EXAMINING THE RELATIONSHIP BETWEEN IMPULSIVE PERSONALITIES AND NEURAL FUNCTIONING IN COCAINE-ADDICTED PARTICIPANTS

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DEDICATION

I would like to thank my thesis committee, in particular Dr. Bryon Adinoff for pushing me to do my best. I would also like to thank my friends and family for all of their support without which I would have not been able to accomplish all that I have.

Thank you all.

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By

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Abstract

BACKGROUND: Those who suffer from addiction are unable to discontinue use despite serious consequences affecting their social, professional, and family lives. Individuals who suffer from the disorder often alienate themselves from loved ones and lose their jobs. Addiction involves continuing a behavior despite severe negative consequences. Numerous studies have identified a relationship between impulsivity and the development of substance abuse. This study examines the relationship of impulsive personality facets and neural functioning associated with inhibition.

SUBJECTS: The study sample included 24 healthy control participants and 56 cocaine-addicted participants. Participants ranged in age from 25 to 54 years old with a mean age of 43.27 (±SD 7.84). The group was comprised of 68 male and 12 female participants, 28.7% self identified as Caucasian, 66.3% African American, 3.8% Hispanic, and 1.3% Asian/Other. Healthy controls and cocaine-addicted participants were similar in age and race but differed in gender (p= .02). The control group had 17 males and 7 females while the cocaine-addicted group had 51 males and 5 females.

METHODS: Demographic information was gathered for all participants. Each participant also completed a Neuroticism Extroversion and Openness (NEO) personality measure and Temperament and Character Inventory (TCI), Structured Clinical Interview for DSM-IV (SCID), Wechsler Test of Adult Reading (WTAR). They then performed the stop signal task (SST) during functional magnetic resonance imaging (fMRI) to gather data on neural activation during Stop-Success (SS) and Stop-Failure (SF). fMRI data was analyzed using FSL imaging software. All statistics were run with SPSS software. Functional ROIs were identified and analyzed in fMRI Expert Analysis Tool query (FEATqueary) to gather data on each participant's change in blood oxygen level dependent (BOLD) activation during Stop-Success (SS) and Stop-Failure

(SF). Impulsive personality facets were then used to identify relationships between BOLD activations of the ROIs.

RESULTS: Between group comparisons found significant differences in mean scores on all of the impulsive personality facets except for Exploratory Excitability and Persistence from the TCI, and Excitement Seeking from the NEO. Neuroimaging results are similar to other studies utilizing the SST finding changes in activation of the middle frontal gyrus, superior frontal gyrus, cingulate gyrus, medial frontal gyrus, insula, caudate and supramarginal gyrus during Stop-Failure; and superior parietal lobule, middle frontal gyrus, precuneus, supramarginal gyrus, inferior temporal gyrus, and middle occipital gyrus during Stop-Success. However, no differences in BOLD activation between groups were observed. Numerous relationships were identified between the personality facets and BOLD activation of the regions of interest (ROIs). To further elucidate this relationship between neural functioning and personality a principal component analysis (PCA) was conducted on all eleven personality facets. The PCA allowed for the identification of an impulse control personality component and an impulse drive personality component. A significant interaction with the impulse drive and the left posterior hippocampus was identified.

DISCUSSION: This study allowed for the examination of how impulsive personality facets relate to, or interact with, neural functioning during a task designed to measure inhibition. Despite failing to find a difference in activation of the ROIs between cocaine-addicted participants and healthy controls, the study successfully identified the cocaine-addicted group to have a significantly more impulsive personality than healthy controls. It also identified numerous relationships between the personality facets and neural functioning. This gives credence to the idea that neural functioning and personalities are associated in some way. Reverse relationships

were observed between the groups in the relationships between the Impulse Drive personality component and SF activation of the hippocampus; and the TCI facet of Purposefulness and SS activation of the right thalmus. These reverse relationships may signify a difference between the groups that may either predispose the cocaine-addicted participants to developing substance abuse, or it may be a neuro-functional change that has resulted due to prolonged exposure to cocaine.

Keywords: Impulsivity, Addiction, fMRI, Inhibition, Personality

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LIST OF ABBREVIATIONS

ACC - Anterior Cingulate Cortex

ADD - Attention Deficit Disorder

ADHD - Attention Deficit Hyperactive Disorder

BET - Brain Extraction Tool

BIS-11 - Barratt Impulsiveness Scale

BMI - Body Mass Index

BOLD - Blood Oxygen Level Dependent

C5 - Self-Discipline

C6 - Deliberation

CPQ - Cognitive Failures Questionnaire

DSM-IV - Diagnostic Statistics Manual – 4th Addition

DTW - Diffusion Weighted Imaging

E5 - Excitement Seeking

EASI-III - Emotionality, Activity, Sociability, and Impulsivity Temperament Survey

EIVQ - Eysenck Impulsivity Questionnaire

FEAT - FMRI Expert Analysis Tool

fMRI - Functional Magnetic Resonance Imaging

FSIQ – Full Scale Intelligence Quotient

HA - Harm Avoidance

HA1 - Anticipatory Worry

HA2 - Fear of Uncertainty

I-7 - Impulsiveness Questionnaire

I.I. - Impulsivity Inventory

IFC - Inferior Frontal Cortex

InDUC - Inventory of Drug Use Consequences

mPFC - Mesial Prefrontal Cortex

MRI - Magnetic Resonance Imaging

N5 - Impulsiveness

NEO-PI-R - Neuroticism Extroversion Openness Personality Inventory

NS - Novelty Seeking

NS1 - Exploratory Excitability

NS2 - Impulsiveness

OFC - Orbitofrontal Cortex

P - Persistence

PC1- Principal Component One

PC2 – Principal Component Two

PCA – Principal Component Analysis

PFC - Prefrontal Cortex

pre-SMA - Presupplemtentary Motor Area

RD - Reward Dependence

rIFG - Right Inferior Frontal Gyrus

ROI - Region of Interest

RRT - Response Reversal Task

SD - Self Directedness

SD2 - Purposefulness

SD5 - Congruent Second Nature

SF- Stop-Failure

SS- Stop-Success

SST - Stop Signal Task

STN - Subthalamic Nucleus

TCI - Temperament and Character Inventory

VAMC - Veterans Administration Medical Center

WCST - Wisconsin Card Sorting Test

WTAR- Wechsler Test of Adult Reading

CHAPTER ONE

Introduction

Substance dependence is a serious problem that an estimated 18% of Americans will face at some point in their lifetime (Galanter & Kleber, 2008). Those who suffer from addiction are unable to discontinue use despite serious consequences affecting their social, professional, and family lives. Many individuals with the disorder alienate themselves from loved ones and lose their jobs. Addiction involves continuing a behavior despite severe negative consequences. It has been suggested that drug use may be defined as an impulsive behavior (Logue, 1995) and there is a body of research suggesting that impulsivity is related to drug use; finding that self reports of impulsivity are positively correlated with substance use disorder (Eisen, Youngman, Grob, & Dill, 1992) (J. H. Patton, Stanford, & Barratt, 1995).

Numerous studies have identified a relationship between impulsivity and the development of substance abuse in at-risk children (Caspi, Moffitt, Newman, & Silva, 1996; C. R. Cloninger, Sigvardsson, & Bohman, 1988; Dawes, Tarter, & Kirisci, 1997; Giancola, Moss, Martin, Kirisci, & Tarter, 1996), and impulsivity measures have consistently been found to be higher in substance-abusing samples than in controls (Ball, Carroll, Babor, & Rounsaville, 1995; Antoine Bechara, 2005; C. R. Cloninger, Sigvardsson, Przybeck, & Svrakic, 1995; Mark T. Fillmore a, 2002; D. Patton, Barnes, & Murray, 1997). However, the exact manner in which impulsivity is related to the pathology of substance abuse has yet to be clearly determined.

Because of the technological advances in neuroimaging, functional magnetic resonance imaging (fMRI) is increasingly used to identify neural mechanisms that may be related to impulsive characteristics in individuals with addiction. Research investigating the neural

functioning in addicted individuals has identified dysfunction in prefrontal regions including the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), mesial prefrontal cortex (mPFC), subthalamic nucleus (STN), dorsolateral prefrontal cortex (DLPFC), presupplementary motor area (pre-SMA), right inferior frontal gyrus (rIFG), caudate, and the inferior frontal cortex (IFC) (Aron, Behrens, Smith, Frank, & Poldrack, 2007; Benarroch, 2008; M.J. Frank, J. Samanta, A.A. Moustafa, & S.J. Sherman, 2007; Kaufman, 2003; Madsen et al., 2010; Nambu, Tokuno, & Takada, 2002; N.D. Volkow, Fowler, & Wang, 1999). Numerous imaging studies exploring the relationship between addiction and impulsivity have identified abnormalities such as hypoactivation of certain regions within the prefrontal cortex (PFC) (de Zubicaray, Andrew, Zelaya, Williams, & Dumanoir, 2000; H. Garavan, 2002; Liddle, Kiehl, & Smith, 2001; N.D. Volkow et al., 1999; Williams, Ponesse, Schachar, Logan, & Tannock, 1999). However, most research has examined only the relationship of behavioral measures of impulsivity with neural activation and has failed to consider a relationship between neural activity and personality measures of impulsivity. Research has suggested that although behavioral measures of impulsivity are less biased to one's own self perception, these measures tend to only assess impulsivity as a single dimension of behavior (Reynolds, Ortengren, Richards, & de Wit, 2006). Using personality, rather than behavioral measures of impulsivity may allow for the examination of distinct personality facets that may underlie the broad spectrum of impulsive behavior as it relates to drug addiction.

This thesis will first discuss the relevant literature regarding impulsivity and addiction, along with the their physiologic underpinnings. The study will attempt to identify a relationship between personality measures of impulsivity and neural functioning associated with inhibition. It is my hypothesis that when compared with controls, cocaine-addicted patients will demonstrate

increased impulsive tendencies as measured by personality as well as show hypoactivation of regions associated with impulsivity. By identifying a relationship between impulsive personality facets and neural functioning, greater insight into how certain personality characteristics may influence or predispose individuals to developing substance use disorders may emerge.

CHAPTER TWO

Review of Literature

Addiction and Impulsivity

The Relationship Between Addiction and Impulsivity

As proposed by Dickman et al. 1990, (S. J. Dickman, 1990) impulsive acts can be functional in certain situations but become dysfunctional when these acts are continued in situations not optimal for such behavior. Thus, while most individuals display impulsive behaviors at various times and in certain situations, dysfunctional impulsivity is more often observed among individuals suffering from some form of psychopathology when compared to healthy individuals. Besides being a key criterion for substance abuse and dependence, impulsivity is a common characteristic of other DSM-IV disorders, appearing in the criteria for borderline personality disorder, antisocial personality disorder, ADD/ADHD, mania, dementia, and eating disorders. Importantly, many of these disorders are often co-morbid with substance abuse. Those diagnosed with a psychopathology that entails meeting criteria for an impulsive characteristic, including individuals with intermittent explosive disorder, pyromania, and impulsive violent offenders, all have higher rates of substance abuse or dependence than the general population (S.Taylor, 1997; Wills, Vaccaro, & McNamara, 1994).

In the United States it is estimated that 637,000 individuals will try cocaine for the first time every year (SAMHS, 2011). However, despite the addictive qualities inherent in the drug, research has suggested that only ~20% of these individuals will develop cocaine dependence (Wagner & Anthony, 2002). It is suggested that impulsive individuals tend to be particularly vulnerable to developing cocaine dependence (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Other studies have identified impulsivity to be related to the development of substance

use disorder. Based on measures of behavioral self-regulation, children with a family history of substance abuse scored higher than children from families that had no such history (Dawes et al., 1997). A study comparing executive cognitive functioning of high-risk children (children from a father with substance abuse) and low risk-children (children from a father without substance abuse), found that self-regulation of goal-directed behavior was impaired in children identified as high-risk compared to those identified as low-risk for substance abuse (Giancola et al., 1996) and that those with impaired executive cognitive functioning had impulsive tendencies. Caspi et al. reported that boys identified as "under-controlled" at age three were three times more likely to demonstrate substance abuse problems at 21 years of age than those identified with "normal" temperament (Caspi et al., 1996).

Numerous studies utilizing self-report measures of impulsivity, behavioral measures of impulsivity, or a combination of both, have identified a relationship between impulsivity and substance use disorders. Allen et al. compared a group of adults with a history of substance dependence with a control group that had no history of addiction (Allen, Moeller, Rhoades, & Cherek, 1998). Each group was assessed on their performance on a self-control paradigm along with self-report measures of impulsivity. The self-control paradigm gave participants the opportunity to choose between an immediate reward with no delay and a larger reward with an increasing delay. The self-report measures used were the Eysenck Impulsivity Questionnaire (EIVQ), the Impulsivity Inventory (I.I.) and the Barratt Impulsiveness Scale (BIS-11). The substance dependence group made more impulsive decisions, as well as maintained a shorter reward delay average, than the control group (Allen et al., 1998). Furthermore, individuals with a history of addiction scored significantly higher on the BIS-11 and EIVQ impulsivity scales when compared to healthy controls (Allen et al., 1998). Other studies using self-report measures have

also found that individuals with a history of substance use disorder scored higher than those who had no history of addiction (Eisen et al., 1992; J. H. Patton et al., 1995). Furthermore, studies that have utilized behavioral measures of impulsivity have found a similar relationship between impulsivity and addiction (Mark T. Fillmore a, 2002; Monterosso, Aron, Cordova, Xu, & London, 2005; K. Rubia, 2003).

Defining Impulsivity in Addiction

Elevations in measures of impulsivity have been consistently found in various drug-abusing samples, supporting the hypothesis that impulsivity may predispose individuals toward the development of substance abuse (Hugh Garavan, 2011; Verdejo-Garcia, Lawrence, & Clark, 2008). However, impulsivity is a very broad construct and consists of multiple traits and behaviors. There are multiple interpretations of what impulsivity is, and it has been variously defined as instantaneous actions lacking forethought or conscious judgment (Hinsie & Campbell, 1970), behavior without adequate thought (Smith, 1952), or the tendency to act with less forethought than other individuals would with the same ability and knowledge (S.J. Dickman, 1993). Moeller et al. defined impulsivity "as a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to the negative consequences of these actions to individual or to others" (F. Gerard Moeller, 2001 p. 1784).

Research has suggested that the characteristics of impulsivity are multi-dimensional (Gerbing, Ahadi, & Patton, 1987) and include behaviors such as acting without thinking (motor impulsivity), making decisions rapidly (cognitive impulsivity), thinking in terms of the present situation instead of the future (non-planning), and difficulty with concentration (attentional impulsivity) (Adinoff et al., 2007; Barratt, 1993; Evenden, 1999; F. Gerard Moeller, 2001). Garavan proposed that impulsivity is composed of two separate dimensions, a reward seeking

drive (impulse drive) and a cognitive control system that attempts to exert control over these drives (impulse control) (Hugh Garavan, 2011). Impulse control can be viewed is the ability to inhibit a previously rewarded response. The inability to inhibit a behavior is known as disinhibition, which refers to the inability to suppress a behavior that has previously been reinforced, but which no longer works to serve the individual in a functional manner.

Disinhibition has relevance to drug cessation because the suppression of a previously reinforced response may be influenced by similar mechanisms responsible for inhibiting a motor response (Fillmore & Rush, 2002; Jentsch & Taylor, 1999; Lyvers, 2000; Monterosso et al., 2005). Furthermore, investigation into disinhibition has found that the failure of inhibition plays a central role in alcoholism and substance abuse (Nigg, 2000; K.J. Sher & T.J. Trull, 1994). It has been found that measures of disinhibition in children at age 11 predict when the child will have his or her first drink (McGue, Iacono, Legrand, Malone, & Elkins, 2001). It appears that disinhibition may play a key role in the development and maintenance of addiction. Therefore, a further examination of disinhibition and its relationship to substance abuse should be pursued.

Measures of Impulsivity

Several cognitive measures of impulsivity have been developed. These can be divided into two categories, one measuring the impulsive aspect of decision-making and one measuring the impulsive aspect of inhibition. Those measuring decision-making include the Response Reversal Task (RRT), the Wisconsin Card Sorting Test (WCST); and those measuring inhibition include the Stop Signal Task (SST), the Go/No-Go task, and the Stroop Color Word Task. Neuroimaging studies have used these tasks to identify neural mechanisms associated with impulsivity identifying that depending on the type of task (decision-making vs. disinhibition) different areas of the brain reveal increased or decreased levels of activation.

The RRT consists of 51 trials of stimuli, which are administered over three consecutive sessions. In each trial two unique figures are displayed to the participant randomly on the right or left side of a screen. The participants are taught to select one of the two figures. After selection, participants are informed whether they won money or lost money. The consequences of their decisions are reversed randomly during the session. The RRT allows for trial-by-trial analysis of responses that are related to the acquisition of rewards or punishments and the reversal of these contingencies. This reversal entails the inhibition of one set of cognitive processes and the implementation of a new set.

The WCST consists of 4 stimulus cards and 128 response cards depicting figures of various forms (crosses, circles, triangles, or stars), colors (red, blue, yellow, or green), and numbers of figures (one, two, three, or four). Each response card can be matched to a stimulus card on one, or a combination, of these 3 stimulus parameters. The matching principles change throughout the test; therefore, participants must figure out the matching principle and modify their responses based on feedback (e.g., correct versus incorrect). The WCST is believed to assess numerous executive functions including strategic planning, organized searching, utilizing environmental feedback to shift cognitive sets, directing behavior toward achieving a goal, and modulating impulsive responses.

The Stroop Color Word task involves participants naming the color of the ink seen on an incongruent word-color stimuli (i.e. “BLUE” written in green ink) (Adleman et al., 2002). Because word reading is a more automatic cognitive process than is color naming, participants must inhibit their first response in order to properly respond. This process allows for the assessment of response inhibition, interference resolution, and behavioral conflict resolution (Adleman et al., 2002). The SST and Go-No/Go tasks are described later in this paper.

The Relationship Between Addiction and Personality Measures of Impulsivity

Measures of Personality

Although previous studies have provided valuable information on neural mechanisms that play a role in impulsivity and addiction, they typically utilize self-report impulsivity questionnaires and behavioral measures to identify a relationship between neural functioning and ratings of impulsivity. Although behavioral measures of impulsivity are less biased to one's own self perception, these measures tend to only assess impulsivity as a single dimension of behavior (Reynolds et al., 2006). Using personality measures of impulsivity allows for the examination of distinct personality facets that may underlie the broad spectrum of impulsive behavior.

There are numerous self-report measures of impulsivity each based on the investigator's theory of personality or definition of impulsivity. The Emotionality, Activity, Sociability, and Impulsivity Temperament Survey (EASI-III) designed by Buss and Plomin (1975) focuses on their four-temperament theory of personality including emotionality, activity, sociability, and impulsivity (Buss & Plomin, 1975). Dickman's Functional and Dysfunctional Impulsivity is based on his two-dimensional construct of impulsivity including functional and dysfunctional impulsivity (S. J. Dickman, 1990). Barratt and colleagues, who measured impulsivity as a factor that is related to personality traits such as extroversion and sensation seeking, (J. H. Patton et al., 1995) created the Barratt Impulsiveness Scale-11 (BIS-11). The Impulsiveness Questionnaire (I-7) developed by Eysenck and colleagues measure impulsiveness as it relates to venturesomeness (Eysenck & Eysenck, 1985).

The Temperament and Character Inventory (TCI) developed by Cloninger assess impulsivity based on a psychobiological model of personality(C. R. Cloninger, Svrakic, & Przybeck, 1993). The NEO-PI-R Developed by Costa and McCrae measures impulsivity through

its five-factor model of personality; its five personality domains are found in a majority of other personality inventories (Costa Jr & McCrae, 1990) (Costa, Busch, Zonderman, & McCrae, 1986). The TCI and NEO measures both allow for analysis of multiple dimensions of personality, which include various facets of impulsivity. The analysis of separate personality factors that contribute to impulsive behavior can be identified through the use of these personality questionnaires (Reynolds et al., 2006).

The NEO and TCI and their Relationship to Addiction and Impulsivity

Both the NEO and TCI personality measures have found empirical support for their potential to systematically organize findings on personality and substance abuse (Sher, Bartholow, & Wood, 2000; K. J. Sher & T. J. Trull, 1994). The TCI relates to substance abuse in that Cloninger's model hypothesizes that behavioral activation, behavioral inhibition, and behavioral maintenance are related to the heritable, genetic, personality dimensions of Novelty Seeking (NS), Harm Avoidance (HA), and Reward Dependence (RD) (C. R. Cloninger, 1987; C. R. Cloninger et al., 1993; Wills et al., 1994). Cloninger proposed that elevated patterns of these three personality dimensions relate to predictable brain behavior relationships that predispose affected individuals to alcohol dependence (C. R. Cloninger, 1987).

Le Bon et al. administered the TCI to a sample of substance abusers and a control group to identify differences between the two (Le Bon et al., 2004). NS scores from the TCI were significantly higher in the substance abuse group than in controls, in particular their scores on Exploratory Excitability (NS1) and Impulsiveness (NS2) (Le Bon et al., 2004). Besides Novelty Seeking being elevated in the substance abuse group, it was also reported that Harm Avoidance (HA) was also significantly elevated compared to controls. Significant differences between groups in the Self Directedness (SD) character dimension were also found (Le Bon et al., 2004).

Basiaux et al., reported that alcohol-dependent patients generally scored higher on Novelty Seeking and lower on Self Directedness than controls (Basiaux et al., 2001). According to Cloninger, lower Self-Directedness may indicate a higher probability of personality disorders and other psychopathology (C. R. Cloninger et al., 1988).

Whitesite et al. performed a factor analysis between the NEO-PI-R and 17 impulsivity scales and discovered four factors thought to define impulsivity (Stephen P. Whiteside, 2001): Lack of Premeditation, Urgency, Sensation Seeking, and Lack of Perseverance. Lack of premeditation, thought to be the primary factor of impulsiveness, was seen most often in all of the conceptualizations of impulsivity and was highly correlated with the NEO-PI-R facet of Deliberation (C6) (Stephen P. Whiteside, 2001). It has been found that cocaine-addicted individuals have significantly lower scores on this facet when compared to healthy controls (Terracciano, Lockenhoff, Crum, Bienvenu, & Costa, 2008). Lack of premeditation involves the lack of planning before responding to a stimuli or performing some act. The second factor, urgency, reflects the tendency to commit rash or regrettable actions; this factor correlates with the NEO-PI-R facet of Impulsiveness (N5) (Stephen P. Whiteside, 2001). Impulsiveness was found to be significantly higher in cocaine-addicted patients when compared to those with no history of addiction (Terracciano et al., 2008). Sensation seeking, the third factor, is the tendency to seek excitement and adventure; this factor correlates highly with the NEO-PI-R facet of Excitement Seeking (E5), and is also found to be significantly greater in substance abusing samples when compared to healthy controls (Stephen P. Whiteside, 2001; Terracciano et al., 2008). The last factor, lack of perseverance, refers to the individual's ability to remain with a task until its completion; it correlates with the NEO-PI-R facet of Self-Discipline (C5), and has

been found to be significantly higher in healthy controls than cocaine-addicted patients (Stephen P. Whiteside, 2001; Terracciano et al., 2008).

Physiologic Underpinnings of Impulsivity and Addiction

There are many shared neurological mechanisms associated with impulsivity and addiction. Disinhibition has been found to be associated with functioning of the right inferior frontal gyrus; subthalamic nucleus; mesial, medial, and inferior frontal and parietal cortices; and the anterior cingulate cortex (Kaufman, 2003; K. Rubia, 2003; K. Rubia et al., 2001; K. Rubia, Smith, Brammer, Toone, & Taylor, 2005). Research investigating neural functioning in addicted individuals has identified dysfunction in prefrontal regions including the ACC, mesial PFC, and numerous others (N.D. Volkow et al., 1999). During cravings, areas of the brain that are activated include circuits involved with reward (nucleus accumbens), motivation (OFC), memory (amygdala and hippocampus), and cognitive control (prefrontal cortex and ACC) (Braver, Barch, Gray, Molfese, & Snyder, 2001; N.D. Volkow et al., 1999). One of the most consistent findings from imaging studies is that of hypoactivation of certain areas of the PFC in substance-abusing samples in comparison to healthy controls when a task measuring disinhibition is utilized during fMRI (de Zubicaray et al., 2000; H. Garavan, 2002; Liddle et al., 2001; N.D. Volkow et al., 1999; Williams et al., 1999). This dysfunction could also account for the impaired control (disinhibition) over the intake of drugs even when the addicted subject expresses the desire to refrain from using (Braver et al., 2001; H. Garavan, 2002).

Studies have found that individuals who have had damage to their OFC begin to exhibit impulsive behaviors, and they tend to respond incorrectly to reinforcers and punishments (A. Bechara, 2004; Budhani, Marsh, Pine, & Blair, 2007; H. Garavan, 2002; H.A. Berlin, 2004; J. Hornak, 2004; N. D. Volkow, Ding, Fowler, & Wang, 1996). Specifically, neuroimaging studies

using fMRI have found that the OFC is activated by monetary rewards and punishments, and that activation of the OFC is in direct correlation with the magnitude of the reinforcer (O'Doherty, Kringelbach, Rolls, Hornak, & Andrews, 2001). Damage to the OFC is associated with disinhibited or socially inappropriate behavior and this may be related to difficulty in responding correctly to rewards and punishers (H.A. Berlin, 2004).

Tasks designed to measure disinhibition have identified regions in the prefrontal cortex that are thought to be involved in inhibiting behavior (Botvinick, Nystrom, Fissell, Carter, & Cohen, 1999; Hester, 2004; Kaufman, 2003; K. Rubia et al., 2001). The ACC is often identified as being central to response inhibition (de Zubicaray et al., 2000; Liddle et al., 2001; Menon, Adleman, White, Glover, & Reiss, 2001), and is believed to be a key neural mechanism in inhibitory control (Williams et al., 1999). Garavan et al. (2002) used the Cognitive Failures Questionnaire (CPQ) to separate highly absent minded individuals from those with low CPQ scores before completing the Go/No-Go task during fMRI. Garavan found that the ACC played a critical role in urgent or difficult inhibitions and that absentminded individuals (those who are less conscious of their behavior and the consequences of their behavior) rely on its involvement for inhibition (H. Garavan, 2002).

Numerous neurocognitive and behavioral tasks have been developed to identify the inhibitory processes that underlie self-control disorders (Fillmore & Rush, 2002). The Go/No-Go task in the past was the standard for assessing inhibition, but due to the development of the Stop Signal Task (SST), research studies have increasingly used the SST (Logan & Cowan, 1984; Logan, Schachar, & Tannock, 1997; Schachar & Logan, 1990). The SST (Schachar & Logan, 1990; Williams et al., 1999), is a specific measure of inhibitory control, in that it measures the ability to withhold at the last minute, an already triggered response (K. Rubia, 2003). Although

both the SST and Go/No-Go both measure inhibition, the Go/No-Go measures other cognitive functions such as decision-making, response competition/response selection, conflict monitoring, and the detection of rare stimuli (K. Rubia, 2003). The SST is designed around a model of cognitive control, which postulates that the ability to inhibit an action is determined by competing activating/inhibiting processes that are elicited by cues to activate or inhibit a response (Fillmore & Rush, 2002). It is thought that the task replicates everyday situations in which a behavior needs to be inhibited unexpectedly (K. Rubia, 2003). The SST may be unique in that it is a direct assessment of an individual's ability to inhibit a pre-potent action (Fillmore & Rush, 2002).

Kaufman et al., 2003 recruited cocaine-dependent patients and controls into separate groups and had them both perform the Go/No-Go task during fMRI. The results from this study indicate that certain cortical areas, especially the ACC and mesial PFC, are less responsive in cocaine addicts compared to healthy controls (Kaufman, 2003). Hypoactivity in these structures was observed not only during successful inhibitions but also during errors, or failures to inhibit a response (Kaufman, 2003). Kaufman et al. suggest that the hypoactivity observed in cocaine addicts is consistent with the pathological drug use pattern (Kaufman, 2003). "Reduced inhibitory control, diminished action monitoring, and diminished responsivity to one's errors may represent an executive function profile of cocaine users that may…serve to prolong the maintenance of drug abuse" (p.7842) (Kaufman, 2003).

Disinhibition and functioning of the prefrontal cortex

Rubia et al. reported on subjects who performed the Go/No-Go and SST during fMRI found that the neurocognitive network responsible for motor inhibition involves the ACC and mesial PFC (K. Rubia et al., 2001). Garavan et al. had subjects perform the Go/No-Go task

during fMRI and found similar results (H. Garavan, 2002). They found that the ACC was activated for inhibition when ongoing response speeds were relatively fast, suggesting that these structures might be especially important in urgent inhibition over fast or automatic behaviors (H. Garavan, 2002). Other neural structures may influence the ability to inhibit behavior, thus playing a role in the development of addiction; these structures include the subthalamic nucleus (STN), right inferior frontal cortex (IFC), presupplementary motor area (pre-SMA), inferior frontal gyrus (rIFG), caudate, and putamen. (Aron et al., 2007; Benarroch, 2008; M.J. Frank et al., 2007; Madsen et al., 2010; Nambu et al., 2002; N.D. Volkow et al., 1999). Aron et al. suggested that the ability to suppress a response relies on the IFC because of its connections, identified through diffusion-weighted imaging (DWI), to the STN and pre SMA (Aron et al., 2007). The rIFG may also play an indirect role in inhibiting a response (Tabibnia et al., 2011)

Summary

Substance use disorders have been consistently found to be associated with impulsive characteristics. In particular, it is thought that disinhibition plays an instrumental role in the development and maintenance of these disorders. Because of the consistent differences found in neural activation during tasks measuring inhibition between substance abusing groups and healthy controls (de Zubicaray et al., 2000; H. Garavan, 2002; Kaufman, 2003; Liddle et al., 2001; Todd S. Braver, 2001; N.D. Volkow et al., 1999), this study will focus on further elucidating the relationship between inhibition and addiction. Within this study, the relationship between inhibition and neural functioning will be examined within a group of cocaine-dependent individuals. A novel approach will be attempted in this study by analyzing the relationship between personality measures of impulsivity and neural activity as assessed by the SST during fMRI.

The personality measures that will be used are the TCI and NEO-PI-R. The TCI is being utilized in this study because of its biopsychosocial perspective, and its relation of the temperament scales to neural function (C. Cloninger, 1991). The NEO-PI-R personality assessment will be used because of its documented validity and the finding that its five personality domains are found in a majority of other personality inventories (Costa Jr & McCrae, 1990; Costa et al., 1986). The facets used from the NEO-PI-R include: Deliberation (C6), Impulsiveness (N5), Excitement Seeking (E5), and Self Discipline (C5). The facets used from the TCI include: Anticipatory Worry (HA1), Fear of Uncertainty (HA2), Exploratory Excitability (NS1), Impulsiveness (NS2), Persistence (P), Purposefulness (SD2), and Congruent Second Nature (SD5).

Based on the literature discussed previously, the proposed study will compare impulsivity ratings (based on the NEO-PI-R and the TCI self report measures) and blood-oxygen-level-dependent (BOLD) activation of structures within the PFC. Activation of these structures will then be analyzed between a group of cocaine-addicted patients and a group of healthy controls. The regions of interest (ROIs) will include the ACC, mPFC, OFC, STN, pre-SMA, rIFG, caudate, dorsolateral prefrontal cortex (DLPFC), and the inferior frontal cortex (IFC). Through this study, the role that inhibition plays in addiction will be further elucidated in hopes of identifying a relationship between personality traits and physiologic factors related to inhibition that may contribute to the development and maintenance of addiction.

Specific Aims:

1. Compare activation of the ACC, mPFC, OFC, STN, pre-SMA, rIFG, caudate, IFC, and the DLPFC between cocaine-addicted patients and healthy controls as well as compare their scores on impulsive personality facets.

2. Identify relationships between the identified ROIs and personality measures of impulsivity.

Hypotheses:

1. Cocaine-addicted patients will show a hypoactivation of the ACC, mPFC, OFC, STN, pre-SMA, rIFG, caudate, IFC, and DLPFC compared to controls. The cocaine-addicted participants will show higher scores on the TCI facets of Exploratory Excitability, Impulsiveness, and Fear of Uncertainty when compared to controls. They will score lower on the TCI facets of Persistence, Purposefulness and Congruent Second Nature when compared to controls. In regards to the NEO facets, cocaine-addicted participants will show higher scores in Impulsiveness and Excitement seeking, and lower scores on Self Discipline and Deliberation when compared to controls.
2. There will be a linear relationship between scores of impulsivity and activation of the ROIs. In particular there will be negative correlations between the TCI facets of Exploratory Excitability, Impulsiveness, Anticipatory Worry and Fear of uncertainty with BOLD activation of the ROIs. There will be positive correlations between Persistence, Purposefulness, and Congruent Second Nature with BOLD activation of the ROIs. In regards to the NEO facets correlations will be negative with the facets of Impulsiveness and Excitement seeking with BOLD activation of the ROIs. There will be a positive correlation between Self Discipline and Deliberation and BOLD activation of the ROIs.

CHAPTER THREE

Methodology

Participants

The data for this study was collected as part of a larger ongoing project entitled "Impulsivity, Neural Deficits, and Cocaine Relapse" sponsored by the National Institute of Drug Abuse. The University of Texas Southwestern Medical Center at Dallas and the Veterans Administration (VA) North Texas Health Care System Institutional Review Boards approved the study protocol. For this thesis, data from volunteer samples of 24 healthy controls and 56 cocaine-addicted participants enrolled in the larger study were included in the analysis. All participants were compensated for their participation in the study.

Cocaine-Addicted Subjects

Cocaine-addicted participants were recruited from different treatment sites in north Dallas. Patients were recruited from Homeward Bound, a residential treatment center, the Dallas VAMC, and Nexus Recovery Center. Patients were expected to stay in treatment from two to four weeks or until completion of all assessments for the study. This period allowed for the verification that all patients were studied during a period when they were free from withdrawal symptoms and abstinent from cocaine use.

All patients were between the ages of 21 and 55 years old, male or female, and of any race or ethnicity. Patients met DSM-IV criteria for cocaine dependence, and identified cocaine as their primary drug of abuse. Patients were excluded if they met criteria for a major medical or neurological disorder, DSM-IV Axis I psychotic, anxiety, or affective disorder, as well as any type of organic brain syndrome. Because of the co-morbid nature of substance abuse and mood

disorders, as well as the commonality of substance induced mood disorders, patients displaying symptoms of such disorders were excluded only if symptoms continued during abstinence.

Control Subjects

Control participants were recruited using Internet and newspaper advertisements as well as fliers posted on community bulletin boards. Control participants were matched for age, race, and education with the patient sample. Controls had no history of substance abuse or dependence (except nicotine or caffeine). As well, controls had no first-degree relatives with a substance use disorder.

Exclusion Criteria for all Participants

All participants could have a BMI no higher than 32, were right handed, and possessed no contraindications for MRI, such as metal implants. Participants taking medication known to affect brain function or change perception, cognition, behavior, or mood (i.e. psychotropics, beta blockers, and certain pain medication) were excluded from the study. All participants spoke English as their native language and had a full-scale intelligence quotient (FSIQ) of at least 70 to insure that they understood the instructions and procedures necessary to complete the neurocognitive testing.

Procedure

Subjects were required to be present for three days of testing. On the first day, participants were given the TCI and NEO-PI-R self report questionnaires, demographic information was gathered, they completed the Wechsler Test of Adult Reading (WTAR), and the Structured Clinical Interview for DSM-IV (SCID) was performed. The second day involved a mock fMRI scan; this was done so that the subjects could get comfortable with the MRI machine. This insured that all functioning observed was related to the SST and not due to the

participant being in an unfamiliar environment. On the last day the participants performed the SST during fMRI, followed by a structural MRI scan.

Measures

Self-Report Personality Measures

All participants were given the NEO-PI-R and the TCI personality questionnaires. Seven TCI facets, and four from the NEO-PI-R were analyzed. The seven facets of the TCI are: Anticipatory Worry and Pessimism (HA1), Fear of Uncertainty (HA2), Exploratory Excitability (NS1), Impulsiveness (NS2), Persistence (P), Purposefulness (SD2), and Congruent Second Nature (SD5). The four facets from the NEO-PI-R are: Impulsiveness (N5), Excitement Seeking (E5), Self-discipline (C5), and Deliberation (C6).

fMRI Scan Acquisition

fMRI was conducted using a 3T Siemens Trio (60 cm diameter patient bore) MRI scanner, equipped with AutoAlign for automated and reproducible slice positioning between subjects and scan sessions and navigator-guided 3D PACE for prospective slice realignment to track head motion. The scan time took less than one hour.

fMRI Task

The Stop Signal Task (SST) was given during fMRI. The targets (right, left and upward facing arrows) were displayed on a mirrored screen above the participants' face while in the MRI. They held one control in their left hand and one in the right. When they saw a rightward facing arrow they pushed the button on the control in their right hand, and the button on the left control was pushed when they saw a leftward facing arrow. The stop signal was an arrow facing upward, when participants saw this image they were not supposed to push any button (targets were displayed for 500 ms). Intervals between stop and go changed due to the subject's success. As the participant made correct responses the delay between go and stop targets became longer,

thus making it more difficult to successfully inhibit a response. Therefore the task was designed with an algorithm to insure 50% successful and 50% unsuccessful inhibition trials.

During fMRI, responses to baseline go trials were first subtracted from the successful stop trials and unsuccessful stop trials to control for brain activation related to motor execution. Two comparisons were obtained: Stop-Success (inhibition success), Stop-Failure (inhibition failure).

Data Analyses

All statistical analyses were performed using SPSS software (SPSS Inc. Chicago, IL). Parametric statistics were used to examine demographic characteristics of the sample and substance use patterns of the patient group. Nominal data was analyzed using chi-square crosstabs analysis; personality variables were assessed through ANOVA. Pearson product-moment correlations were conducted to assess the relationship of the activation within the ROIs and scores of impulsivity assessed through the NEO-PI-R and TCI. Overall activation of the ROIs, and scores of impulsivity were compared between the patient and control group.

fMRI Analysis

fMRI analysis was conducted through the use of FEAT (fMRI Expert Analsysis Tool), which is part of FSL (FMRIB's Software Library, www.fmrib.ox.ac. Uk/fsl). FSL is an image analysis and statistical tool for use with fMRI, MRI, and diffusion tensor imaging. Pre-statistical processing included slice-timing correction using Fourier-space time-series phase-shifting; motion correction using MCFLIRT; non-brain removal using BET; spatial smoothing using a Gaussian kernal of FWHM 4mm; mean-based intensity normalization of all volumes by the same factor; and highpass temporal filtering (Gaussian-weighted LSF straight line fitting, with sigma =15.0 seconds).

Hypothesis Testing

A post-hoc power analysis was conducted to determine whether the sample size provided for in the grant is sufficient to provide significant results in our between group analyses. Assuming $\alpha = 0.01$ and a desired effect size of .80 for a sample of 60 patients and 20 controls, the estimated power ($1 - \beta$ err prob) = .676 for the independent samples between group analyses. Assuming $\alpha = 0.01$ (two-sided) and a desired effect size of .80 for a sample of 60 patients and 20 controls, the estimated power ($1 - \beta$ err prob) = 1.00 for correlational analyses. Suggested by this power analysis, the proposed sample size should be able to detect significant findings if present.

> Hypothesis I: *Cocaine addicted patients will show a hypoactivation of the ACC, mPFC, OFC, STN, pre-SMA, rIFG, and caudate compared to controls. The cocaine-addicted participants will show higher scores on the TCI facets of Exploratory Excitability, Impulsiveness, and Fear of Uncertainty when compared to controls. They will score lower on the TCI facets of Persistence, Purposefulness and Congruent Second Nature when compared to controls. In regards to the NEO facets, cocaine-addicted participants will show higher scores in Impulsiveness and Excitement seeking, and lower scores on Self Discipline and Deliberation when compared to controls.*

The ROIs for analysis will be functionally determined. Whole brain FEAT analysis will be conducted and clusters of activation within the anatomic ROIs will be identified. These clusters will be used as masks in FEAT query to identify the mean BOLD activation for each participant. BOLD responses during Stop-Failure and Stop-Success will be used within the analysis. ANOVA will then be preformed on the mean activation for each ROI to identify between group differences in neural activation. ANOVA will also be conducted on the mean scores on the personality facets of interest to examine between group differences.

Hypothesis II: *There will be a linear relationship between scores of impulsivity and activation of the ROIs. In particular there will be negative correlations between the TCI facets of Exploratory Excitability, Impulsiveness, Anticipatory Worry and Fear of uncertainty with BOLD activation of the ROIs. There will be positive correlations between Persistence, Purposefulness, and Congruent Second Nature with BOLD activation of the ROIs. In regards to the NEO facets correlations will be negative with the facets of Impulsiveness and Excitement seeking with BOLD activation of the ROIs. There will be a positive correlation between Self Discipline and Deliberation and BOLD activation of the ROIs.*

Correlations will be examined to identify any relationships between the personality facets of interest and the mean BOLD activation of the ROIs.

CHAPTER FOUR

Results

Subject Demographics and Clinical Characteristics

The study sample included 24 healthy control participants and 56 cocaine-addicted participants. Participants ranged in age from 25 to 54 years old with a mean age of 43.27 (±SD 7.84). The group was comprised of 68 male and 12 female participants 28.7% self identified as Caucasian, 66.3% African American, 3.8% Hispanic, and 1.3% Asian/Other. Healthy controls and cocaine-addicted participants were similar in age and race but differed in gender ($p = .02$)(see Table 1 for clinical and demographic data). There were significantly more females in the control group than in the cocaine-addicted group. Cocaine-addicted subjects were more likely to be African-American, male, and smokers. The cocaine-addicted sample had fewer years of education and lower scores associated with intelligence as measured by the WTAR compared with the control group.

Clinical Characteristics

The patient group generally reported at least several years of problematic cocaine use (range 1 to 34 years), using 69 to 8364 days during their lifetime. The majority reported having abused multiple substances (82% alcohol, 51% THC, 18% opiate, 16% stimulants other than cocaine, 7% anxiolytics/sedatives, and 4% other).

The healthy control group scored significantly lower on all measures of the Inventory of Drug Use Consequences (InDUC) Past 90 days and Lifetime. Cocaine-addicted participants' lifetime total InDUC score was 38.8 compared to controls whose average score was 5.4. 90 Day INDUC scores were significantly higher with cocaine-addicted participants scoring 76.8 compared to controls scoring 1.04.

Impulsive Personality Measures

Between group comparisons found significant differences in mean scores on all of the impulsive personality facets except for Exploratory Excitability and Persistence from the TCI, and Excitement Seeking from the NEO-PI-R (Table 2). Of the facets analyzed from the TCI, cocaine-addicted participants scored significantly higher than controls on Impulsiveness, Anticipatory Worry, and Fear of Uncertainty. The cocaine-addicted sample scored significantly lower than then the control group on Purposefulness and Congruent Second Nature from the TCI.

In regards to the facets examined from the NEO, the cocaine-addicted samples scored significantly higher on the Impulsiveness facet when compared to controls. However they scored significantly lower than controls on self-discipline and Deliberation from the NEO.

Stop Signal Task and fMRI BOLD Findings

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 5.98, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Z (Gaussianised T/F) statistic images were thresholded using clusters determined by $Z>2.3$ and a (corrected) cluster significance threshold of $P=0.05$ (Worsley, 2001). Stop-Success (figure 1ab) and Stop-Failure (figure 2ab) contrasts were collected during fMRI for both groups.

During Stop-Failure the control group showed changes in BOLD activation of the middle frontal gyrus, superior frontal gyrus, cingulate gyrus, medial frontal gyrus, insula, caudate and supramarginal gyrus (Table 3). Cocaine-addicted individuals showed BOLD activation changes in similar structures as well as the precuneus, middle temporal gyrus, and parahippocampal gyrus (Table 4). During Stop-Success the areas of activation within the control group included the superior parietal lobule, middle frontal gyrus, precuneus, supramarginal gyrus, inferior

temporal gyrus, and middle occipital gyrus (Table 5). The cocaine-addicted group also showed changes in the caudate, insula, superior temporal gyrus, thalamus, and inferior parietal lobule (Table 6). Areas that showed consistent changes within both groups included bilateral activation of the anterior insula and OFC, ACC, right thalamus, supramarginal gyrus, left putamen, and brainstem. However, there were no between group differences found for either Stop-Success or Stop-Failure.

Region of Interest Identification, Creation, and Activation

The FEAT analysis demonstrated that not all of the hypothesized ROIs showed significant changes in BOLD activation during the SST. Therefore, the reported activation clusters mentioned previously, including those found in the anterior insula, OFC, ACC, right thalamus, supramarginal gyrus, left putamen, and brainstem, were identified as functional ROIs. In attempts to identify functional ROIs that were more likely to show changes in activation within both groups a second level FEAT analysis was conducted of all 80 participants. Activation clusters were thresholded to $z>6$ so that only activation greater than then the set threshold would be included in the functional ROI (figure 3ab). This allowed for the ROI to only represent the region of peak activation. ROIs were identified for both the Stop-Success (SS) and Stop-Failure (SF) contrasts; Figure 4 displays the masks of the ROIs used for analyses including the ACC (SS, SF), brainstem (SS, SF), and ROI including areas of both the left lateral OFC and the anterior insula (SS, SF), left putamen (SS, SF), a ROI including the right lateral OFC and anterior insula (SS, SF), right thalamus (SS), and supramarginal gyrus (SF).

The mean BOLD change in activation for each ROI, for each participant, was than evaluated through the use of FEATqueary, which is native to the FSL imaging program. Table 7 contains the mean activation found in each ROI for the entire study sample as well as individual

groups. Upon further analysis of the ROIs it was found that the control group and cocaine-addicted group did not did not have any statistically significant differences in BOLD activation (Table 8).

Personality and BOLD Activation Relationships

Pearson product-moment correlations were performed to identify relationships between the BOLD activation of the ROIs and participants' scores on impulsive personality facets. Correlations were identified in the entire subject group (Table 9) as well as in the control (Table 10) and cocaine-addicted groups (Table 11). There were numerous differences and similarities between the two groups outlined in table 12.

All Participants' Activation and Personality Correlations

When examining the relationship between impulsive personality facets and BOLD activation of the ROIs for the entire study sample, 13 statistically significant relationships ($p<.05$) were identified. During Stop-Failure, activation of the brainstem was related to the TCI facets measuring Exploratory Excitability ($r=.254$, $p=.020$) and Impulsiveness ($r=.274$, $p=.014$). Activation in the brainstem was correlated with NEO-PI-R facet measuring Deliberation ($r=-.336$, $p=.002$). Activation during Stop-Failure in the region containing the right lateral OFC and anterior insula was correlated with the TCI facets measuring Exploratory Excitability ($r=.259$, $p=.02$) and Anticipator Worry ($r=.302$, $p=.007$) and the NEO-PI-R facet measuring Excitement Seeking ($r=-.273$, $p=.030$). BOLD activation during Stop-Failure in the left lateral OFC and anterior insula ROI was found to be related to the TCI facet of Anticipatory Worry ($r=.238$, $p=.037$). During Stop-Success, activation of this same ROI was found to correlate with the TCI facets Anticipatory Worry ($r=.260$, $p=.020$) and Fear of Uncertainty ($r=.242$, $p=.030$). Activation during Stop-Failure in the supramarginal gyrus was related to the TCI facets Anticipatory Worry

(r=.261, p=.019) and Persistence (r=-.243, p=.030). Anterior cingulate activation during Stop-Failure was correlated with the TCI facet of Persistence (r=-.277, p=.030), and left putamen activation during Stop-Success was related to the TCI facet of Purposefulness (r=-.220, p=.050).

Control Participant Activation and Personality Correlations

In analyzing the relationships between BOLD activation and impulsive personality facets, the control group demonstrated 18 total significant correlations. Activation during Stop-Failure in the brainstem was correlated with the TCI facet Impulsiveness (r=.274, p=.014) and the NEO-PI-Rfacet of Self Discipline (r=-.412, p=.045). Activation of this same ROI during Stop-Success was related to the TCI facet Fear of Uncertainty (r=.431 p=.023). The activation during Stop-Failure of the ROI including the right lateral OFC and anterior insula was related to the TCI facets of Impulsiveness (r=.493, p=.014), Fear of Uncertainty (r=.482, p=.017), and Anticipatory Worry (r=.302, p=.007). This region was also associated with the NEO-PI-Rfacet of Excitement Seeking (r=-.273, p=.030). The activation of this region during Stop-Success was related to the TCI Impulsiveness facet (r=.577, p=.003). Activation during Stop-Failure in the left lateral OFC and anterior insula correlated with the TCI facets of Impulsiveness (r=.426, p=.038) and Anticipatory Worry (r=.238, p=.037). The supramarginal gyrus was found to be associated with the TCI facets Anticipatory Worry (r=.261, p=.019) and Persistence (r=.243, p=.030) during Stop-Failure. This ROI was also found to be related to the NEO-PI-Rfacet Excitement Seeking (r=.428, p=.032). The activation of the ACC during Stop-Failure was related to the TCI facet of Persistence (r=-.277, p=.030). During Stop-Failure the left putamen correlated with the TCI facets of purposefulness (r=.425, p=.038) and Congruent Second Nature (r=.507, p=.012). During Stop-Success the activation of this ROI was related to the TCI facet of Purposefulness (r=.481, p=.017) and the NEO-PI-Rfacet of Excitement Seeking (r=.464, p=.022).

Cocaine-Addicted Participants' Activation and Personality Correlations

Cocaine-addicted participants demonstrated 18 relationships between BOLD activation and impulsive personality facets. Activation during Stop-Failure in the brain stem was related to the TCI facet Exploratory Excitability (r=.280, p=.037) and the NEO-PI-Rfacets Deliberation (r=-.391, p=.003) and Excitement Seeking (r=.279, p=.038). Activation during Stop-Failure of the region including the right lateral OFC and anterior insula was found to be related to the TCI facets Exploratory Excitability (r=.280, p=.037) and Anticipatory Worry (r=.343, p=.010). During Stop-Success this region was related to the TCI facet Puprosefulness (r=-.266, p=.033). The region including the left OFC and anterior insula was related to the TCI facet of Anticipatory Worry during Stop-Failure (r=.310, p=.024), and Stop-Success (r=.270, p=.044). Activation of the supramarginal gyrus during Stop-Failure was related to the TCI facets of Impulsiveness (r=.278, p=.038), Anticipatory Worry (r=.360, p=.007), Persistence (r=-.264, p=.049), and Purposefulness (r=-.272, p=.042). The activation of the ACC during Stop-Failure was related to the TCI facet of Persistence (r=-.305, p=.022). During Stop-Success the activation of the right thalamus was related to the TCI facets of Anticipatory Worry (r=.265, p=.049) and Purposefulness (r=-.299, p=.025). Activation was also related to the NEO-PI-Rfacet of Impulsiveness (r=.305, p=.022). The left putamen was related to the TCI facet of Purposefulness (r=-.333, p=.012) and the NEO-PI-Rfacet of Deliberation (r=-.292, p=.029) during Stop-Success.

Exploratory Analysis

To further examination the role that impulsive personalities play in neural functioning without decreasing statistical power by using eleven separate personality variables. It was decided that the eleven personality facets needed to be combined in order to have one or two impulsive personality variables a principle component analysis (PCA) was used to determine the

factor scores for each personality facet. The PCA was run in SPSS using a direct oblimin rotation (non-orthogonal). The scree plot (figure 5) indicated that two components could statistically account for the majority of the variance found within the personality facets, eigenvalues for the remaining components suggest that they contribute little to the explanation of variance. Table 13 contains the factor loadings for both of the components. The major domains of principal component 1 (PC1) include Deliberation (NEO C6), Congruent Second Nature (TCI S5), Self Discipline (NEO C5), and Purposefulness (TCI S2). The major domains found in principle component 2 (PC2) include Fear of Uncertainty (TCI HA2), Excitement Seeking (NEO E5), Exploratory Excitability (TCI NS1), and Anticipatory Worry (TCI HA1).

Relationships Between Personality Components and Neural Functioning

The two personality components were used in a second level FEAT analysis as covariates to analyze how impulsive personality facets interacted with neural activation. This FEAT analysis included contrasts that depicted correlations between activation and both personality components as well as allowed for the identification of significant interactions between neural activation and the personality components both between and within both groups. This analysis was run two separate times. The first time it was run without controlling for gender or FSIQ, the second analysis included these variables. No significant differences in activation clusters were identified between the two separate analyses.

Three activation clusters were found to have a negative correlation between PC1 and BOLD activation in controls and cocaine-addicted patients during Stop-Failure. These activation clusters were found in the middle occipital gyrus, inferior frontal gyrus, and the postcentral gyrus (Figure 6) (Table 14). Two clusters, one in the precuneus and one in the middle temporal gyrus (Figure 7)(Table 15), were found to be negatively associated with personality component 1

during Stop-Success. When the personality components were used to explore the interaction of personality and neural functioning between groups, one cluster, found in the hippocampus, showed a significant difference in its interaction between the two groups (Figure 8). The activation of this cluster demonstrated that there is a significant interaction between PC2 and neural functioning of the hippocampus during Stop-Failure.

The activation cluster within the left hippocampus was used as a mask (Figure 9) in a FEATquery so that the relationship of PC2 and activation of the left hippocampus could be further explored. This analysis elucidated a negative correlation between personality component 2 and BOLD activation in the control group ($r=-.590$, $p=.002$) (figure 10) and a positive trend in the cocaine-addicted group ($r=.218$, $p=.106$) (figure 11). It should be noted that one control participant was removed from the correlation analysis due to their mean activation score (-.883) being over three standard deviations below the mean activation for the control group ($M= -.019$, $SD=.232$).

CHAPTER FIVE

Discussion

Differences in Personality

By utilizing personality facets as a measure of impulsivity, the relationship between impulsive personalities and neural functioning, as measured during the SST, could be examined. This technique allowed for differences in personality between healthy controls and cocaine-addicted participants to be compared, as well as explore how these personality facets may be related to the impulsive aspect of disinhibition.

The cocaine-addicted sample demonstrated greater impulsive characteristics compared to the control cohorts. Cocaine-addicted participants scored significantly higher on the TCI and NEO facets of Impulsiveness as well as the NEO facet of Impulsiveness compared to control participants. Cocaine-addicted participants reported believing that they make decisions quickly on incomplete information. They also reported having the view of themselves as being unable to inhibit an automatic impulse, in particular in the face of urges and cravings, an aspect of personality that is very relevant for an addicted population. However, the healthy control group reported believing themselves to be more reflective and analytical in their decision-making as well as more likely to think before automatically acting on an impulse. When addicted individuals encounter a trigger to use they begin to have cravings or urges to use their substance of choice. This difference in reported personality characteristics demonstrates the idea that cocaine-addicted participants feel they will not be able to inhibit their desire to use when faced with a trigger. Unlike the cocaine-addicted participants, the healthy control participants reported that they believe they can easily resist temptation in the face of strong urges or cravings.

This study also found that cocaine-addicted participants scored significantly higher on personality facets measuring Anticipatory Worry and Fear of Uncertainty compared to healthy control participants. Cocaine-addicted participants reported that they perceive themselves as fearful, insecure, and pessimistic. They also reported that they feel they cannot tolerate being in unfamiliar situations. However, control participants believe themselves to be more confident and calm and that they would not mind being in a new or unfamiliar situation. This may suggest that cocaine-addicted participants act more impulsively in uncomfortable situations or to alleviate negative mood or affect.

Cocaine-addicted participants scored significantly lower on the TCI facet Purposefulness when compared to the control group. The control group reported that they perceive themselves as more goal oriented and tend to act in a more purposeful manner having clear sense of direction, while the cocaine-addicted participants felt as though they lacked meaning and purpose in their lives. There was a similar difference in scores on the NEO facet of Self-Discipline. The control group believes they are more deliberate in their actions being able to maintain attention to a task despite distraction or failure, while the cocaine-addicted participants lack this self-control. These significant differences in the personality of the two groups paint two very different pictures. The reported personality type of the cocaine-addicted sample is much more impulsive and self-doubting when compared to controls. Furthermore, this cocaine-addicted group reported that they do not have confidence in themselves to inhibit a previously reinforced response, a personality trait that is vital to maintaining sobriety.

Neural Functioning During the SST

The neuroimaging findings were consistent with other research studies utilizing the SST with similar structures showing changes in activation during both Stop-Failure and Stop-Success (Horn, Dolan, Elliott, Deakin, & Woodruff, 2003; Kaufman, 2003) (Braver et al., 2001; de Zubicaray et al., 2000; H. Garavan, 2002; H.A. Berlin, 2004; K. Rubia, 2003) (Kaufman, 2003; Li, Huang, Constable, & Sinha, 2006; Katya Rubia et al., 2001). Rubia et al., 2001 recruited 15 healthy participants to perform the SST during fMRI. The study found that during inhibition there was change in BOLD activation in similar structures found in this study including the anterior cingulate cortex, precentral gyrus, superior frontal gyrus, and inferior parietal lobule (Katya Rubia et al., 2001). Another study utilizing 24 healthy control participants found similar activation during performance of the SST. Li et al. 2006, identified activation clusters during Stop-Success in the middle frontal gyrus, middle frontal gyrus, and the superior frontal gyrus (Li et al., 2006). Similar activation clusters were identified during Stop-Failure as well, including clusters in the lingual gyrus, precentral gyrus, medial frontal gyrus, superior frontal gyrus, thalamus, insula, and superior frontal gyrus (Li et al., 2006).

Kaufman et al., 2003 recruited 13 active cocaine-using patients and 14 healthy controls; again similar activation clusters were identified during performance of the Go/No-Go, a task similar to the SST. During successful inhibition, similar activation clusters were found in this current study and the Kaufman study; including clusters in the middle frontal gyrus, inferior frontal gyrus, superior frontal gyrus, thalamus, insula, and putamen (Kaufman, 2003). When participants failed to inhibit a response similar activation clusters were found in the middle frontal gyrus, medial frontal gyrus, superior frontal gyrus, precentral gyrus, inferior frontal gyrus, cingulate gyrus, middle temporal gyrus, putamen, and insula (Kaufman, 2003).

However, unlike other studies (de Zubicaray et al., 2000; H. Garavan, 2002; Liddle et al., 2001; N.D. Volkow et al., 1999; Williams et al., 1999), no differences in activation were identified between the cocaine-addicted group and healthy controls in this current study. Li et al., 2007 recruited 15 abstinent cocaine-addicted participants and 15 healthy controls (Li et al., 2007). Within Li's study abstinent cocaine-addicted participants showed hypoactivation, when compared with healthy controls, in the angular gyrus, supramarginal gyrus, lingual, and prigenual gyrus (Li et al., 2007). Unlike this current study Li et al. had a much smaller study sample.

Kaufman et al. 2003, compared the BOLD activation of 13 cocaine-dependent participants who were actively using cocaine, with 14 healthy controls during the Go/No-Go (Kaufman, 2003). The results of Kaufman's study found the ACC and mesial PFC to be less responsive in the cocaine-addicted group when compared to healthy controls (Kaufman, 2003). Kaufman's study employed cocaine-dependent participants that were actively using (last use within 72 hours) as opposed to the present study that utilized cocaine-addicted participants that were studied while abstinent from cocaine. The observed differences found in the Kaufman study may be attributed to functional changes in the brain that occur while an individual is actively using cocaine. If that were the case we would expect to see a lack functional differences between the two groups in this current study.

This current study failed to identify any differences in BOLD activation between the two groups, suggesting that there are no neuro-functional difference in response inhibition between healthy controls and cocaine-addicted participants. However this study sample was different, both in size and clinical characteristics, from studies that found differences in BOLD activation. This study employed a much larger study sample than those studies that identified differences in

BOLD activation. Furthermore, the cocaine-addicted participants were abstinent from cocaine for at least two weeks prior to being studied.

The Relationship Between Personality and Neural Functioning

Numerous relationships between personality facets and BOLD activation were found to be similar between the cocaine-addicted group and the healthy control group. Similar positive relationships found between personality facets and ROIs include Exploratory Excitability (TCI NS1) and activation during SF of the brainstem ROI suggesting that as individuals in both groups feel the need for excitement in their surroundings they recruit more neural resources from this region when they fail to inhibit a response. Similar positive relationships were observed between Anticipatory Worry (TCI HA1) and SF activation of the left and right lateral OFC and anterior insula ROI. This suggests that as individuals believe they cannot tolerate uncertainty or unfamiliar circumstances they recruit more neural resources from these ROIs when they fail to inhibit a response.

Similar negative relationships were also identified between Persistence (TCI P) and SF activation of the ACC and supramarginal gyrus ROIs. This suggests that as individuals feel they are more distractible and unable to complete difficult tasks they recruit fewer resources from these regions when they fail to inhibit a response. However, there were a few correlations, identified to be significant based on previous research, in the cocaine-addicted group that were found to either be different or not found in healthy control group.

Cocaine-addicted participants showed a positive relationship between activation during Stop-Failure of the left lateral OFC and anterior insula ROI and the TCI facet of Anticipatory Worry. Cocaine-addicted participants endorsed personality traits that depicted them as being unable to tolerate uncertainty or unfamiliar circumstances. Activation of the left OFC and

anterior insula have been found to show increases in activation when individuals successfully inhibit a response. (Horn et al., 2003). This positive correlation suggests that the more cocaine-addicted individuals feel uncomfortable or uncertain the more neural resources they utilize from this ROI when they fail to inhibit a motor response. This personality trait was also found to be associated with activation of the right thalamic ROI during Stop-Success. The thalamus has shown increased activation when a participant deliberates or contemplates a decision (Michael J Frank, Johan Samanta, Ahmed A Moustafa, & Scott J Sherman, 2007). The thalamus is also functionally connected to the hippocampus (Stein et al., 2000) and plays a role in episodic memory (Aggleton et al., 2010). This positive correlation between the thalamus and anticipatory worry may suggest that as cocaine-addicted individuals feel less comfortable the more they rely upon activation of the thalamus during inhibition, perhaps when a memory has been activated causing them emotional discomfort.

Cocaine-addicted participants scored significantly lower on the TCI facet of Purposefulness (TCI S2). Individuals that score high on this facet believe that they struggle to find direction, purpose, and meaning in their lives. This personality facet was found to be negatively correlated with the Stop-Success activations of the right lateral OFC and anterior insula, R. thalamus, and supramarginal gyrus. These regions have been identified as playing a role in the maintenance of attention and focus to tasks (Katya Rubia et al., 2000). Cocaine-addicted participants demonstrated a negative relationship to the R. thalamus ($r = -.272$, $p = .042$) while control participants demonstrated a positive relationship ($r = .481$, $p = .017$). This difference in correlations of Purposefulness with activation during Stop-Success of the right thalamus is an interesting finding. As cocaine-addicted participants believe that they have less purpose in life they recruit fewer resources from the right thalamus when inhibiting a response,

whereas when controls feel they have less purpose in life they recruit more resources from the right thalamus. Because of the association between functioning of the right thalamus and attention it may be suggested that because the cocaine-addicted participants feel they have less purpose in life they fail to pay proper attention to tasks. This finding demonstrates a difference between groups in how this aspect of personality relates to neural functioning differently between cocaine-addicted individuals and those that are healthy. The difference in this correlation, between cocaine-addicted participants and controls, may suggest a dysfunction in activation of the right thalamus within cocaine-addicted participants. This dysfunction may predispose these individuals to developing cocaine-dependence, or it may serve as evidence for neural dysfunction caused by long-term cocaine use.

Impulse Drive and Impulse Control Personality Components

In order to further understand the relationship between impulsive personalities and neural functioning a PCA was performed on the eleven personality facets, which resulted in the development of two distinct personality components. These components were then used in FEAT analysis to examine how these personality constructs interacted with neural activation neural during the SST within cocaine-addicted and healthy control participants, as well as between groups. As mentioned previously in this paper, impulsivity is a composed of multiple dimensions. The two components identified through the PCA appear to represent two separate aspects of impulsivity. Garavan proposed two separate dimensions of impulsivity, impulse drives and impulse control (H. Garavan, 2002). The impulse drive is reward seeking, while impulse control can be viewed as the ability to inhibit a previously reinforced response. The two separate personality components found through the PCA appear to describe the dimensions of impulsivity that Garavan proposed. PC1's main factors include Deliberation (NEO C6), Congruent Second

Nature (TCI S5), Self Discipline (NEO C5), and Purposefulness (TCI S2). These facets reflect Garavan's concept of impulse control in that they are associated with how people think before they act, and whether or not they are behaving congruently with the way the desire. They also reflect how goal oriented people are and whether they can follow through on tasks despite distraction or boredom. Thus, these personality facets relate to decision-making and impulse control.

PC2's main factors include Fear of Uncertainty (TCI HA2), Excitement Seeking (NEO E5), Exploratory Excitability (TCI NS1), and Anticipatory Worry (TCI HA1). These facets reflect an individual's ability to tolerate unfamiliar circumstances, how confident they are in themselves, and their need for environmental stimulation. Individuals that feel comfortable, confident and desire external stimulation may act in an impulsive manner having their behavior dictated by the desire for reward or pleasure. The components that were elucidated through the PCA fall into place with these two separate dimensions of impulsivity. PC1 reflects the impulse control personality component while PC2 reflects the impulse drive personality component.

The Interaction Between Impulse Control and Impulse Drive and Neural Funcioning

When the impulse drive and impulse control personality components were used to examine relationships with neural functioning during inhibition three activation clusters were identified to correlate negatively with Impulse Control during Stop-Failure. The activation clusters identified to have a negative relationship with impulse control were found in the middle occipital gyrus, inferior frontal gyrus, and postcentral gyrus. This suggests that as both cocaine-addicted participants and healthy controls have higher scores on impulse control they recruit less neural resources from these regions when the fail to inhibit a response. Two activation clusters within the precuneus and middle temporal gyrus were also identified as being negatively

correlated with impulse control and Stop-Success neural activation. These findings suggests that as individuals have increased levels of impulse control they do not need as much activation from these regions to successfully inhibit a response.

When the impulse control and impulse drive personality components were used to analyze interaction effects with neural activation a cluster within the left posterior hippocampus demonstrated a significant interaction between groups (cocaine-addicted vs. control) of the impulse drive personality component and BOLD activation during Stop-Failure.

The left hippocampus has been associated with the inhibition, or suppression of unwanted memories (Anderson et al., 2004). It has been found that controlling unwanted memories is associated with reduced hippocampal activation (Anderson et al., 2004). Cocaine-addicted participants may be attempting to control unwanted memories for two reasons. First, cocaine-addicted individuals may be trying to control memories of past use in order to decrease their desire to use. Second, because of the documented relationship between past trauma and addiction (Davis, Mill, & Roper, 1997; Schepis, Rao, Yadav, & Adinoff, 2011; Sinha, 2008), the may be suppressing memories that cause them to have negative affect or mood.

It may be suggested that because this group may frequently be trying to suppress a memory they have a baseline hypoactivation of the hippocampus. This might contribute to why cocaine-addicted participants demonstrate this interaction between impulse drive and left hippocampal activation. This study demonstrated that as cocaine-addicted participants have higher impulse drives they recruit more left hippocampal activation during inhibition failure, whereas when controls have higher impulse drives they recruit less neural resources during inhibition failure. This reverse interaction between groups in the relationship that the impulse drive personality component has with activation of the left hippocampus suggests a dysfunction

that may predisposes individuals to developing substance abuse. This may also suggest changes in neural functioning that are a result of prolonged abuse of cocaine.

Strengths and Limitations

In conducting research into substance abuse, it is difficult to recruit a sample that can be easily generalized to the general population. The majority of our sample consisted of lower SES African American males. This fact makes it hard to generalize the findings to all clinical populations. However, this study is unique in the large number of participants from which data was collected. A majority of fMRI studies have recruited 10-20 participants for each group, but this study employed 56 cocaine-addicted participants and 24 healthy controls, giving this study more power allowing for more certainty on significant findings.

Another limitation to the study is the fact that the cocaine-addicted group and healthy control group were not matched in terms of education or FSIQ. These differences may account for differences in cognitive functioning that are separate from what the study was designed to identify. Additionally, the groups were screened for active Axis I disorders (other than substance dependence) medical or neurological disorders, as well as if they were currently taking any psychotropic medications. While it is beneficial to have rigorous inclusion/exclusion criteria, in that it allows for better experimental control, it greatly limits the generalizability of the findings. Substance-dependent individuals frequently present with co-morbid Axis I disorders, medical problems, and are on numerous psychotropic medications. Furthermore, the current study is cross-sectional; therefore, the data collected does not lend itself for further assumptions concerning causality between neural functioning as it relates to inhibition and personality. Furthermore the SST is a measure of motor inhibition, and does not assess inhibition while the participant experiences cravings or urges, nor does it have any relationship to reward or

punishment. Therefore, the findings should not be generalized to inhibition as it relates to inhibiting a previously reinforced response in the face of urges or cravings.

Conclusion

This study examined how impulsive personality facets relate to, or interacts with, neural functioning during a task designed to measure disinhibition. Despite failing to find a difference in activation of the ROIs between cocaine-addicted participants and healthy controls, the study successfully showed that a cocaine-addicted sample has a significantly more impulsive personality than healthy controls. It was also seen that some of these personality facets might be related to neural functioning. This gives credence to the idea neural functioning and personality are connected, that there is a link between cognition and personality traits. Although the exact interaction was not entirely clear through this study, a few noteworthy findings were observed. The fact that the impulse drive personality component interacted differently on the left hippocampus in the cocaine-addicted sample in comparison to healthy controls deserves further investigation. It is also noteworthy that reverse relationships were observed between the groups in the relationships between the Impulse Drive Component and SF activation of the hippocampus; and the TCI facet of Purposefulness and SS activation of the right thalamus. These reverse relationships may signify a difference between the groups that may either predispose the cocaine-addicted participants to developing substance dependence disorders, or it may be a neuro-functional change that has resulted due to prolonged exposure to cocaine. As research into the relationship of impulsive personalities and neural functioning continues, the inclusion of the impulse drive component, impulse control component, as well as other neuro-cognitive measures of impulsivity should be utilized to further elucidate this complex relationship.

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Table 1

Demographics and Clinical Characteristics

		Total	Control	Cocaine-Addicted	p value
Gender, *n* (%)					0.020*
	Male	68 (85)	17(70.8)	51(91.1)	
	Female	12 (15)	7(29.2)	5(8.9)	
Age, mean (SD) (years)		46 (7.80)	39.5(8.40)	41.75(7.54)	0.26
Race, *n* (%)					0.41
	White	23	10 (41.7)	13	
	African American	53	12 (50)	41	
	Asian/Other	1	1 (4.2)	0	
	Hispanic	3	1 (4.2)	2	
Years of Education mean (SD)(years)		13 (1.76)	14 (1.58)	12 (1.58)	0.000*
WTAR *FSIQ* (Mean) (SD)		90 (17.38)	99 (10.63)	88.5 (8.56)	0.002*

*Value significant at α level of $p < .05$.

Table 2

Mean Scores From the TCI and NEO Personality Measures

Personality Facet	All Participants	Control	Cocaine-addicted Participants	df	F	Sig.
Exploratory Excitability (TCI NS1)	6.25 (2.24)	6.63 (1.84)	6.09 (2.39)	1	0.959	0.33
Impulsiveness (TCI NS2)	4.43 (2.41)	2.67 (1.69)	5.18 (2.29)	1	23.386	0.000*
Anticipatory Worry (TCI HA1)	3.61 (2.37)	2.25 (1.45)	4.2 (2.45)	1	13.087	0.001*
Fear of Uncertainty (TCI HA2)	3.58 (1.52)	2.75 (1.23)	3.93 (1.5)	1	11.505	0.001*
Persistence (TCI P)	5.47 (1.76)	5.96 (1.27)	5.27 (1.9)	1	2.648	0.108
Purposefulness (TCI S2)	5.8 (1.9)	7.33 (.87)	5.14 (1.85)	1	30.494	0.000*
Congruent Second Nature (TCI S5)	7.96 (2.87)	10.88 (1.33)	6.71 (2.41)	1	63.005	0.000*
Impulsiveness (NEO N5)	54.64 (11.9)	42.46 (8.7)	59.86 (8.91)	1	64.915	0.000*
Excitement Seeking (NEO E5)	52.98 (8.26)	53.13 (8.53)	52.91 (8.21)	1	0.011	0.916
Self Discipline (NEO C5)	46.22 (12.19)	53.42 (9.89)	43.14 (11.84)	1	13.883	0.000*
Deliberation (NEO C6)	45.79 (12.84)	56.63 (11.69)	41.14 (10.32)	1	34.921	0.000*

*$p<.05$

Table 3

Activation Clusters for the Control Group During Stop-Failure

Structure	X coor	Y coor	Z coor	Brodmann area
Middle Frontal Gyrus	46.78	10.28	33.07	BA9
Superior Frontal Gyrus	0.27	16.05	52.65	BA8
Inferior Parietal Lobule	46.46	-45.15	42.22	BA40
Angular Gyrus	-31.24	-57.27	34.36	BA39
Inferior Parietal Lobule	35.42	-53.71	34.02	BA40
Cingulate Gyrus	2.34	17.61	36.61	BA32
Precentral Gyrus	47.01	6.43	14.69	BA44
Caudate	-12.1	7.61	4.79	Caudate Head
Superior Temporal Gyrus	50.51	-42.56	15.51	BA13
Insula	30.57	20.95	1.37	*
Superior Frontal Gyrus	5.57	-4.18	67.04	BA6
Medial Frontal Gyrus	0.13	4	60.51	BA6
Superior Temporal Gyrus	-49.01	12.22	-2.6	BA22
Insula	-37.94	10.13	-0.81	BA13
Supramarginal Gyrus	-40.45	-49.59	33.13	BA40
Fusiform Gyrus	41.65	-50.55	-17.82	BA37

Table 4

Activation Clusters for the Cocaine-addicted Group During Stop-Failure

Structure	X coor	Y coor	Z coor	Brodman area
Precuneus	23.2	-68.02	35.17	BA 7
Cingulate Gyrus	6.48	14	34.98	BA 32
Cuneus	-18.47	-82.35	26.74	BA 18
Middle Temporal Gyrus	46.04	-60.32	1.43	BA 37
Inferior Parietal Lobule	-52.39	-45.57	21.69	BA 40
Insula	-36.96	13.03	-3.36	BA 13
Culmen	-3.04	-30.76	-7.81	*
Inferior Temporal Gyrus	-39.15	-65.03	-3.02	BA 37
Inferior Frontal Gyrus	-52.17	8.21	14.33	BA 44
Precuneus	-7.06	-53.4	48.6	BA 7
Lingual Gyrus	13.83	-64.07	4.61	BA 18
Lentiform Nucleus	-21.82	11.11	-5.2	Putamen
Declive	25.2	-72.6	-12.16	*
Precentral Gyrus	42.35	-10.96	33.57	BA 6
Cingulate Gyrus	2.43	-49.22	41.69	BA 31
Parahippocampal Gyrus	-22.09	-57.6	-2.43	BA 19
Middle Frontal Gyrus	44.27	3.49	45.38	BA 6
Middle Frontal Gyrus	-52.24	6.58	39.56	BA 6
Middle Temporal Gyrus	-44.82	-56.08	6.57	BA 39
Superior Frontal Gyrus	-27.46	45.21	27.75	BA 10
Inferior Parietal Lobule	49.8	-38.26	42.7	BA 40
Lingual Gyrus	-7	-71.23	0.39	BA 18
Superior Frontal Gyrus	-12.64	-9.12	71.35	BA 6
Precentral Gyrus	-44.76	-7.57	51.35	BA 6
Parahippocampal Gyrus	8.25	-39.14	2.58	BA 30

Table 5

Activation Clusters for the Control Group During Stop-Success

Structure	X coor	Y coor	Z coor	Brodman area
Superior Parietal Lobule	30.84	-49.24	38.25	BA 7
Middle Frontal Gyrus	46.22	11.87	33.27	BA 9
Precuneus	25.13	-63.89	30.02	BA 7
Inferior Parietal Lobule	49.78	-43.84	40.53	BA 40
Supramarginal Gyrus	-39.19	-48.4	34.25	BA 40
Precuneus	-27.88	-60.1	37.18	BA 19
Inferior Temporal Gyrus	49.83	-58.35	-0.23	BA 19
Cuneus	27.02	-74.24	13.07	BA 30
Middle Occipital Gyrus	-46.76	-74.45	-3.68	BA 19

Table 6

Activation Clusters for the Cocaine-addicted Group During Stop-Success

Structure	X coor	Y coor	Z coor	Brodman area
Inferior Parietal Lobule	36.52	-49.18	36.48	BA 40
Insula	31.21	21.79	-0.56	*
Precuneus	-24.13	-78.4	25.16	BA 31
Insula	-31.26	24	2.82	BA 13
Middle Frontal Gyrus	-27.71	-9.15	44.12	BA 6
Middle Occipital Gyrus	-41.08	-71.05	2	BA 37
Caudate	10.32	8.36	3.87	Caudate Head
Culmen	-4.94	-30.74	-7.82	*
Lingual Gyrus	-3.21	-72.93	-3.31	BA 18
Thalamus	4.55	-14.58	5.96	Medial Dorsal Nucleus
Lingual Gyrus	11.93	-67.73	2.55	BA 18
Precentral Gyrus	-54.04	10.58	7.24	BA 44
Declive	-24.02	-77.62	-16.41	*
Middle Frontal Gyrus	-46.44	32.11	26.78	BA 46
Superior Temporal Gyrus	-56.14	-39.5	16.63	BA 13
Middle Frontal Gyrus	38.77	30.16	16.32	BA 46
Lingual Gyrus	8.06	-94.12	-1	BA 17
Superior Frontal Gyrus	-29.36	45.11	29.54	BA 9
Middle Occipital Gyrus	11.82	-89.39	13.8	BA 18
Superior Temporal Gyrus	-50.48	-50.35	6.91	BA 39

Table 7

Mean BOLD Activation of the Regions of Interest

Region of Interest	All Participants	Control	Cocaine-addicted Participants
anterior cingulate SF	0.166 (.148)	0.170 (.124)	0.164 (.158)
anterior cingulate SS	0.156 (.155)	0.122 (.156)	0.171 (.154)
Brain Stem SF	0.144 (.18)	0.113 (.115)	0.157 (.201)
Brain Stem SS	0.161 (.23)	0.109 (.224)	0.183 (.232)
L. lateral OFC and anterior insula SF	0.183 (.156)	0.190 (.165)	0.180 (.154)
L. lateral OFC and anterior insula SS	0.150 (.178)	0.128 (.182)	0.159 (.177)
L. putamen SF	0.081 (.135)	0.081 (.134)	0.082 (.136)
L. putamen SS	0.084 (.125)	0.065 (.120	0.091 (.129)
R. lateral OFC and anterior insula SF	0.175 (.179)	0.171 (.169)	0.176 (.185)
R. lateral OFC and anterior insula SS	0.177 (.169)	0.174 (.177)	0.179 (.167)
R. thalamus SS	0.072 (.216)	0.106 (.308)	0.057 (.163)
supramarginal gyrus SF	0.130 (.119)	0.142 (.116)	0.126 (.119)

Mean (SD)

Table 8

ANOVA of ROIs Between Groups

Region Of Interest	df	Mean Square	F	Sig.
anterior cingulate SF	1	.001	.032	.859
anterior cingulate SS	1	.039	1.642	.204
Brain Stem SF	1	.032	.983	.325
Brain Stem SS	1	.090	1.702	.196
L. lateral OFC and anterior insula SF	1	.002	.068	.795
L. lateral OFC and anterior insula SS	1	.016	.511	.477
L. putamen SF	1	.000	.001	.976
L. putamen SS	1	.012	.731	.395
R. lateral OFC and anterior insula SF	1	.000	.013	.910
R. lateral OFC and anterior insula SS	1	.000	.015	.901
R. thalamus SS	1	.039	.834	.364
supramarginal gyrus SF	1	.004	.298	.587

Table 9

Correlation Matrix for All participants

Personality Facet	anterior cingulate (SF)	anterior cingulate (SS)	Brain Stem (SF)	Brain Stem (SS)	L. lateral OFC + anterior insula (SF)	L. lateral OFC + anterior insula (SS)	L. putamen (SF)	L. putamen (SS)	R. later OFC + anterior insula (SF)	R. later OFC + anterior insula (SS)	R. thalamus (SF)	R. thalamus (SS)	Supramarginal Gyrus (SF)
Exploratory Excitability (TCI NS1)	-	-	r=.254 p=.02	-	-	-	-	-	r=.259 p=.02	-	-	-	-
Impulsiveness (TCI NS2)	-	-	r=.274 p=.014	-	-	-	-	-	-	-	-	-	-
Anticipatory Worry (TCI HA1)	-	-	-	-	r=.238 p=.037	r=.260 p=.020	-	-	r=.302 p=.007	-	-	-	r=.261 p=.019
Fear of Uncertainty (TCI HA2)	-	-	-	-	-	r=.242 p=.030	-	-	-	-	-	-	-
Persistence (TCI P)	r=-.277 p=.030	-	-	-	-	-	-	-	-	-	-	-	r=-.243 p=.030
Purposefulness (TCI S2)	-	-	-	-	-	-	-	r=-.220 p=.050	-	-	-	-	-
Congruent Second Nature (TCI S5)	-	-	-	-	-	-	-	-	-	-	-	-	-
Impulsiveness (NEO N5)	-	-	-	-	-	-	-	-	-	-	-	-	-
Excitement Seeking (NEO E5)	-	-	-	-	-	-	-	-	r=-.273 p=.030	-	-	-	-
Self Discipline (NEO C5)	-	-	-	-	-	-	-	-	-	-	-	-	-
Deliberation (NEO C6)	-	-	r=-.336 p=.002	-	-	-	-	-	-	-	-	-	-

*Only significant correlations are shown for p<.05

Table 10

Correlation Matrix for Control Participants

Personality Facet	anterior cingulate (SF)	anterior cingulate (SS)	Brain Stem (SF)	Brain Stem (SS)	L. lateral OFC + anterior insula (SF)	L. lateral OFC + anterior insula (SS)	L. putamen (SF)	L. putamen (SS)	R. later OFC + anterior insula (SF)	R. later OFC + anterior insula (SS)	R. thalamus (SF)	R. thalamus (SS)	Supramarginal Gyrus (SF)
Exploratory Excitability (TCI NS1)	-	-	r=.274 p=.014	-	r=.426 p=.038	-	-	-	r=.493 p=.014	r=.577 p=.003	-	-	-
Impulsiveness (TCI NS2)	-	-	-	-	-	-	-	-	-	-	-	-	-
Anticipatory Worry (TCI HA1)	-	-	-	-	r=.238 p=.037	-	-	-	r=.302 p=.007	-	-	-	r=.261 p=.019
Fear of Uncertainty (TCI HA2)	-	-	-	r=.461 p=.023	-	-	-	-	r=.482 p=.017	-	-	-	-
Persistence (TCI P)	r=-.277 p=.030	-	-	-	-	-	-	-	-	-	-	-	r=-.243 p=.030
Purposefulness (TCI S2)	-	-	-	-	-	-	r=.425 p=.038	r=.481 p=.017	-	-	-	-	-
Congruent Second Nature (TCI S5)	-	-	-	-	-	-	r=.507 p=.012	-	-	-	-	-	-
Impulsiveness (NEO N5)	-	-	-	-	-	-	-	-	-	-	-	-	-
Excitement Seeking (NEO E5)	-	-	-	-	-	-	-	r=.464 p=.022	r=-.273 p=.030	-	-	-	r=.428 p=.032
Self Discipline (NEO C5)	-	-	r=-.412 p=.045	-	-	-	-	-	-	-	-	-	-
Deliberation (NEO C6)	-	-	-	-	-	-	-	-	-	-	-	-	-

*Only significant correlations are shown for p<.05

Table 11

Correlation Matrix for Cocaine-Addicted Participants

Personality Facet	anterior cingulate (SF)	anterior cingulate (SS)	Brain Stem (SF)	Brain Stem (SS)	L. lateral OFC + anterior insula (SF)	L. lateral OFC + anterior insula (SS)	L. putamen (SF)	L. putamen (SS)	R. later OFC + anterior insula (SF)	R. later OFC + anterior insula (SS)	R. thalamus (SF)	R. thalamus (SS)	Supramarginal Gyrus (SF)
			r=.280										
Exploratory Excitability (TCI NS1)	-	-	p=.037	-	-	-	-	-	-	-	-	-	-
Impulsiveness (TCI NS2)	-	-	-	-	-	-	-	-	-	-	-	-	r=.278 p=.038
					r=.310	r=.270			r=.343			r=.265	
Anticipatory Worry (TCI HA1)	-	-	-	-	p=.024	p=.044	-	-	p=.010	-	-	p=.049	r=.360 p=.007
Fear of Uncertainty (TCI HA2)	-	-	-	-	-	-	-	-	-	-	-	-	-
	r=-.305												r=-.264
Persistence (TCI P)	p=.022	-	-	-	-	-	-	-	-	-	-	-	p=.049
								r=-.333		r=-.266		r=-.299	r=-.272
Purposefulness (TCI S2)	-	-	-	-	-	-	-	p=.012	-	p=.033	-	p=.025	p=.042
Congruent Second Nature (TCI S5)	-	-	-	-	-	-	-	-	-	-	-	-	-
												r=.305	
Impulsiveness (NEO N5)	-	-	-	-	-	-	-	-	-	-	-	p=.022	-
			r=.279										
Excitement Seeking (NEO E5)	-	-	p=.038	-	-	-	-	-	-	-	-	-	-
Self Discipline (NEO C5)	-	-	-	-	-	-	-	-	-	-	-	-	-
Deliberation (NEO C6)	-	-	-	-	-	-	-	-	-	-	-	-	-

*Only significant correlations are shown for

Table 12

Differences and Similarities Between Groups

Personality Facet	Structure	Control	Cocaine-addicted participants
Exploratory Excitability (TCI NS1)	brainstem (SF)	r=.274, p=.014	r=.280 p=.037
	L. lateral OFC and anterior insula (SF)	r=.426, p=.038*	NS
	R. lateral OFC and anterior insula (SF)	r=.493 p=.014*	NS
	R. lateral OFC and anterior insula (SS)	r=.577 p=.003*	NS
Impulsiveness (TCI NS2)	supramarginal gyrus (SF)	NS	r=.278 p=.038*
Anticipatory Worry (TCI HA1)	L. lateral OFC and anterior insula (SF)	r=.238 p=.037	r=.310 p=.024
	L. lateral OFC and anterior insula (SS)	NS	r=.270 p=.044*
	R. lateral OFC and anterior insula (SF)	r=.302 p=.007	r=.343 p=.010
	R. thalamus (SS)	NS	r=.265 p=.049*
	supramarginal gyrus (SF)	r=.261 p=.019	r=.360 p=.007
Fear of Uncertainty (TCI HA2)	brainstem (SS)	r=.461 p=.023*	NS
	R. lateral OFC and anterior insula (SF)	r=.482 p=.017*	NS
Persistence (TCI P)	ACC (SF)	r=-.277 p=.030	r=-.305 p=.022
	supramarginal gyrus (SF)	r=-.243 p=.030	r=-.264 p=.049
Purposefulness (TCI S2)	L. putamen (SS)	r=.481 p=.017	r=-.333 p=.012
	R. lateral OFC and anterior insula (SS)	NS	r=-.266 p=.033*
	R. thalamus (SS)	r=.481 p=.017	r=-.299 p=.025**
	supramarginal gyrus (SF)	NS	r=-.272 p=.042*
Congruent Second Nature (TCI S5)	L. putamen (SF)	r=.507 p=.012*	NS
Impulsiveness (NEO N5)	R. thalamus (SS)	NS	r=.305 p=.022*
Excitement Seeking (NEO C5)	brainstem (SF)	NS	r=.279 p=.038*
	L. putamen (SS)	r=.464 p=.022*	NS
	R. lateral OFC and anterior insula (SF)	r=-.273 p=.030*	NS
	supramarginal gyrus (SF)	r=.428 p=.032*	NS
Self Discipline (NEO C5)	brainstem (SF)	r=-.412 p=.045*	NS

(SS) = Stop-Success (SF) = Stop-Failure *Correlation exisits in only one group **Correlations reverse direction between groups, NS= Not Significant

Table 13

Loading Factors of Personality Facets for Each Component

Personality Facet	Compoment 1 Loading	Component 2 Loading
Deliberation (NEO C6)	0.81	-0.276
Congruent Second Nature (TCI S5)	0.73	-0.091
Self Discipline (NEO C5)	0.719	0.032
Purposefulness (TCI S2)	0.676	0.123
Impulsiveness (TCI NS2)	-0.639	0.113
Persistence (TCI P)	0.433	0.375
Fear of Uncertainty (TCI HA2)	-0.24	-0.634
Excitement Seeking (NEO E5)	0.058	0.611
Exploratory Excitability (TCI NS1)	0.086	0.573
Impulsiveness (NEO N5)	-0.488	0.392
Anticipatory Worry (TCI HA1)	-0.468	-0.395

Table 14

Activation Clusters negatively correlated with Component 1 During Stop-Failure

Structure	X coor	Y coor	Z coor	Brodman Area	Voxles
Middle Occipital Gyrus	-20.36	-90.89	11.7	BA 18	3011
Inferior Frontal Gyrus	52.11	42.58	-0.88	BA 46	1398
Postcentral Gyrus	-3.31	-50.68	65.09	BA 7	972

Table 15

Activation Clusters Negatively Associated with Component 1 during Stop-Success

Structure	X coor	Y coor	Z coor	Brodmann Area	Voxels
Precuneus	8.01	-63.82	60.68	BA 7	995
Middle Temporal Gyrus	63.07	-56.91	5.38	BA 21	860

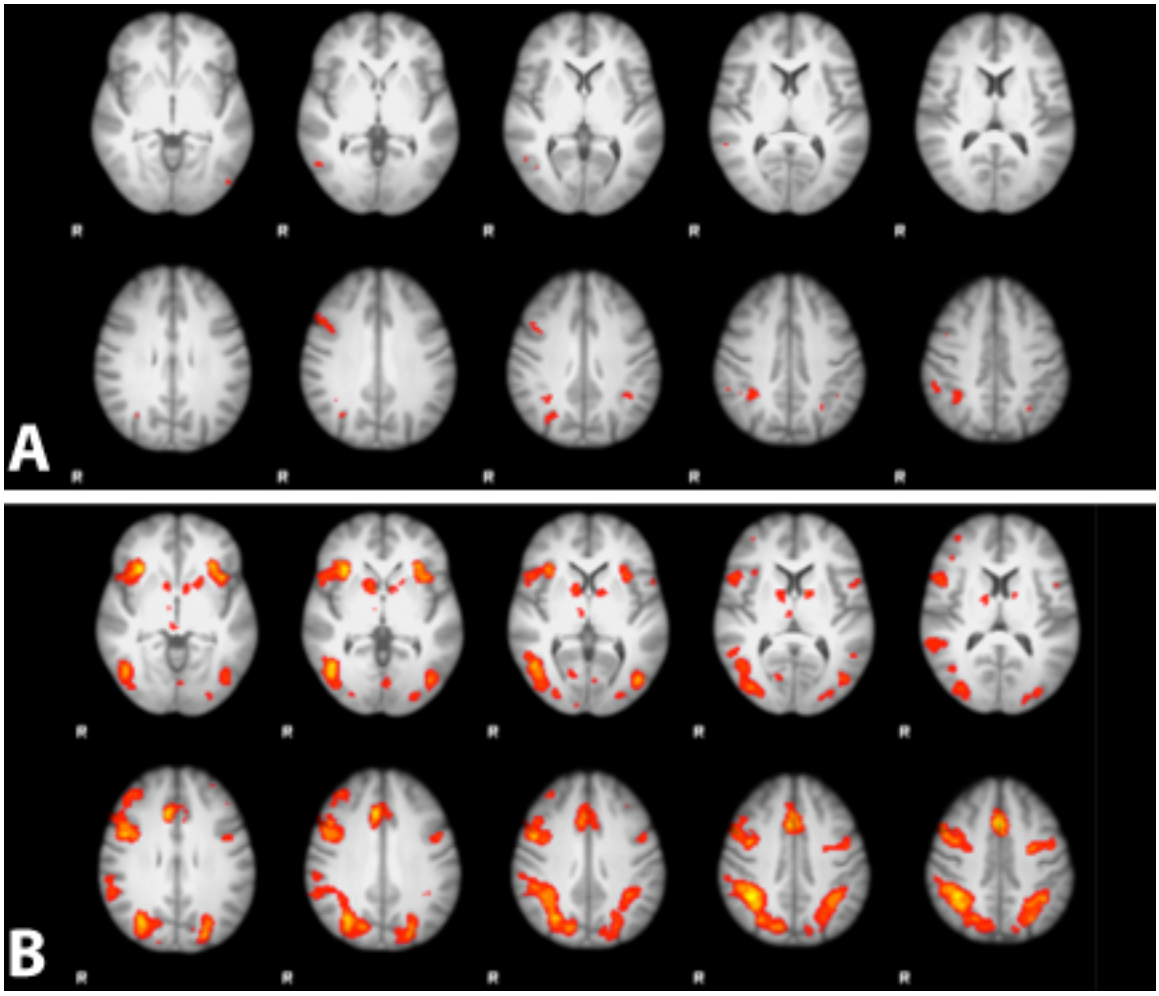

Figure 1AB. Depicts the changes in BOLD activation During Stop-Failure in the control group (A). Changes in BOLD activation were found in the the middle frontal gyrus, superior frontal gyrus, inferior parietal lobule, angular gyrus, cingulate gyrus, precentral gyrus, medial frontal gyrus, insula, caudate and supramarginal gyrus. Figure 2B shows activation in the cocaine-addicted group. Changes in Bold activation were seen in the precuneus, cingulate gyrus, cuneus, middle temporal gyrus, middle temporal gyrus, inferior parietal lobule, insula, culmen, inferior temporal gyrus, inferior frontal gyrus, lingual gyus, lentiform nucleus, precentral gyrus and parahippocampal gyrus.

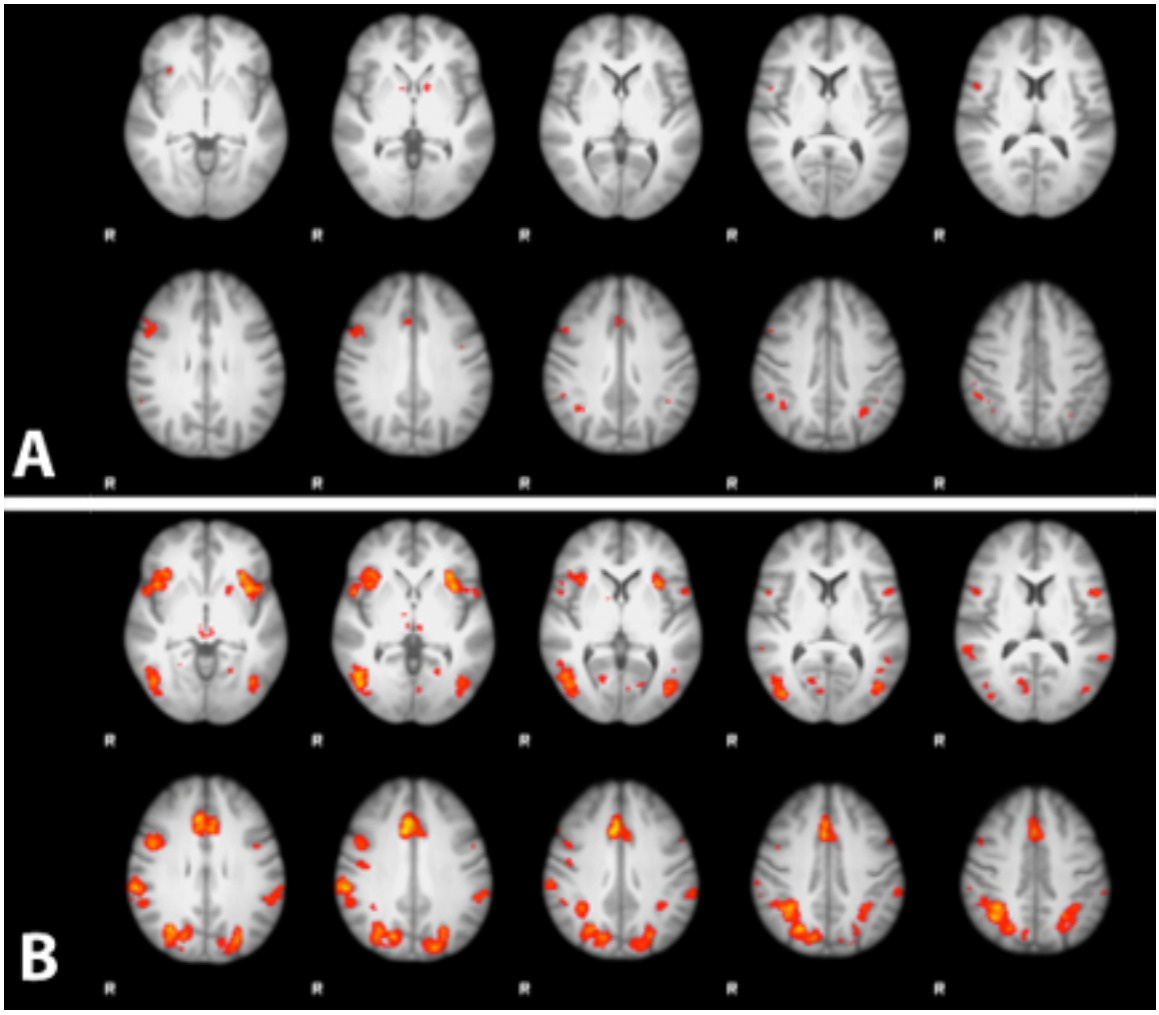

Figure 2AB: Depicts activation clusters identified in the control group during Stop-Success (A). Changes in BOLD activation were seen in the superior parietal lobule, middle frontal gyrus, precuneus, inferior parietal lobule, supramarginal gyrus, inferior temporal gyrus, cuneus, and the middle occipital gyrus. 3B depicts activation clusters in the cocain-addicted participants. Clusters were found in the inferior parietal lobule, insula, precuneus, middle frontal gyrus, middle occipital gyrus, caudate, culmen, lingual gyrus, precentral gyrus, declive, middle frontal gyrus, superior temporal gyrus, thalamus, and superior frontal gyrus.

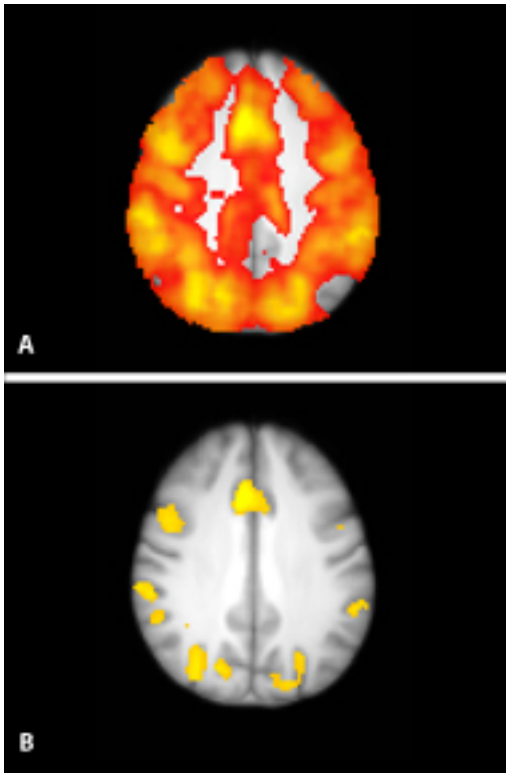

*Figure 3A*B. The top cell depicts neural activation in the entire group prior to thresholding. Figure 4B depicts the clusters thresholded at z>6. These thresholded clusters were used as functional ROIs.

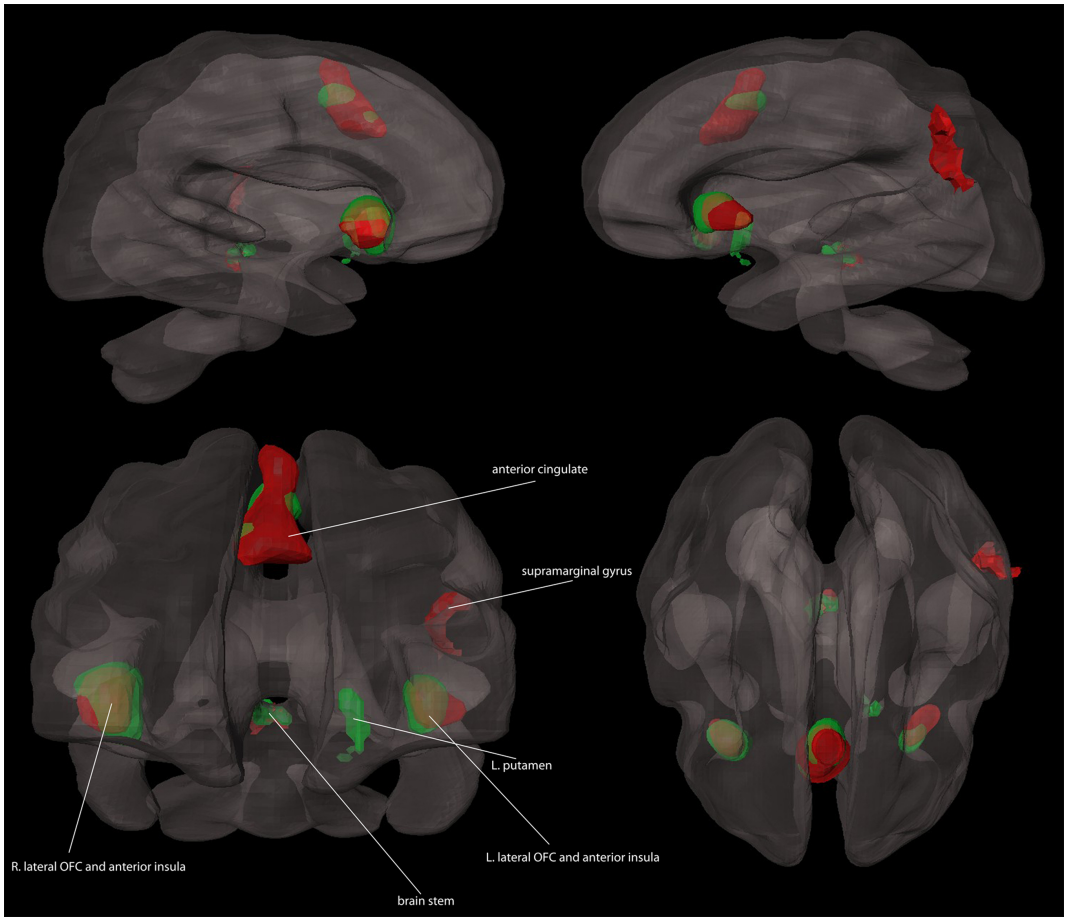

Figure4. 3D visualization of the ROIs inside the brain. Depicted in red are the Stop-Failure ROIs and in green are the Stop-Success regions. The ROIs depicted include the anterior cingulate (SS,SF), L. lateral OFC and anterior insula (SS,SF), R. lateral OFC and anterior insula (SS,SF), L. putamen (SS), brain stem (SS,SF), and supramarginal gyrus (SF). The ROIs for the R. thalamus and L. putamen (SF) are not visualized due to the small voxel size of the ROIs.

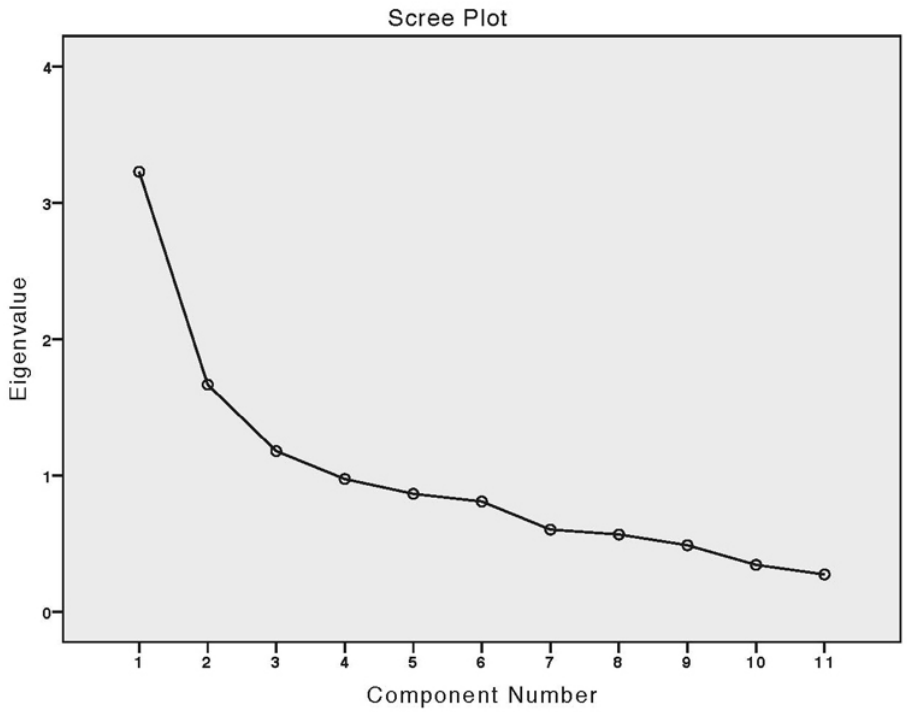

Figure 5. Scree plot from principal component analysis.

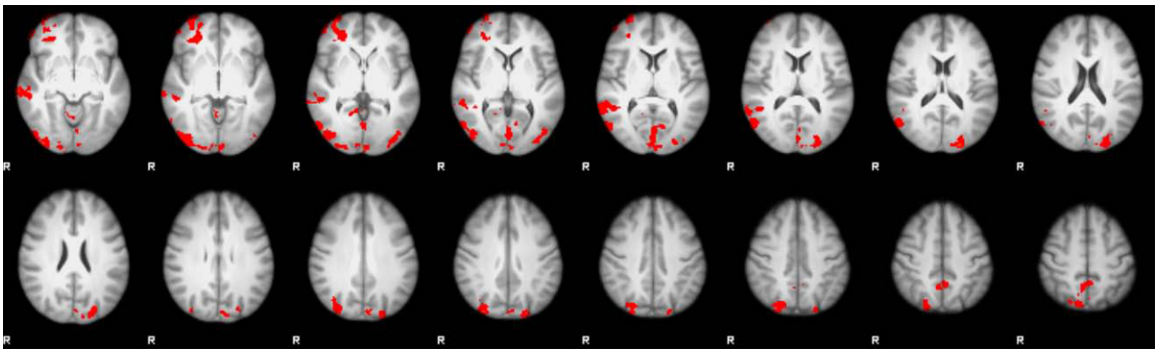

Figure 6. Displayed are activation maps identifying clusters that have a negative relationship with personality component 1 during Stop-Failure. Clusters were identified in the middle occipital gyrus, inferior frontal gyrus, and the postcentral gyrus.

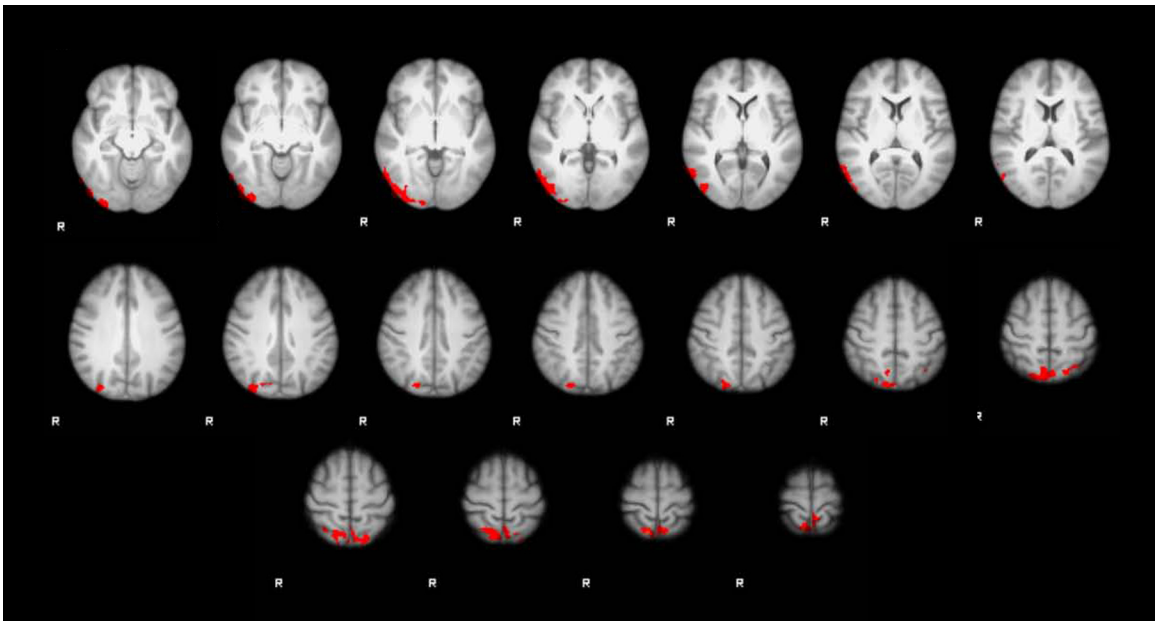

Figure 7. Displayed are activation maps depicting activation clusters that were found to be negatively correlated with personality component 1 during Stop-Success. Clusters were found to be activated in the precuneus and middle temporal gyrus.

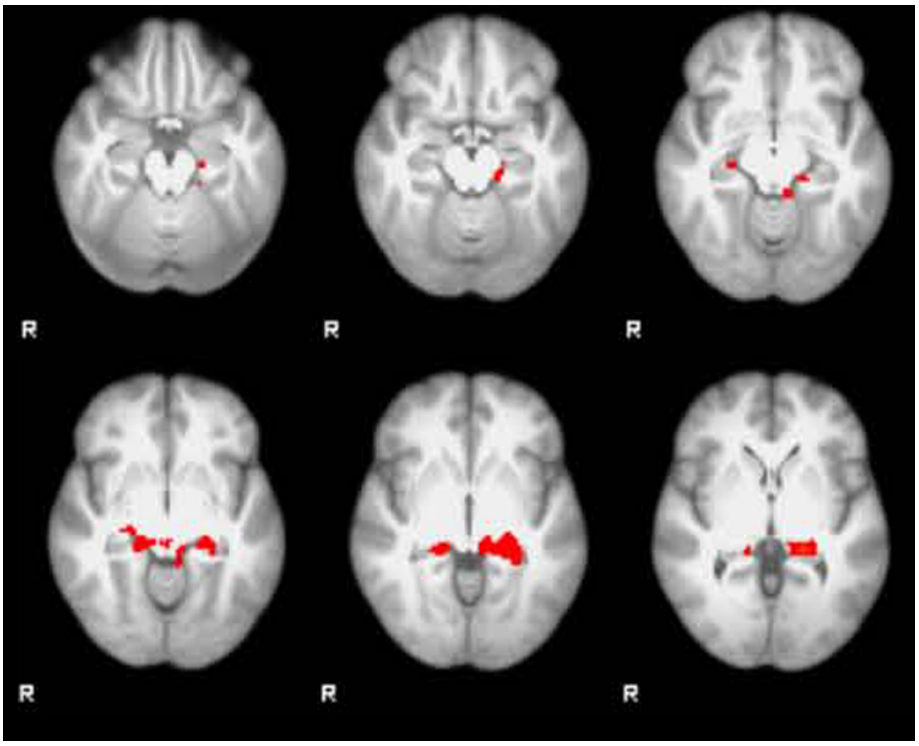

Figure 8. Depicts the activation cluster shown to have an interaction effect with personality component 2.

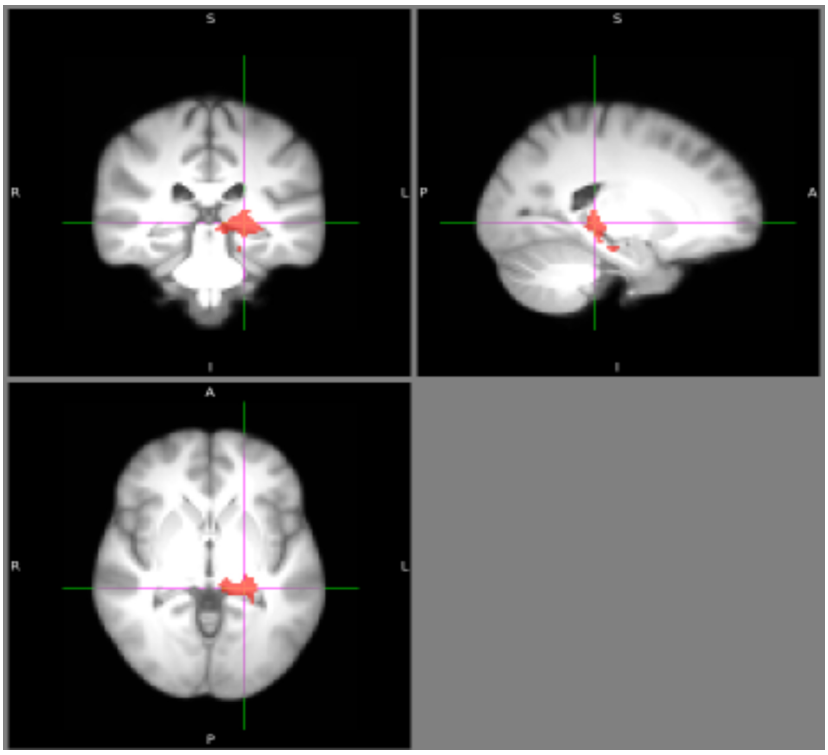

Figure 9. The mask of the cluster found in the left hippocampus. This mask was used in FEATquery to identify BOLD activation for each participant.

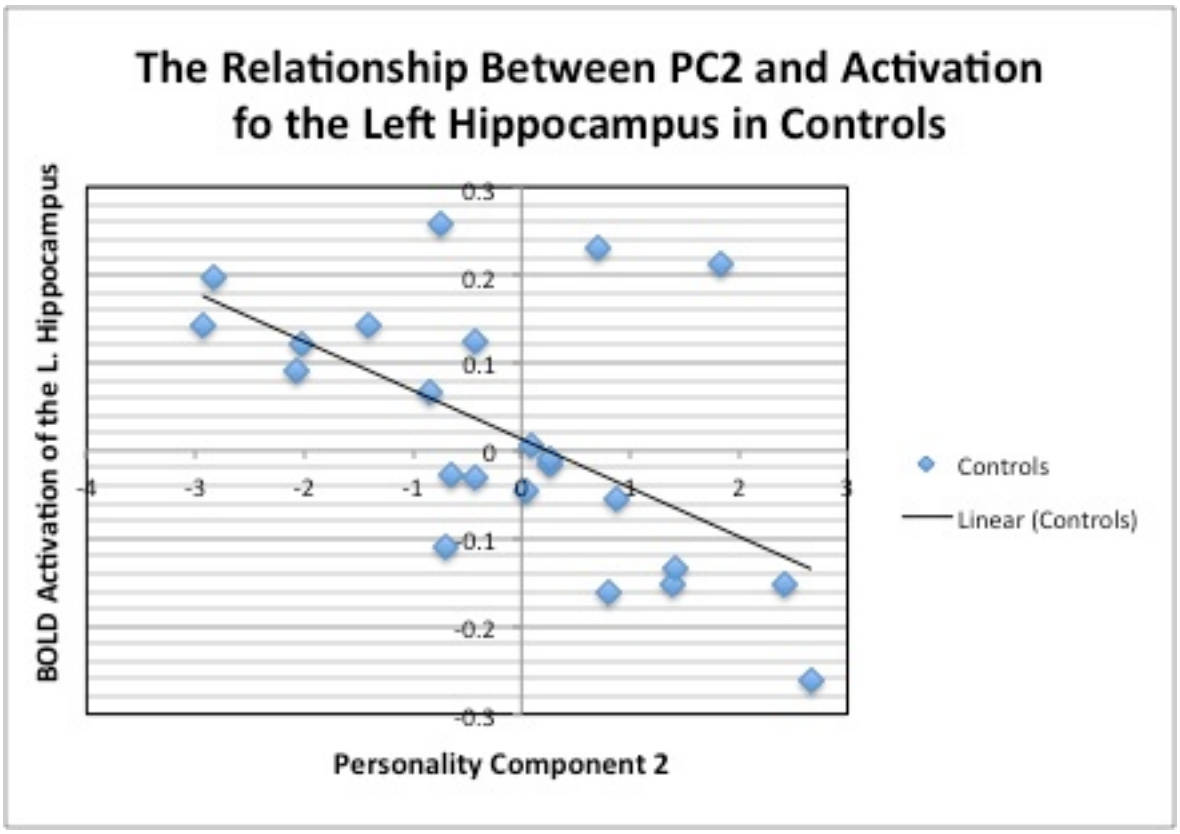

Figure 10. Scatter plot identifying a negative correlation between BOLD activation of the left hippocampus and personality component 2.

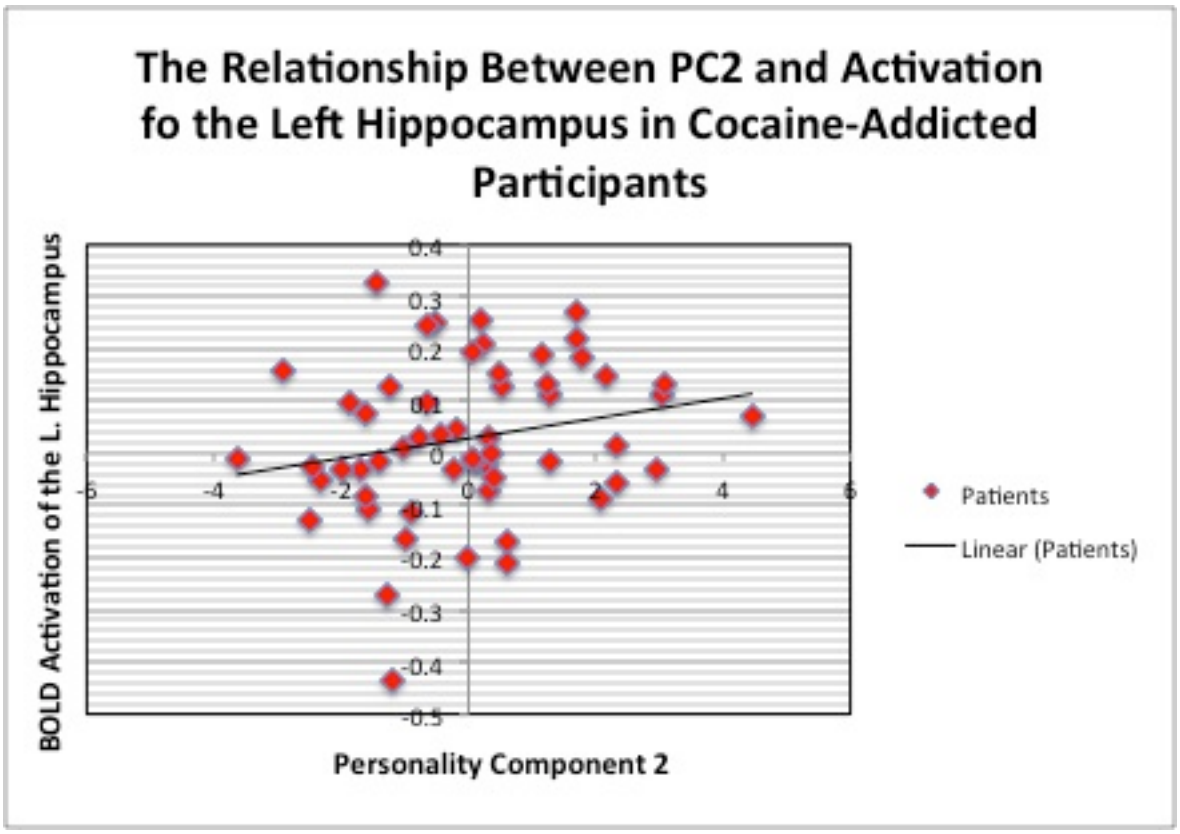

Figure 11. Scatter plot identifying a positive trend between BOLD activation of the left hippocampus and personality component 2.

BIOGRAPHICAL SKETCH

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EDUCATION

INSTITUTION AND LOCATION	DEGREE	YEARS	FIELD OF STUDY
The University of Kansas, Lawrence	B.S.	2004-2008	Psychology
The University of Texas Southwestern School of Allied Health Sciences, Dallas TX	M.R.C	2010-2013	Rehabilitation Counseling Psychology

Positions and Employment

2008-2010 Research Associate
2010-2012 Graduate Research Associate
2012-2013 Clinical Data Specialist

Clinical Experience

2007-2008 Applied Behavioral Analyst
2011-2012 Counseling Intern at Homeward Bound Residential Treatment Center
2012 Counseling Intern for Personal and Social Adjustment Training Group at University of Texas Southwestern Medical Center, Department of Rehabilitation Services
2012-2013 Academic Coach, Coaching for Academic Success

Presentations and Publications

1. Brown DJ, **Jester B**, Winkler M, Sanchez J, Chun M, Nien CJ, Lam L, Lay A, Mincker DS, Jester JV: Detection and 3-D localization of elastin and collagen in the human optic nerve head (ONH). Exp Eye Res (in Press)
2. Brown DJ, **Jester B**, Winkler M, Sanchez J, Chun M, Nien CJ, Lam L, Lay A, Mincker DS, Jester JV: Detection and 3-D localization of elastin and collagen in the human optic nerve head (ONH). Exp Eye Res (in Press)

3. Simpson J, Nien CJ, Flynn K, **Jester BE**, Cherqui S, Jester JV: Quantitative in vivo and ex vivo confocal microscopy analysis of corneal cystine crystals in the Ctns -/- knockout mouse. Mol Vis (in Press).

4. Hao M, Flynn K, Nien-Shy C, **Jester BE**, Winkler M, Brown DJ, schiazza OL, Bille J, Jester JV: In vivo non linear optical (NLO) imaging in live rabbit eyes using the Heidelberg tow-photon laser ophthalmoscope. Exp Eye Res 91:308-314, 2010.

5. Jester JV, Winkler M, **Jester BE**, Nien C, Chai D, Brown DJ: Evaluating corneal collagen organization using high resolution non linear optical (NLO) macroscopy. Eye & Contact Lens 36:260-264, 2010.

6. Chai D, Ngai P, **Jester BE**, Jester JV, Brown DJ: Measurement of elastic modulus of the optic nervew head (ONH) and peripapillary sclera. Invest. Ophthalmol. Vis. Sci. 2011 52: E-Abstract 6250.

7. **Jester BE**, Nien CJ, Winkler M, Brown DJ, Jester JV: Volumetric reconstruction of the mouse meibomian gland using high resolution non-linear optical imaging. Anatomical Rec 294:185-192, 2011. (cover image)

8. Winkler M, **Jester BE**, Nien-Shy C, Chai D, Brown DJ, Jester JV: High resolution macroscopy (HRMac) of the eye using non-linar optical imaging. SPIE 2010:7589:758901-758907.

9. **B. Jester**, J. B., T.S. Harris, M.d. Devous, J.S. Spence, R. Briggs, R. Walker, K. Rubia, B. Adinoff (2012). The Relationship Between Prefrontal Activity During Disinhibition and Personality Measures of Impulsivity in Cocaine-addicted Subjects. Metroplex Days. University of Texas, Arlington.