scan. It includes questions regarding MRI contraindications such as metallic implants (e.g., cardiac pacemakers, braces, screws), claustrophobia, and pregnancy.

Structured Clinical Interview for DSM-IV-TR Non-Patient Version (SCID-I/NP) Substance Use Disorders Module E (First et al., 2002)**.** This clinician-administered, non-patient version of the SCID Substance Use Disorders module is specifically designed for research settings. It has been found to demonstrate fair to excellent median interrater reliability for both alcohol (κ=.65-1.0) and drug abuse and dependence (κ=.77-1.0) (Lobbestael, Leurgans, & Arntz, 2011; Zanarini et al., 2000). It has also been found to demonstrate fair to good test-retest reliability for alcohol abuse and dependence (κ=.77), as well as drug abuse and dependence (κ=.76) (Zanarini et al., 2000). It was used to determine current or past substance abuse or dependence, categorized by seven separate drug classifications (i.e., alcohol, amphetamine, cannabis, hallucinogen, opioid, phencyclidine, sedative/hypnotic/anxiolytic).

Timeline Followback (TLFB) (Sobell, Maisto, Sobell, & Cooper, 1979). The TLFB is used to obtain self-reported estimates of substance use in the past 30 days using a calendar format. Interviewers worked backwards from the visit date, day by day and asked participants to identify personally meaningful events (e.g., birthdays, holidays) to facilitate recall of substance use. *Frequency of cocaine use* was calculated as the percentage of days in which the participant used cocaine during the past 30 days. The TLFB has demonstrated high test-retest reliability with intraclass correlation coefficients (ICC) ranging from 0.70 to 0.94 (all *p*s<0.001) among samples

of outpatient substance abuse patients (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000). In addition, it has demonstrated good convergent and discriminant validity from other measures, such as the Addiction Severity Index (ASI) (McLellan, 1985), Michigan Alcoholism Screening Test (MAST) (Selzer, 1971), and the Drug Abuse Screening Test (DAST) (Skinner, 1982) and good agreement with patients' self-reported and collaterals' report of patients' substance use and urinalysis results (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000).

Wechsler Abbreviated Scale of Intelligence (WASI-II) (Wechsler & Hsiao-Pin, 2011). The WASI-II is an abbreviated version of the Wechsler Adult Intelligence Scales (WAIS-III) (Wechsler, 1997) that provides intelligence quotient (IQ) measures. The Vocabulary subtest of the WASI-II was administered during the screening procedure. Cognitive impairment and learning disabilities have been found to be associated with aberrant neural activity during task, thus, participants were deemed ineligible for the study if they had a Vocabulary subtest score below 48, corresponding to a full IQ of below 85. In addition, this criterion was implemented to ensure that participants were capable of providing informed consent and comprehend study instructions.

Working memory and inhibitory control tasks.

Working memory task. All participants completed an N-Back task (Yang, Ross, Zhang, Stein, & Yang, 2005) utilized to assess working memory, as shown in **Figure 4**. The block design task consists of an alternating block design between three conditions: a baseline vigilance condition (0-back) and two working memory conditions (1-back and 2-back). During the baseline vigilance condition, participants were instructed to press a button on a joystick whenever an "X" was presented. During the working memory conditions, participants were

instructed to press a button on a joystick whenever the letter displayed was the same as the letter presented "n" ago (e.g., one or two presentations ago). In total, there are 12 blocks, each 30 seconds long, consisting of either 15 1-back or 15 2-back trials. The duration of the entire task was approximately 10 minutes. *Working memory task performance* was measured by accuracy, calculated as the number of correct working memory trials ("hits").

Inhibitory control task. All participants completed a Go/No-Go task (Kaufman et al., 2003). This event-related design task is used to assess motor inhibitory control, as shown in **Figure 5**. Participants viewed a 1-Hertz serial stream of alternating letters ("X" and "Y" as "Go" stimuli) and were instructed to continuously press a button on a joystick for each stimuli, but inhibit their responses when Go stimuli were presented consecutively (repeated second stimuli as lure/"No-Go" stimuli). Individual ability levels of participants were determined during a practice session in the mock scanner before the MRI scan. Participants practiced four levels of difficulty for which the stimuli presentations were varied at 600, 700, 800, and 900ms. Following the stimuli presentations, a blank screen was presented in order to take up the remainder of the 1-Hertz serial stream of alternating letters. The level of difficulty for each participant was selected in order to most closely achieve near equal numbers of successful inhibitions and errors of commission, as well as comparable behavioral performance across participants in each group. The duration of the entire task was approximately 15 minutes. *Inhibitory control task performance* was measured with the number of successful inhibitions given the presence of group differences.

Experimental Design Considerations

Although self-report measures of impulsivity-related constructs are widely utilized, we decided to measure inhibitory control with a laboratory-based behavioral task (i.e., Go/No-Go).

There is mixed evidence regarding alignment of self-report and laboratory measures of impulsivity-related constructs among substance users (Meda et al., 2009; Reynolds, Ortengren, Richards, & de Wit, 2006; Sharma, Markon, & Clark, 2014), with the most critical evaluations asserting that the two modalities of measurements may assess different components of the construct. Such arguments may originate from general concerns surrounding the face validity of self-report measures due to factors such as socially desirable responding (SDR) (Cyders & Coskunpinar, 2011). Furthermore, there is a high degree of variability in self-reported behaviors among substance users, such as frequency and severity of substance use (Maisto, McKay, & Connors, 1990). Thus, a behavioral measure of inhibitory control may be a more reliable, valid method of capturing differences in inhibitory control performance between cocaine users and healthy controls.

Studies have utilized a variety of behavioral paradigms in order to measure inhibitory control, predominantly relying on Go/No-Go, Stop-Signal, and Stroop tasks. As discussed earlier, the Go/No-Go most accurately models the need to inhibit the pre-potent response of engaging in cocaine-seeking and -taking behaviors. The task accomplishes this by requiring successful "action restraint," (Eagle et al., 2008; Schachar et al., 2007) involving withholding a pre-potent response that has not yet been initiated in response to lure/no-go stimuli (Morein-Zamir & Robbins, 2014; Smith et al., 2014). In contrast, stimuli in Stop-Signal tasks can be conceptualized as "inconsistent mappings," (Verbruggen & Logan, 2008) requiring individuals to withhold a response when a go signal is followed by a stop signal. Appropriately, this inhibitory action can be understood as "action cancellation," (Eagle et al., 2008; Schachar et al., 2007) as a response that has already been initiated, needs to be withheld. When cocaine users encounter cocaine triggers, they need to engage in action selection from a variety of cognitive and

behavioral alternatives, ideally one centered on withholding, as opposed to responding to a stimuli that explicitly prompts an inhibitory action.

Behavioral and Task Data Acquisition and Analysis

Preliminary analyses. Initial analyses were conducted among study variables in order to (1) examine significant violations of normality and (2) identify potential covariates of study variables, thus prompting their inclusion in analyses of Aims 1 and 2. Normality was assessed by examining histograms of frequency distributions, generating normality probability plots of all variables of interest, and conducting Shapiro-Wilk tests. No transformations to the data to approximate normality were deemed necessary. Theoretically relevant sociodemographic variables selected *a priori* (e.g., age, gender, ethnicity/race) were analyzed using Pearson's correlations, chi-square analyses, and independent samples t-tests and were included as covariates if they were found to be significantly related to study variables.

N-Back and Go/No-Go task performance data acquisition and analyses. Task performance data for the N-Back and Go/No-Go tasks were collected using E-Prime Version 2.0 (Schneider, Eschman, & Zuccoloto, 2007). Task performance variables for the N-Back (e.g., hits, response time) and Go/No-Go (e.g., successful inhibitions, errors of commission and omission, response time) were extracted from E-Prime, exported into Microsoft Excel Version 14, and entered into SPSS Version 22 (IBM Corp, 2013). Descriptive statistics (i.e., mean and standard deviations) were calculated for all study variables. Participants were considered outliers for task performance and excluded from further analyses if their N-Back and/or Go/No-Go task performance was two standard deviations or greater from group means. Independent samples t-tests were conducted in order to examine group differences in N-Back and Go/No-Go task performance.

Imaging Acquisition and Analyses

Acquisition. All imaging data was collected on a Siemens 3T Magnetom Trio MR Scanner (Siemens, Erlangen, Germany) with a 12-channel head coil at NIDA Intramural Research Program (IRP) in Baltimore, Maryland. Blood oxygen level-dependent (BOLD) functional echo-planar imaging (EPI) T2*-weighted images were acquired in 39 axial slices (thickness=4mm) covering the whole brain with repetition time (TR)/echo time (TE)=2s/27ms, field of view (FOV)=220x220mm, flip angle (FA)=78°, in-plane resolution=3.44x3.44mm, and acquisition plane=30° axial to coronal, AC-PC (Deichmann, Gottfried, Hutton, & Turner, 2003). Whole-brain T1-weighted structural images (MPRAGE) (1mm^3 isotropic voxels, TR/TE=1.9s/3.51ms, and FA=9°) were also collected for anatomical reference.

Pre-processing. Anatomical and functional MRI data was analyzed using FSL FEAT (FMRI Expert Analysis Tool) Version 6, part of FMRIB'S Software Library (FSL, www.fmrib.ox.ac.uk/fsl). Pre-processing of data included motion correction (MC) with MCFLIRT to ensure consistency between voxel positions and actual anatomical locations, high-pass temporal filtering (Gaussian-weighted least squares straight line fitting with sigma=50s) to increase signal to noise ratio, grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor to warp images to fit to the standard template brain, and skull-stripping of structural images with the Brain Extraction Tool (BET). Functional MRI scan data were excluded if relative mean displacement was greater than 0.3mm in any plane. Functional MRI data were registered to the T1-weighted anatomical data and the structural MRI data to the 2mm Montreal Neurological Institute (MNI) standard-space template using FMRIB's Linear Image Registration Tool (FLIRT) with an affine transformation using 12 degrees of freedom (i.e., linear transformation) to match the sizes and positions of the acquired images.

Whole-brain analysis. In order to examine recruitment and engagement of working memory processes during the working memory task and potential group differences, within- and between-group whole brain activation maps were generated for the contrast [(2-Back)-(1-Back)], including demeaned values of the gender covariate. FMRIB's Local Analysis of Mixed Effects (FLAME) Stage 1. *Z* Gaussianized *T/F* statistic images were thresholded at $Z>3.0$ and a corrected cluster significance threshold of $p=0.05$.

Regions-of-interest (ROIs) selection. *A priori* regions-of-interest (ROIs) were selected from Wesley and Bickel's (Wesley & Bickel, 2014) meta-analysis of foci from working memory studies, and included the right and left inferior parietal lobule (R. and L. IFG), frontal pole (R. and L. FP), middle frontal gyrus (R. and L. MFG), inferior frontal gyrus (R. and L. IFG), right insula (R. INS), and right precuneus (R. PREC). They were created from lateralized masks from the Harvard Oxford Subcortical and Cortical probabilistic atlases set at 10% and overlaid on the MNI152 standard-space T1-weighted average structural template image. The average time-series for the set of voxels defined by each ROI for each run of the N-Back task was extracted using the fslmeants command-line utility and then combined across both runs.

Working memory network functional connectivity. Individual-level data was compiled in a *t*-by-*r* matrix, where *t* was the set of time points (length of a single time-series) and *r* was the number of *a priori* ROIs (10) for each participant. Both group- and individual-level models were selected using the Group Iterative Multiple Model Estimation (GIMME) program (Gates & Molenaar, 2012). GIMME has been utilized successfully to produce connectivity maps in a significant number of studies, most notably in the investigation of substance use including the examinations of the relationship between functional connectivity and cognitive performance among nicotine-deprived smokers (Nichols, Gates, Molenaar, & Wilson, 2014) and between

functional connectivity, cognitive control, and emotion processing among alcohol users (Beltz et al., 2013). GIMME utilizes an iterative search procedure in order to determine the best fitting model for the group data, starting with a null (empty) model. Lagrange Multiplier equivalents, (i.e., modification indices) are compiled in a matrix indicating how much variation in the ROI signal would be explained if the specific path of interest is freed (Gates, Molenaar, Hillary, Ram, & Rovine, 2010). The procedure consists of selecting paths in a forward selection procedure until the model is no longer significantly improved. This was first executed at the group-level that maximized the fit for the majority of the participants' models in the specified group, producing the network connectivity map among the *a priori* ROIs. This was then executed at the individual-level to refine each participant's model to account for individual differences, beginning with the paths found in the group-level search. Non-significant paths are pruned from the individual-level models, producing models that favor parsimony (reduced complexity). GIMME generated (1) *network connectivity efficiency*, or the number of contemporaneous paths in the working memory network, (2) *network connectivity strengths*, or the average beta weight for all retained paths in the working memory network, and (3) *individual path strengths*, or the individual beta weights for all retained paths. More specifically, greater *network connectivity efficiency* will be reflected by a smaller number of contemporaneous paths (less complexity), greater *network connectivity strengths* and *individual path strengths* are reflected by larger average beta weights. Past studies have utilized similar mediation analyses to examine connectivity as a mediator between sensation-seeking and alcohol use in youth (Weiland et al., 2013) and testosterone and alcohol use in adolescents (Peters, Jolles, Van Duijvenvoorde, Crone, & Peper, 2015)

Study Aims

In order to examine whether working memory network connectivity mediates the relationship between group and working memory task performance (**Aim 1**) and inhibitory control processes (**Aim 2**), two separate parallel mediation models were tested per Aim using the PROCESS macro for SPSS (Hayes, 2012) **(Figures 6 and 7)**. This mediation analysis estimated the total effect (i.e., direct + indirect effects), direct effects of the independent variable (IV) on the DV (path c'), IV on the mediator (path a), the mediator on the DV (path b), and indirect effects of the IV on the DV through the mediator, according to principles of mediation (MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002). For the first parallel mediation model, the independent variable (IV) was group, the mediators were working memory network connectivity efficiency and strength, and the DV was working memory task performance (accuracy; **Aim 1**) and inhibitory control task performance (successful inhibitions; **Aim 2**). For the second parallel mediation model, the mediators were the individual path strengths. PROCESS generated individual beta coefficients (unstandardized weights), standard errors (SE), t-values, and *p*-values for each estimated direct effect for each path. Significance testing of the indirect effects was calculated using 1000-sample, bias-corrected (BC) bootstrapping to compute 95% confidence intervals (CI). If zero was not included in the 95% CI, it was argued that the indirect effect was significant at $p<0.05$.

Sample size considerations. Mediation analyses for both Aims utilized bootstrapping procedures programmed into the PROCESS macro for SPSS (Hayes, 2012). Bootstrapping procedures are ideal to utilize when determining the significance of potential mediators in analyses with sample sizes as small as 20 participants (Efron & Tibshirani, 1994; Preacher &

Hayes, 2004). Accordingly, the bootstrapping procedures will direct SPSS to draw 1000 sample indirect effects with replacement using the existing data as the proxy "population" data.

RESULTS

Sample Characteristics

Sample characteristics are presented in **Table 1**. There were no group differences in age, ethnicity/race, IQ, and education. There were significantly more females among the healthy controls than the cocaine users. Thus, gender was included as a covariate in all group analyses. Cocaine users reported additional use of substances, including alcohol, heroin, marijuana, methamphetamine, ecstasy, sedatives, phencyclidine (PCP), and prescription opiates (**Table 2**).

Task Performance

Task performance on the N-Back and Go/No-Go tasks is presented in **Table 3**. For the N-Back, there were no group differences in task performance (accuracy) or response time on correct trials. For the Go/No-Go, cocaine users had a significantly more errors of commission and less successful inhibitions compared to healthy controls. There were no group differences in errors of omission or response time on correct trials. These results suggest that cocaine users are performing comparably to healthy controls on the N-Back task, but not the Go/No-Go task, particularly in terms of their ability to withhold responses when necessary.

Association between Sample Characteristics and Task Performance

For the N-Back task, task performance across all working memory trials was significantly associated with IQ (r=0.54, p<0.001). Task performance was not significantly associated with gender (t(45)=-0.11, p=ns), age (r=-0.18 p=ns), or ethnicity/race (F(3,42)=2.07, p=ns). Among cocaine users, task performance was not significantly associated with level of nicotine

dependence (r=-0.05, p=ns). For the Go/No-Go task, task performance was not significantly associated with gender ($t(45)$=-1.12, p=ns), age (r=-0.06, p=ns), ethnicity/race ($F(3,42)$=0.14, p=ns), IQ (r=0.09, p=ns), or level of nicotine dependence (r=-0.16, p=ns).

Whole Brain Neural Activation in Response to Working Memory Load

Whole brain neural activation in response to working memory load during the N-Back was obtained with the contrast [(2-back)-(1-back)]. Cocaine users and healthy controls displayed expected neural response to working memory load in regions implicated in components of working memory and additional cognitive control processes, in line with working memory literature (Baddeley, 2003; Owen et al., 2005; Wager & Smith, 2003; Wesley & Bickel, 2014) (**Tables 4 and 5**). Such regions included the middle frontal gyrus (organizational strategy use, manipulation of information), inferior frontal gyrus (attentional control, storage, retrieval), inferior parietal lobule (encoding, rehearsal), frontal pole (integration), precentral and postcentral gyri (sensorimotor integration) suggesting individuals reliably recruited and engaged working memory processes in response to working memory load.

Healthy controls demonstrated greater activation than cocaine users in response to working memory load in the right frontal pole, right and left middle frontal gyrus, right supramarginal gyrus, and right paracingulate gyrus (**Table 6 and Figure 8)**. Cocaine users did not demonstrate greater activation than healthy controls in any regions. These findings are in line with previous studies that also provide evidence for decreased activation in regions implicated in working memory processes among cocaine users, suggesting functional differences in recruitment and/or engagement of working memory processes among cocaine users and healthy controls in response to working memory load.

Working Memory Network Connectivity as a Mediator Between Group and Working Memory Task Performance (Aim 1)

Model 1 (Table 7)

Total and direct effects. There were no significant total or direct effects of group on working memory network connectivity efficiency or strength. In addition, there were no significant direct effects of working memory network connectivity efficiency or strength on working memory task performance.

Indirect effects. All bias-corrected, 1000-sample bootstrapped 95% confidence intervals contained zero, suggesting that no within network working memory network connectivity parameters emerged as significant mediators between group and working memory task performance.

Model 2 (Table 7)

Total and direct effects. There were no significant total effect or direct effects of group on individual working memory network connectivity paths. There was a significant direct effect of the individual working memory network connectivity path from the right insula (R. INS) to the right inferior frontal gyrus (R. IFG), in line with the 95% confidence interval that did not include zero. There were no other significant direct effects of on individual working memory network connectivity paths on working memory task performance.

Indirect effects. All bias-corrected, 1000-sample bootstrapped 95% confidence intervals contained zero, suggesting that no within network working memory network connectivity parameters emerged as significant mediators between group and working memory task performance.

Working Memory Network Connectivity as a Mediator Between Group and Inhibitory Control Task Performance (Aim 2)

Model 1 (Table 8)

Total and direct effects. There was a significant total effect of group on inhibitory control task performance (**Table #),** as well as significant direct effects of working memory network connectivity efficiency and strength on inhibitory control task performance, in line with the 95% confidence intervals that did not include zero. There were no other direct effects of group on working memory network connectivity efficiency or strength. In addition, there were no significant direct effects of working memory network connectivity efficiency or strength on inhibitory task performance.

Indirect effects. All bias-corrected, 1000-sample bootstrapped 95% confidence intervals contained zero, suggesting that no within network working memory network connectivity parameters emerged as significant mediators between group and inhibitory control task performance.

Model 2 (Table 8)

Total and direct effects. There were no significant total effect or direct effects of group on individual working memory network connectivity paths. There was a significant direct effect of the individual working memory network connectivity path from the right precuneus (R. PREC) to the right inferior parietal lobule (R. IPL), in line with the 95% confidence interval that did not include zero. There were no other significant direct effects of on individual working memory network connectivity paths on inhibitory control task performance.

Indirect effects. All bias-corrected, 1000-sample bootstrapped 95% confidence intervals contained zero, suggesting that no within network working memory network connectivity

parameters emerged as significant mediators between group and working memory task performance.

DISCUSSION

This study examined group differences between cocaine users and healthy controls in neural response to a working memory task and whether working memory network connectivity accounts for group differences in both working memory and inhibitory control task performance. As expected, and in line with previous working memory studies (Moeller et al., 2010; Tomasi et al., 2007b), cocaine users demonstrated reduced activation during the working memory task compared to healthy controls in neural regions implicated in working memory processes, including the bilateral middle frontal gyri, right pre- and post-central gyri, and right frontal pole. In addition, in line with past inhibitory control studies (Fernández-Serrano et al., 2012; Hester & Garavan, 2004; Hester et al., 2007; Kaufman et al., 2003; Lane et al., 2007; Verdejo-García et al., 2007; Verdejo-García & Pérez-García, 2007), cocaine users demonstrated deficits in inhibitory control task performance, compared to healthy controls. Contrary to study hypotheses, working memory network connectivity did not account for group differences in working memory or inhibitory control task performance.

Although the primary aims were not supported, it is of note that particular characteristics of working memory network connectivity were significantly associated with working memory and inhibitory control task performance. First, the strength of the specific functional connection from the right insula (R. INS) to the right inferior frontal gyrus (R. IFG) was significantly associated with working memory task performance, such that greater connection strength was significantly associated with decreased task performance. The R. INS and R. IFG are well

understood to be involved in a larger cognitive control network (Cole & Schneider, 2007), including the preparation and execution of goal-oriented tasks, such as those involving working memory processes (e.g., inhibition of distractors, maintenance, rehearsal) (Chein & Fiez, 2001; McNab et al., 2008). Other studies have highlighted the importance of the connection between the insular cortex and R. IFG. Of particular note, Cisler and colleagues (2013) found stronger connectivity between the insula and the R. IFG among cocaine dependent individuals compared to healthy controls. More specifically, the R. INS and R. IFG are hypothesized to be critical components of the right lateralized ventral attentional system, supporting the allocation of attention to salient, unpredicted stimuli and spatial organization (Corbetta, Kincade, & Shulman, 2002). Although there were no significant group differences in the strength of this specific path between cocaine users and healthy controls, greater connection between the R. INS and R. IFG may thus reflect generally greater inefficiency, as reflected by a need for compensatory recruitment of attentional resources and monitoring, as working memory load increases.

Second, overall working memory network efficiency and strength and the strength of the specific functional connection from the right precuneus (R. PREC) to the right inferior parietal lobule (R. IPL) were significantly associated with inhibitory control task performance, such that greater overall network efficiency and strength and specific path connection strength were significantly associated with increased task performance. The precuneus and inferior parietal lobule are understood to be critical components of the default mode network (DMN), which is typically described as being more active or "on-line" during rest or passive conditions (Raichle, 2015). During external-based tasks, like working memory tasks, reduction of DMN activity is believed to be critical to allocate neural resources to the task-positive network (TPN), including the recruitment and engagement of higher order cognitive processes (Fox et al., 2005).

Moreover, greater reduction of DMN activity has been found as task difficulty and cognitive demand increase (McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003). Thus, this finding is in line with other studies that have provided evidence for strong functional coupling between DMN regions during working memory tasks, which is attributed to the facilitation and monitoring of the DMN throughout the task execution (Gilbert, Simons, Frith, & Burgess, 2006; M. Hampson et al., 2006). Regulation of the DMN may contribute to greater allocation of neural resources to working memory processes, as well as those, in turn contributing to inhibitory control task performance.

Given the lack of significant group differences between cocaine users and healthy controls in working memory network connectivity, it is important to consider possible factors that may contribute to these findings. Although previous working memory studies among cocaine and other substance users have utilized versions of the well-validated N-Back task, it is important to determine whether the N-Back task with two working memory conditions is the most appropriate paradigm to utilize in order to examine differences in working memory network connectivity. Group differences in neural response to a working memory task have been well document using both whole-brain and region-of-interest (ROI) analyses; however, it is possible that an N-Back task with greater working memory demands (e.g., 3- or 4-Back) may be a better paradigm to examine working memory network connectivity. While under greater cognitive load (i.e., working memory load), efficient communication between neural regions may be especially critical in the recruitment, allocation, and engagement of neural resources.

Additional factors that may be contributing to these findings are the basic eligibility criteria used to recruit cocaine users. Cocaine users were required to endorse regular use of cocaine, but were not required to meet criteria for DSM-IV substance dependence. However,

based on self-report measures, only 25% of participants reported using cocaine greater than or equal to four times a week, 50% of participants reported using cocaine greater than or equal to two times a week, and 12.5% of participants reported using cocaine only greater than or equal to two times a week. As such it is likely that this sample contains recreational cocaine users who according to past work, do not exhibit the same cognitive deficits as regular cocaine users. In one study, the magnitude of inhibitory control deficits of recreational cocaine users, as defined as using cocaine monthly for a minimum of two years and not meeting DSM-IV substance abuse criteria, was proportional to the degree of life cocaine exposure (Colzato, van den Wildenberg, & Hommel, 2007). In another study with the same recreational cocaine use criteria, recreational cocaine polydrug users did not demonstrate working memory deficits with equivalent performance to healthy controls (Colzato, Huizinga, & Hommel, 2009). Taken together, a sample including only participants meeting criteria for cocaine use disorder may reduce unintended variability in the data.

In addition to high variability in cocaine use frequency and severity, cocaine users in the study were required to be current smokers, while healthy controls could not meet that criterion. Given that all cocaine users were also all current smokers, the influence of nicotine may have contributed to the lack of group differences in working memory task performance and network connectivity. Past studies have demonstrated the positive effects of nicotine compared to placebo on working memory performance, as measured by greater accuracy (Ernst et al., 2001; Kumari et al., 2003) and reduced response times (Heishman, Kleykamp, & Singleton, 2010) on accurate trials. In addition, nicotine has also been found to contribute to increased neural activity in regions implicated in working memory (e.g., anterior cingulate cortex, superior parietal cortex) (Kumari et al., 2003). In this study, cocaine users smoked a cigarette 60 minutes before the start

of their fMRI scan, thus nicotine could have contributed to enhanced working memory task performance, contributing to comparable working memory task performance between cocaine users and healthy controls.

Taken together, findings from this study suggest the contribution of particular characteristics of working memory connectivity, such as attention allocation and engagement, and regulation of the DMN in working memory and inhibitory control task performance.

Limitations and Future Directions

Several limitations of this study are of note. Participants were recruited from the community, therefore, included non-treatment-seeking cocaine users. Accordingly, the results cannot be extended to treatment-seeking cocaine users at this time. In addition, the study findings should be cautiously limited to an understanding of the verbal, single-letter working memory task utilized. Thus, it is important to determine if and how other N-Back tasks using different modalities of stimuli (e.g., spatial, auditory) may reflect task performance and neural response differences between cocaine users and healthy controls. This is especially critical given that literature has demonstrated that working memory operates differently across modalities (Reuter-Lorenz et al., 2000; Smith, Jonides, & Koeppe, 1996). For example, verbal working memory has been found to activate primarily the left hemisphere, including the inferior parietal and lateral frontal blobs, supramarginal gyrus, and premotor areas (Reuter-Lorenz et al., 2000; Smith et al., 1996), while spatial working memory has been found to activate a more dispersed pattern of neural activation across both hemispheres, including the inferior frontal and posterior parietal lobes, right occipital gyrus, right premotor area, and right dorsolateral prefrontal cortex (Jonides et al., 1998; Smith et al., 1996; Smith, Jonides, Marshuetz, & Koeppe, 1998). Furthermore, the modality is also important to consider in terms of what kind of stimuli are most relevant to

cocaine use and related experiences. Finally, the N-Back task utilized in this study was limited to only two working memory conditions, the 1- and 2-Back. Although more demanding working memory conditions (e.g., 3- or 4-Back) will likely result in poorer task performance, a greater working memory load may provide more insight into the recruitment and engagement of working memory neural resources in response to a working memory task by providing a stronger contrast of parameter estimates for neural activity. Greater working memory load may more accurately reflect the cognitive demands placed on substance users engaging in goal-oriented activities, while also attempting to regulate responses to hypersalient internal and external stimuli related to substance use. Lastly, the working memory and inhibitory control tasks were counterbalanced; however, task order should be included as a covariate in order to examine the potential effect of order on task performance and neural response to the working memory task.

Future work should consider the most appropriate and comprehensive method for quantifying potential group differences between cocaine users and healthy individuals in the neural mechanisms contributing to working memory and inhibitory control task performance. Although there are numerous ways to measure neural response during a working memory task, one particularly comprehensive approach may be to examine potential group differences in the degree of network modularity. Network modularity, also known as community structure quantifies the efficiency of network defined by a subset of nodes that are more densely interconnected with each other than other nodes and dedicated to dissociable functions (Menon, 2011). Measuring the degree of modularity is based on two principles (Stevens, Tappon, Garg, & Fair, 2012). First, dense connections within network sub-systems result in more efficient processing, demonstrated by maximal within-module connections. Second, sparse connections between sub-systems contribute to reduced noise, demonstrated by minimal between-module

connections. Taken together, greater network modularity reflects more optimal functional organization (Dosenbach et al., 2006). Stevens and colleagues (2012) found that network modularity predicted individual differences in working memory capacity in healthy controls using a visual memory task. Thus, network modularity may provide a particularly promising approach to examine the neural mechanisms contributing to working memory and inhibitory control deficits in cocaine users.

Summary

Despite these limitations, this study and future work have the potential to contribute novel data to the neural mechanisms contributing to executive control deficits in cocaine users while importantly considering the relatedness of executive control processes.

APPENDIX 1: TABLES

Table 1. *Means (and standard deviations) of self-report sample characteristics*

	Cocaine Users (*n*=23)	**Healthy Controls** (*n*=24)	**Statistic**
Age (years)	40.39 (8.66)	38.58 (8.68)	$t(45)=0.71$
Gender (% male)	91.30	58.33	$\chi^2(1)=6.72$*
Ethnicity/Race (Black/Hispanic/White/Other)	16/0/6/1	18/1/4/0	$\chi^2(3)=2.52$
IQ	101.52 (12.32)	107.72 (12.46)	$t(37)=-1.56$

Note: *$p<0.05$.

Table 2. *Frequency of substance use*

		Cocaine Users (*n*=23)	Healthy Controls (*n*=24)
Cocaine	≥ 4 times/week	25.0%	--
	≥ 2 times/week	50.0%	--
	≥ 2 times/month	12.5%	--
	≤ monthly	6.3%	--
Alcohol	≥ 4 times/week	18.8%	--
	≥ 2 times/week	25.0%	9.1%
	≥ 2 times/month	18.7%	9.1%
	≤ monthly	31.3%	45.5%
Heroin	≥ 2 times/month	6.3%	--
	≤ monthly	6.3%	--
Marijuana	≥ 2 times/week	6.3%	--
	≥ 2 times/month	6.3%	--
	≤ monthly	37.5%	--
Methamphetamine	≥ 4 times/week	6.3%	--
	≤ monthly	6.3%	--
Ecstasy	≥ 4 times/week	6.3%	--
Sedatives	≥ 4 times/week	6.3%	--
Phencyclidine (PCP)	≤ monthly	6.3%	--
Prescription Opiate	≤ monthly	12.5%	--
Smoking	FTND Score	3.33 (2.11)	--
	Number of cigarettes/day	9.87 (8.17)	--

Note: FTND = Fagerström Test for Nicotine Dependence.

Table 3. *Task performance on the N-Back and Go/No-Go*

	Cocaine Users (*n*=23)	**Healthy Controls** (*n*=24)	**Statistic**
N-Back			
Performance			
All trials accuracy	46.17 (8.62)	48.33 (6.98)	*t*(45)=-0.95
1-back accuracy	25.35 (3.59)	26.21 (3.79)	*t*(45)=-0.80
2-back accuracy	19.78 (5.63)	22.13 (4.70)	*t*(45)=-1.55
Response time (ms)			
All trials correct	594.77 (137.61)	638.23 (157.61)	*t*(45)=-1.00
1-back correct	587.97 (145.87)	613.77 (156.88)	*t*(45)=-0.58
2-back correct	605.02 (137.36)	666.46 (182.12)	*t*(45)=-1.30
Go/No-Go			
Performance			
Errors of commission	23.48 (8.11)	18.25 (7.08)	*t*(45)=2.36*
Errors of omission	37.09 (42.24)	39.29 (64.98)	*t*(45)=-0.14
Successful inhibitions	26.52 (8.11)	31.75 (7.08)	*t*(45)=-2.36*
Response time (ms)			
Correct	406.43 (49.80)	402.98 (56.49)	*t*(45)=0.22

Note: *$p<0.05$. Mean (standard deviation).

Table 4. *Clusters and max Z-values in response to working memory load [(2-Back)-(1-Back)] among healthy controls*

Cluster Index	Voxels	*p*	Z-Max X (mm)	Z-Max Y (mm)	Z-Max Z (mm)
R. postcentral gyrus - R. precentral gyrus	183	3.00×10^{-3}	20	-30	68
L. precentral gyrus - L. postcentral gyrus, R. precentral gyrus	135	1.70×10^{-2}	-2	-30	64
L. parietal operculum cortex - L. central opercular cortex, L. supramarginal gyrus (anterior division)	131	1.98×10^{-2}	-44	-28	24

Note: R = right, L = left. Clusters determined by Z>3.0 and a (corrected) cluster significance threshold of p=0.05.

Table 5. *Clusters and max Z-values in response to working memory load [(2-Back)-(1-Back)] among cocaine users*

Cluster Index	Voxels	*p*	Z-Max X (mm)	Z-Max Y (mm)	Z-Max Z (mm)
R. central opercular cortex - R. frontal operculum cortex, R. insular cortex	339	$9.54x10^{-7}$	38	8	8
L. inferior frontal gyrus (pars opercularis) - L. precentral gyrus, L. frontal operculum cortex	258	$1.85x10^{-5}$	-50	10	10
R. superior frontal gyrus - L. superior frontal gyrus	242	$3.46x10^{-5}$	2	42	42
L. middle frontal gyrus - L. frontal pole, L. superior frontal gyrus	125	$5.62x10^{-3}$	-28	34	34
L. insular cortex - L. central opercular cortex	116	$8.78x10^{-3}$	-36	4	4
L. precentral gyrus - L. central opercular cortex, L. planum polare, L. superior temporal gyrus (anterior division), L. temporal pole, L. planum temporale	107	$1.39x10^{-2}$	-60	2	2
L. precentral gyrus - L. inferior frontal gyrus (pars opercularis), L. central opercular cortex, L. frontal operculum corterx	95	$2.59x10^{-2}$	-52	6	6
R. precentral gyrus - R. temporal pole	88	$3.77x10^{-2}$	66	6	6

Note: R = right, L = left. Clusters determined by Z>3.0 and a (corrected) cluster significance threshold of p=0.05.

Table 6. *Clusters and max Z-values in response to working memory load [(2-back)-(1-back)] for the contrast of cocaine users < healthy controls.*

Cluster Index	Voxels	*p*	Z-Max X (mm)	Z-Max Y (mm)	Z-Max Z (mm)
R. frontal pole - R. middle frontal gyrus	592	8.01×10^{-9}	40	40	32
R. precentral gyrus - R. postcentral gyrus	432	5.36×10^{-7}	60	-3	48
R. paracingulate gyrus - L. cingulate gyrus (anterior division), R. cingulate gyrus (anterior division)	337	8.94×10^{-6}	0	32	34
R. frontal pole	195	9.83×10^{-4}	40	62	6
L. middle frontal gyrus - L. frontal pole	185	1.42×10^{-3}	-40	36	32
R. middle frontal gyrus - R. inferior frontal gyrus (pars triangularis), R. inferior frontal gyrus (pars opercularis)	104	3.75×10^{-2}	56	24	32

Note: R = right, L = left. Clusters determined by $Z>3.0$ and a (corrected) cluster significance threshold of $p=0.05$.

Table 7. *Aim 1 mediation results of mediators in the relationship between group and working memory task performance (accuracy), adjusted for gender*

	Coefficient	SE	BC Boostrap 95% CI
Model 1			
Total effect of group on accuracy	2.40	2.49	(-2.62, 7.43)
Direct effect of group on mediators			
Network efficiency (a_1)	-0.55	0.98	(-2.52, 1.42)
Network strength (a_2)	0.02	0.02	(-0.03, 0.06)
Direct effect of mediators on accuracy			
Network efficiency (b_1)	-0.67	0.72	(-2.11, 0.78)
Network strength (b_2)	-36.45	32.53	(-102.10, 29.20)
Indirect effect of group on accuracy through mediators			
Network efficiency	0.37	1.14	(-1.11, 4.17)
Network strength	-0.58	1.22	(-5.14, 0.89)
Model 2			
Total effect of group on accuracy	2.99	2.66	(-2.38, 8.35)
Direct effect of group on mediators			
R. IPL to R. MFG (a_1)	0.02	0.08	(-0.15, 0.18)
R. FP to L. FP (a_2)	-0.11	0.07	(-0.26, 0.03)
R. IFG to L. IFG (a_3)	0.14	0.09	(-0.04, 0.32)
R. PREC to R. IPL (a_4)	0.03	0.08	(-0.12, 0.19)
L. IPL to R. IPL (a_5)	0.08	0.09	(-0.08, 0.24)
R. INS to R. IFG (a_6)	0.10	0.09	(-0.07, 0.28)
R. FP to R. IFG (a_7)	0.05	0.08	(-0.11, 0.21)
R. MFG to R. IFG (a_8)	0.07	0.08	(-0.09, 0.22)
L. MFG to L. IPL (a_9)	-0.01	0.10	(-0.20, 0.19)
R. MFG to L. MFG (a_{10})	0.02	0.08	(-0.13, 0.17)
Direct effect of mediators on accuracy			
R. IPL to R. MFG (b_1)	2.08	6.33	(-10.82, 14.98)
R. FP to L. FP (b_2)	3.78	6.90	(-10.28, 17.84)
R. IFG to L. IFG (b_3)	1.35	5.17	(-9.17, 11.87)
R. PREC to R. IPL (b_4)	1.37	6.32	(-11.51, 14.24)
L. IPL to R. IPL (b_5)	-5.14	5.78	(-16.92, 6.64)
R. INS to R. IFG* (b_6)	-11.56	4.97	(-21.69, -1.43)
R. FP to R. IFG (b_7)	-2.68	6.45	(-15.82, 10.46)
R. MFG to R. IFG (b_8)	-5.45	6.57	(-18.83, 7.92)
L. MFG to L. IPL (b_9)	-2.10	5.14	(-12.57, 8.38)
R. MFG to L. MFG (b_{10})	-2.21	5.97	(-14.36, 9.95)
Indirect effect of group on accuracy through mediators			
R. IPL to R. MFG (c_1)	0.04	0.70	(-1.22, 1.88)
R. FP to L. FP (c_2)	-0.43	0.91	(-3.49, 0.59)
R. IFG to L. IFG (c_3)	0.19	1.36	(-2.21, 3.49)
R. PREC to R. IPL (c_4)	0.05	0.59	(-0.64, 2.24)
L. IPL to R. IPL (c_5)	-0.41	0.95	(-2.94, 0.95)
R. INS to R. IFG (c_6)	-1.21	1.04	(-4.53, 0.18)
R. FP to R. IFG (c_7)	-0.13	0.95	(-3.09, 1.01)
R. MFG to R. IFG (c_8)	-0.37	1.24	(-5.16, 0.76)
L. MFG to L. IPL (c_9)	0.02	0.58	(-1.22, 1.22)
R. MFG to L. MFG (c_{10})	-0.04	0.64	(-2.60, 0.70)

Note: 95% CI does not include zero. SE=standard error; BC=bias-corrected; CI=confidence interval.

Table 8. *Aim 2 mediation results of mediators in the relationship between group and inhibitory control task performance (successful inhibitions), adjusted for gender*

	Coefficient	SE	95% CI
Model 1			
Total effect of group on successful inhibitions*	4.95	2.42	(0.07, 9.83)
Direct effect of group on mediators			
Network efficiency	-0.55	0.98	(-2.52, 1.42)
Network strength	0.02	0.02	(-0.03, 0.06)
Direct effect of mediators on correct inhibitions			
Network efficiency*	1.38	0.67	(0.03, 2.72)
Network strength*	66.61	30.31	(5.44, 127.79)
Indirect effect of group on successful inhibitions through mediators			
Network efficiency	-0.76	1.66	(-5.43,1.53)
Network strength	1.07	1.77	(-1.37,5.88)
Model 2			
Total effect of group on successful inhibitions	4.82	2.59	(-0.40, 10.04)
Direct effect of group on mediators			
R. IPL to R. MFG (a_1)	0.02	0.10	(-0.15, 0.18)
R. FP to L. FP (a_2)	-0.11	0.07	(-0.26, 0.03)
R. IFG to L. IFG (a_3)	0.14	0.09	(-0.04, 0.32)
R. PREC to R. IPL (a_4)	0.03	0.08	(-0.12, 0.19)
L. IPL to R. IPL (a_5)	0.08	0.08	(-0.08, 0.24)
R. INS to R. IFG (a_6)	0.10	0.09	(-0.07, 0.28)
R. FP to R. IFG (a_7)	0.05	0.08	(-0.11, 0.21)
R. MFG to R. IFG (a_8)	0.07	0.08	(-0.09, 0.22)
L. MFG to L. IPL (a_9)	-0.01	0.10	(-0.20, 0.19)
R. MFG to L. MFG (a_{10})	0.02	0.08	(-0.13, 0.17)
Direct effect of mediators on successful inhibitions			
R. IPL to R. MFG (b_1)	-2.12	3.02	(-4.36, 7.96)
R. FP to L. FP (b_2)	8.10	5.90	(-3.93, 20.13)
R. IFG to L. IFG (b_3)	7.20	4.42	(-1.80, 16.21)
R. PREC to R. IPL* (b_4)	12.15	5.41	(1.14, 23.17)
L. IPL to R. IPL (b_5)	-1.82	4.95	(-11.90, 8.26)
R. INS to R. IFG (b_6)	6.97	5.52	(-1.70, 15.64)
R. FP to R. IFG (b_7)	3.66	5.52	(-7.59, 14.90)
R. MFG to R. IFG (b_8)	-7.48	5.62	(-18.92, 3.97)
L. MFG to L. IPL (b_9)	3.37	4.40	(-5.59, 12.34)
R. MFG to L. MFG (b_{10})	0.40	5.10	(-10.00, 10.90)
Indirect effect of group on accuracy through mediators			
R. IPL to R. MFG (c_1)	-0.04	0.58	(-2.04, 0.71)
R. FP to L. FP (c_2)	-0.92	1.03	(-4.48, 0.19)
R. IFG to L. IFG (c_3)	1.01	1.05	(-0.36, 4.53)
R. PREC to R. IPL (c_4)	0.42	1.04	(-1.05, 3.48)
L. IPL to R. IPL (c_5)	-0.14	0.70	(-2.32, 0.63)
R. INS to R. IFG (c_6)	0.73	0.63	(-0.13, 2.43)
R. FP to R. IFG (c_7)	0.18	0.76	(-0.72, 2.68)
R. MFG to R. IFG (c_8)	-0.50	0.91	(-4.72, 0.35)
L. MFG to L. IPL (c_9)	-0.03	0.59	(-1.49, 0.95)
R. MFG to L. MFG (c_{10})	0.01	0.50	(-0.97, 1.05)

Note: 95% CI does not include zero. SE=standard error; BC=bias-corrected; CI=confidence interval.

Table 9. *Correlations (r) between study variables*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1 Accuracy (N-Back)	--	--	--	--	--	--	--	--	--	--	--	--	--	--
2 Correct Inhibitions (Go/No-Go)	0.07	--	--	--	--	--	--	--	--	--	--	--	--	--
3 Network efficiency	-0.01	-0.02	--	--	--	--	--	--	--	--	--	--	--	--
4 Network strength	-0.07	0.18	-0.85***	--	--	--	--	--	--	--	--	--	--	--
5 R. FP to L. FP	-0.01	0.12	0.16	-0.02	--	--	--	--	--	--	--	--	--	--
6 R. IFG to L. IFG	0.02	0.31*	0.33*	-0.14	0.04	--	--	--	--	--	--	--	--	--
7 R. PREC to R. IPL	0.04	0.36*	-0.07	0.22	-0.16	0.16	--	--	--	--	--	--	--	--
8 L. IPL to R. IPL	-0.07	0.11	-0.31*	0.39**	-0.04	0.17	-0.11	--	--	--	--	--	--	--
9 R. INS to R. IFG	-0.32*	0.32*	0.07	0.08	0.06	0.04	0.06	-0.05	--	--	--	--	--	--
10 R. FP to R. IFG	-0.12	0.13	0.15	-0.08	-0.33*	0.15	0.11	0.23	0.05	--	--	--	--	--
11 R. MFG to R. IFG	-0.05	-0.08	0.21	-0.14	0.21	0.30*	-0.03	-0.05	-0.05	0.03	--	--	--	--
12 L. MFG to L. IPL	-0.13	0.28	0.19	0.05	0.26	0.20	0.18	0.20	0.07	0.20	0.23	--	--	--
13 R. MFG to L. MFG	-0.02	-0.01	-0.16	0.23	-0.05	-0.18	0.05	0.15	-0.02	-0.16	-0.17	-0.04	--	--
14 R. IPL to R. MFG	0.02	-0.01	0.32*	-0.15	-0.06	0.06	0.37*	-0.15	0.02	0.15	0.34*	-0.01	0.05	--

Note: *p<.05; **p<.01; ***p<.001

APPENDIX 2: FIGURES

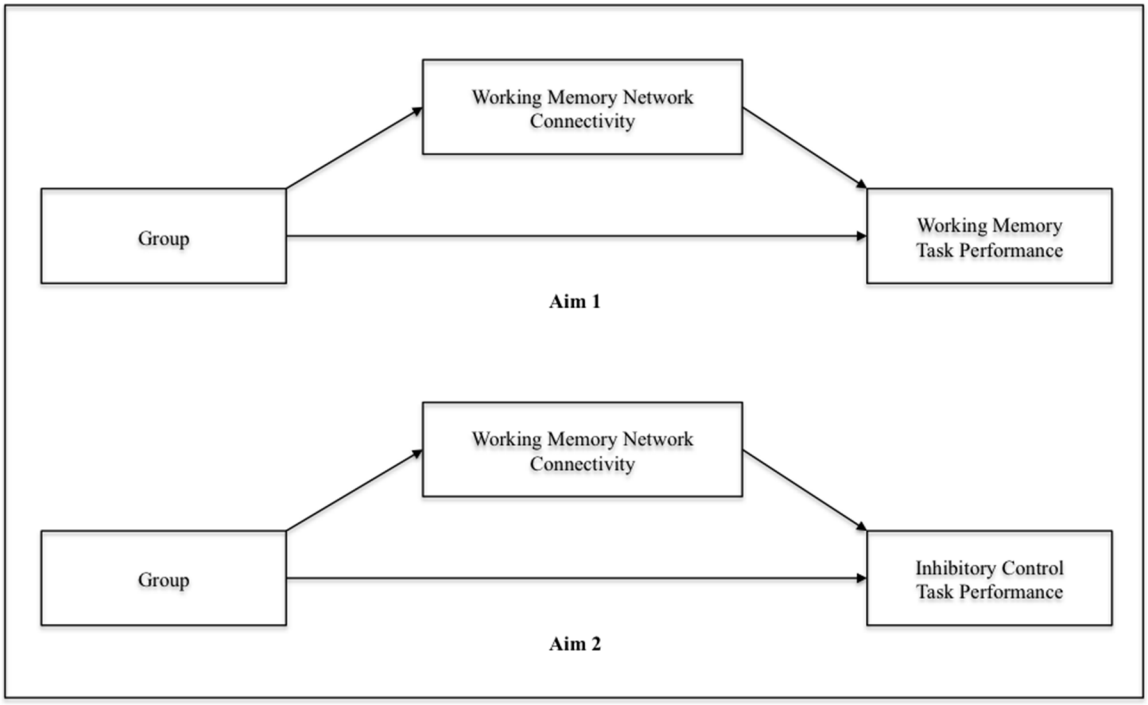

Figure 1. Conceptual models for Aims 1 and 2.

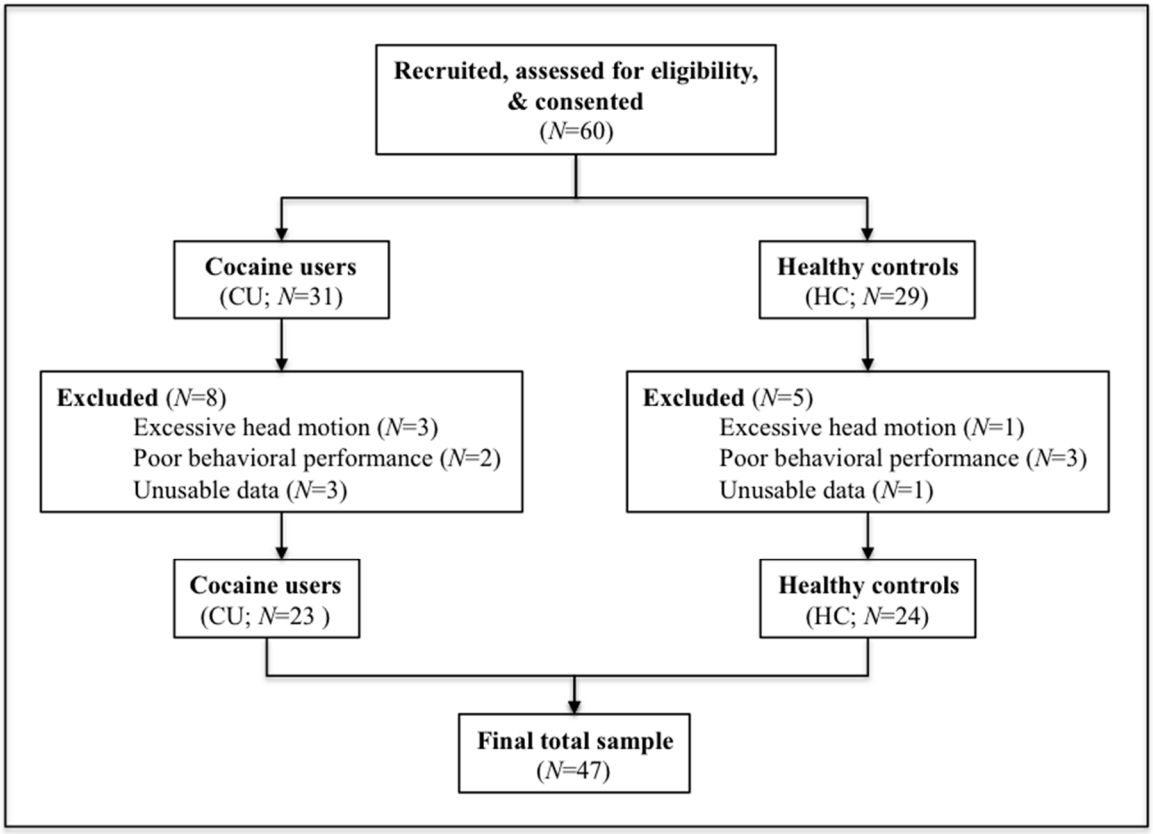

Figure 2. Consort diagram.

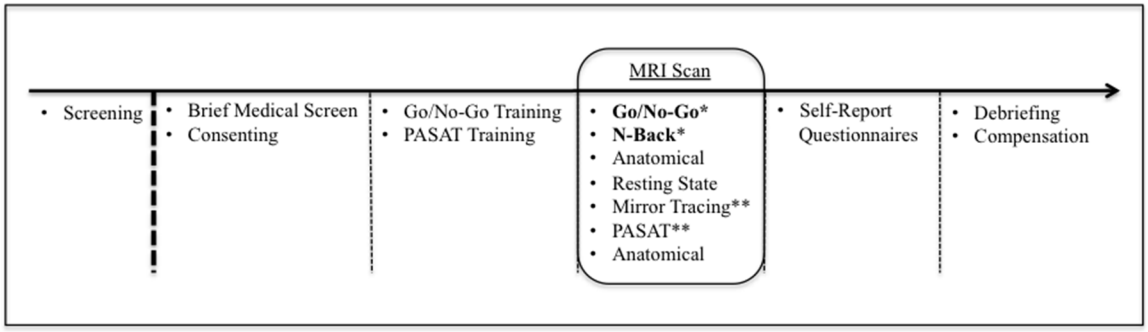

Figure 3. Timeline of study visit for all participants. Note: *,** = counterbalanced tasks.

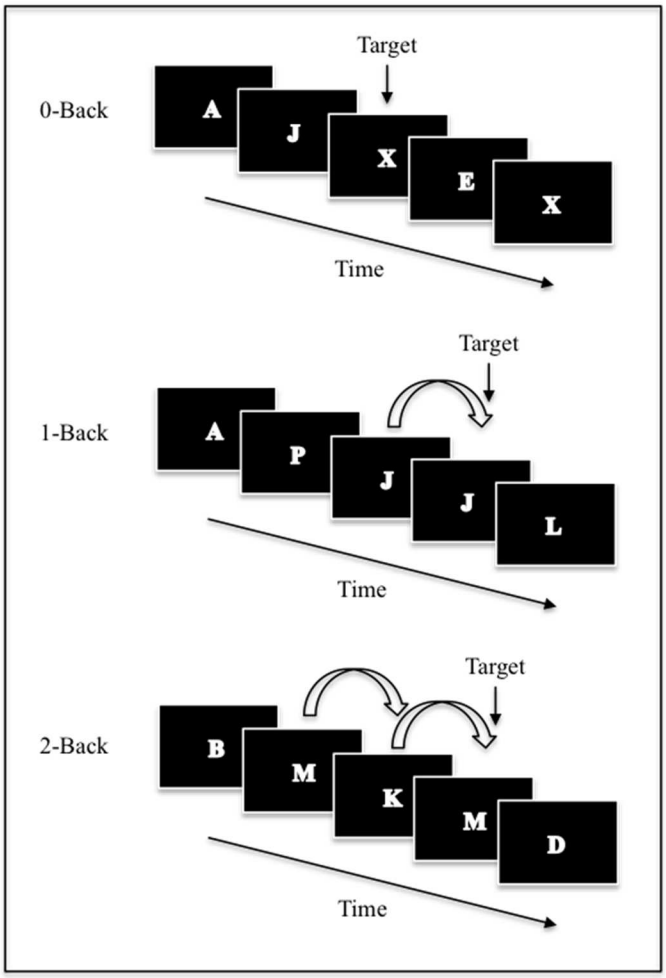

Figure 4. N-Back task.

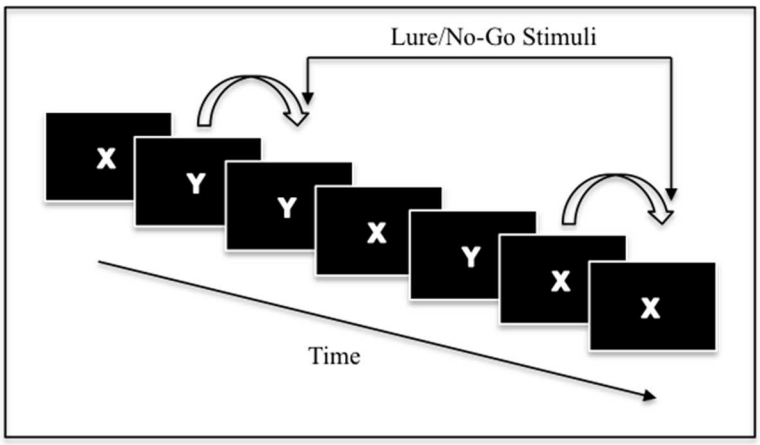

Figure 5. Go/No-Go task.

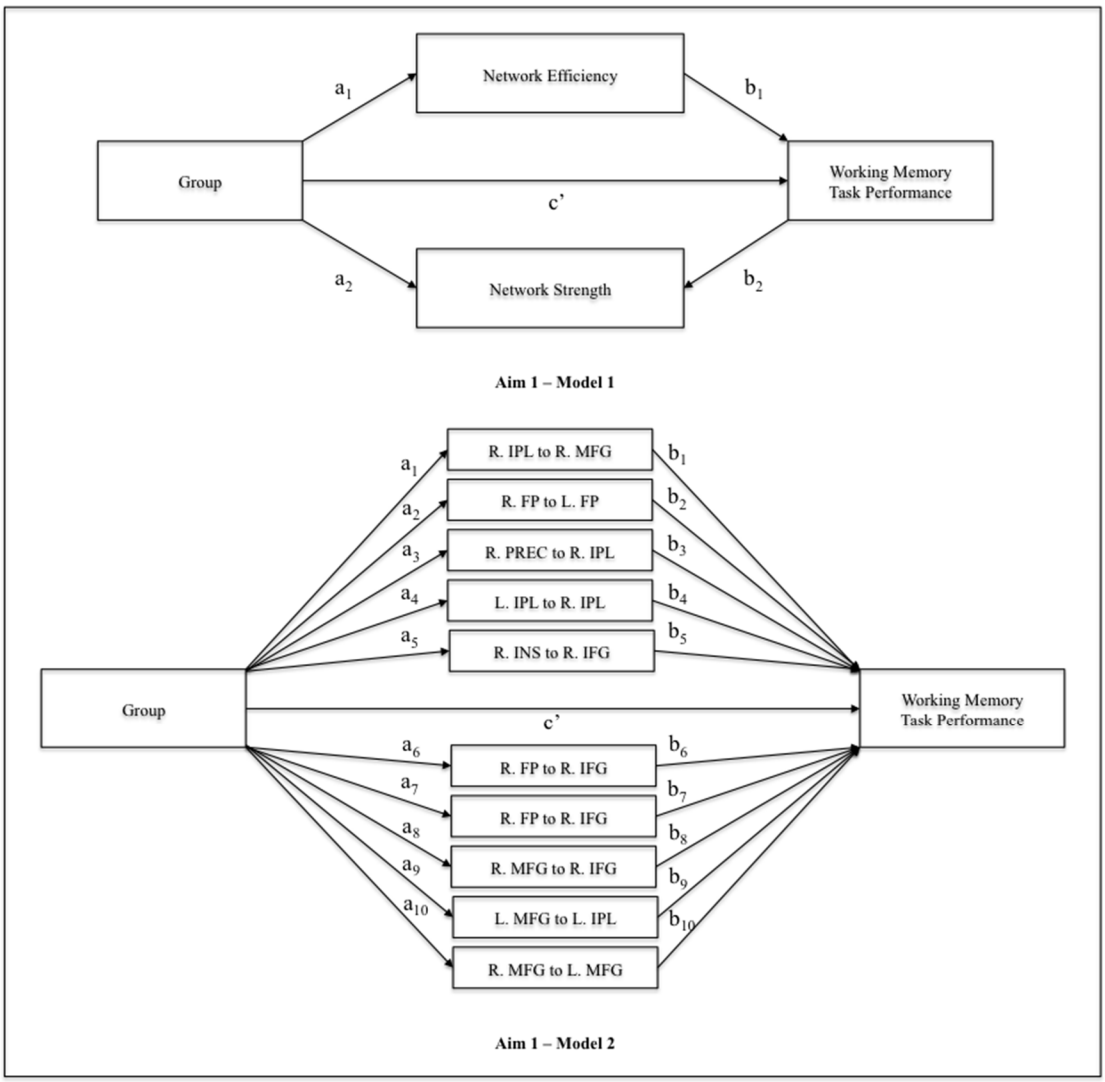

Figure 6. Mediation models 1 and 2 for Aim 1.

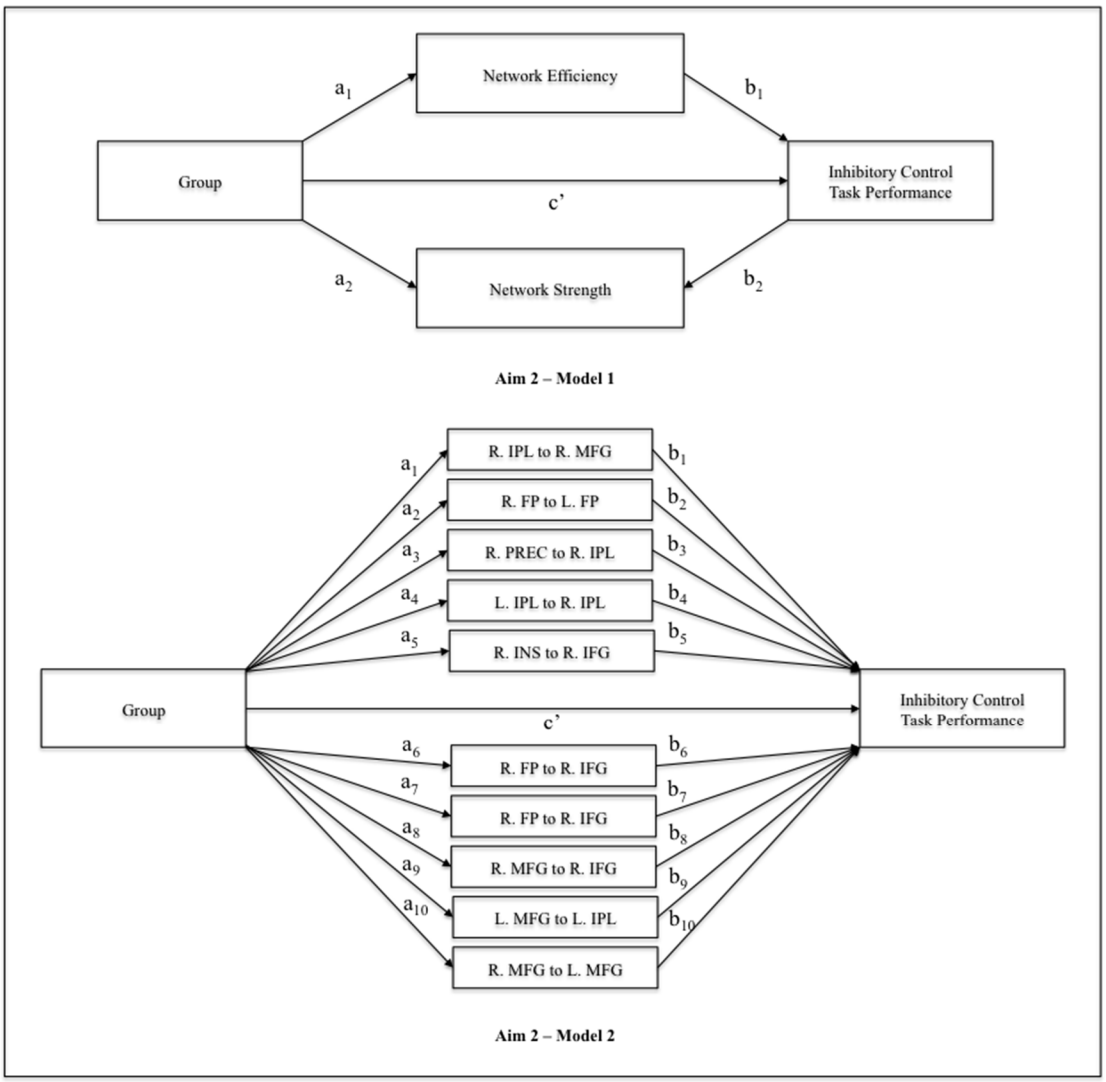

Figure 7. Mediation models 1 and 2 for Aim 2.

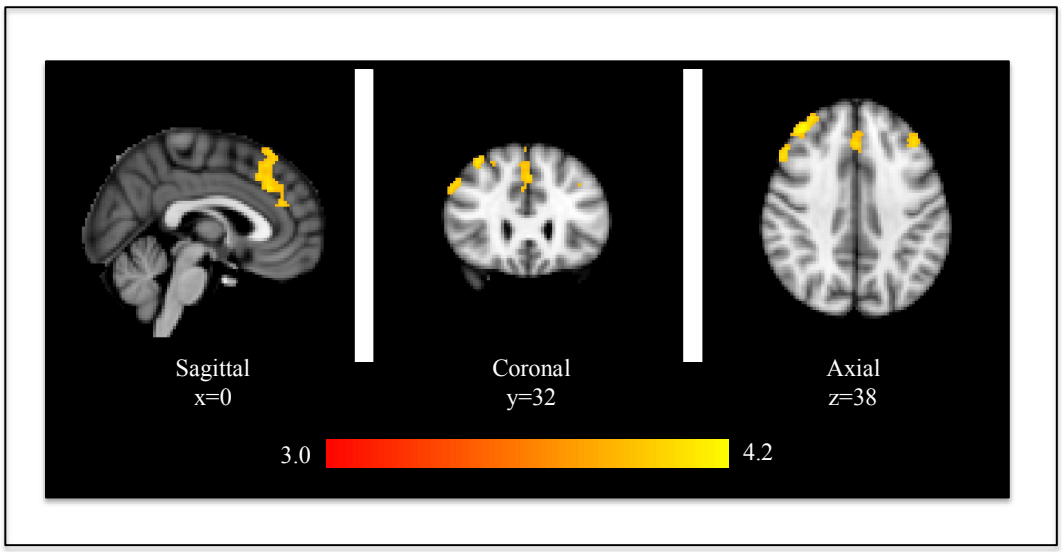

Figure 8. Significant clusters in response to working memory load [(2-back)-(1-back)] for the contrast of cocaine users < healthy controls. Clusters determined by $Z>3.0$ and a (corrected) cluster significance threshold of $p=0.05$.

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