ABSTRACT

Impulsivity and Frontal Asymmetry in Substance-Dependent Individuals

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Right-frontal cortical activity at rest has been associated with impulsive and aggressive behaviors. Impulsivity has also been shown to play an important role in substance dependence as an antecedent and consequence of drug use. Past research has suggested that impulsivity is a multi-dimensional construct, with characteristic factors observed throughout different stages of a drug abuse trajectory. The present study sought to investigate frontal asymmetry in impulsive versus not-impulsive substance-dependent individuals receiving rehabilitation treatment. Eighteen male substance-dependent individuals (impulsive = 10) receiving treatment were recruited to participate in a resting EEG paradigm to assess frontal cortical activity. Results from a mixed-design ANOVA analysis showed a trend for impulsive individuals towards increased right relative to left frontal cortical activity compared to non-impulsive individuals. This effect was observed at mid-frontal electrode sites. Results suggest that increased right frontal cortical activity could be associated to impulsivity manifested during the abstinent/rehabilitation stage of drug abuse.

Impulsivity and Frontal Asymmetry in Substance-dependent Individuals

by

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CHAPTER ONE

Introduction

Impulsivity

Impulsive behaviors have been studied and measured for years from many theoretical perspectives and using various assessment techniques. Despite a large body of work, there is a lack of consensus in terms of defining impulsivity in a way that encompasses all its variations, functions, and physiological/neural mechanisms. Many authors have accepted a definition of impulsivity that includes actions that reflect unplanned, prematurely executed, and risky thoughts and behaviors. These impulsive behaviors usually result in undesired outcomes (Evenden, 1999). However, this definition often excludes impulsivity dimensions that don't involve risky/ unplanned actions or situations where the outcome is not negative. The assumption that impulsivity represents a one-dimensional construct often misleads us to a search for a single neurobiological marker for impulsivity, thus diverting us from finding multiple underlying neural correlates (Gerbing, Ahadi, and Patton, 1987). An incomplete definition of a construct can also lead to the creation of less reliable self-report measures, and incomplete behavioral assessments (see Bettencourt, Talley, Benjamin, & Valentine, 2006; Depue & Collins, 1999; Evenden, 1999; Whiteside & Lynam, 2001 for reviews). Nevertheless, an impulsivity component has been implicated in almost every personality theory as an important behavioral construct that is observed in its many variations within our every-day life. With the purpose of clarifying the differences between how

impulsivity was defined in past research and how it is construed in contemporary literature, some of those personality theories are herein reviewed.

Personality Theories and Impulsivity

Eysenck & Colleagues (1977) have identified three personality dimensions that have been influential across the personality assessment literature. These dimensions (extraversion, neuroticism, and psychoticism) have been described and modified over decades and are still used today. Within this theory impulsivity was initially included in the extraversion dimension (Eysenck & Eysenck, 1977), which was later divided into four separate components: risk taking, non-planning, liveliness, and narrow impulsiveness. Out of these, risk taking, liveliness, and non-planning were found to be more strongly correlated with the extraversion dimension while narrow-impulsiveness was more correlated with neuroticism and psychoticism (Eysenck & Eysenck, 1977). Based on their findings the Eysenck and colleagues developed two impulsivity sub-factors: venturesomeness and impulsiveness. These were placed within the extraversion and psychoticism dimensions, respectively (Eysenck, Pearson, Easting, & Allsopp, 1985). Venturesomeness relates to the impulsive individual that seeks risky situations consciously, while impulsiveness refers to an individual who acts "on the spur of the moment" without fully considering possible dangerous or risky outcomes. Nevertheless, Eysenck has pointed out that various items in his questionnaire reflecting different personality factors could also be associated with impulsivity (Eysenck et al., 1985). Thus the difficulty lies in a comprehensive definition as well as the measurement of the theoretical construct; this is made more difficult with the multiplicity of factors that influence or/and are influenced by impulsivity.

Zuckerman and Colleagues (1993) created a personality model that could be used as an alternative to the "Big Five" personality theory. The five factor model (FFM) of personality ("The Big Five") is a generalization about the correlated variation of personality traits (McCrae & Costa Jr, 1999). The authors defined these factors as: neuroticism, extraversion, openness, agreeableness, and conscientiousness. The theory for this model focuses on the distinction between basic tendencies (abstract psychological potentials) and characteristic adaptations (their concrete manifestations in the personality system). The five factor theory states that personality traits are deeper psychological entities that can only be inferred from behavior and experience. Self-reports of personality and observer ratings are based on such inferences. The FFM also states that personality traits are a function of biology, and all human beings share a common genome, thus the structure of personality ought to be universal. In Zuckerman's alternative model, impulsivity falls within a factor composed of several sensation seeking and impulsivity scales. Zuckerman calls this factor Impulsive Sensation Seeking (IMPSS). Items in this scale refer to impulsivity as acts that involve lack of planning and acting without thinking as well as novelty seeking and risk taking behaviors. Zuckerman's IMPSS replaces Costa & McCrae's "Openness to Experience" factor. Like Costa & McCrae, Zuckerman emphasizes the biological-evolutionary basis of personality traits and their consistency across humankind.

Cloninger's theory of personality (Cloninger, Svrakic, & Przybeck, 1993) is founded on physiological correlates of human behavior. The author described three genetically independent temperaments (novelty seeking, harm avoidance, and reward dependence) that represent distinct personality dimensions. Despite the fact that

impulsivity is not considered a distinct temperament various sub-factors of impulsivity are found across all three dimensions. Each temperament is thought to be related to a specific neurotransmitter system: harm avoidance – serotonergic system; reward dependence – norepinephrine system; and novelty seeking – dopaminergic system (Evenden, 1999). Since an impulsivity component can be seen embedded in all three systems, one can suspect that either various neurotransmitter systems are involved in the development of impulsive behaviors, or impulsivity is born of an interaction involving two or more of the three neurochemical systems. Another possibility is that there is yet an undiscovered "system" that accounts for impulsive behavior.

Buss & Plomin proposed a theory that includes four distinct personality dimensions: activity, emotionality, sociability, and impulsivity (Buss & Plomin, 1975). Regardless of the differences between these dimensions the authors note that they interact with each other, and that this interaction is what influences behavior. The impulsivity dimension contains sub-factors that are implicated in impulsive behaviors: persistence, decision time, and sensation seeking. Nevertheless, the authors conclude that inhibitory control (or the lack off) is the essential factor influencing impulsivity (Buss & Plomin, 1975). As such, inhibitory control as related to impulsive behaviors is usually expressed in terms of the individual's ability to delay gratification.

The inclusion of impulsivity within the major global personality theories reflects the importance of this construct for the study and adequate description of human behavior. However, these global theories have not been successful in fully explaining the complex theoretical nature of the impulsivity dimension they contain. In addition, global

personality theories have also failed to create an impulsivity measurement method that takes into account all of its sub-trait components.

Impulsivity Theories

Barratt's theory of impulsivity. Barratt and colleagues have developed various impulsivity scales based on a general systems model of personality that are commonly used for research and in clinical practice (Barratt, 1993; Gerbing, Ahadi, & Patton, 1987; Patton & Stanford, 1995). Barratt proposed that a psychometric approach is not enough to define human personality traits (including impulsivity). Instead, he claimed that various cognitive, physiological and behavioral measures should be used to assess personality (Barratt, 1993). Based on this theory impulsiveness is considered a first-order personality trait derivative of various neural underpinnings. Furthermore, based on factor analytical studies involving thousands of subjects, impulsiveness can be divided into three sub-traits: motor, non-planning, and attentional. The first two sub-traits have been repeatedly psychometrically replicated while the third sub-trait has been more difficult to define (Barratt, 1993; Patton & Stanford, 1995; Whiteside & Lynam, 2001).

Newman's physiological theory of impulsivity. Newman & Colleagues (Newman & Wallace, 1993; Wallace, Newman, & Bachorowski, 1991) developed a theory of impulsivity by merging Eysenck's theory of personality with Gray's theory of approach/avoidance learning. Gray's theory (Gray, 1987) is based on the existence of three systems: Behavioral Activation System (BAS), Behavioral Inhibition System (BIS), and Non-Specific Arousal System (NAS). An approach system is activated by environmental cues associated with non-punishment and reward. In balance, the

avoidance system is activated by environmental cues related to punishment and non-reward. When activated, excitatory projections from each system are received by the NAS, which then intensifies any behavior associated with either system (Gray, 1987; Whiteside & Lynam, 2001). Newman and his colleagues suggested that Eysenck's extraversion factor reflects a relative strength of the BAS over BIS and neuroticism reflects a relative strength of the NAS (Whiteside & Lynam, 2001). Gray suggested three characteristics associated with impulsive behaviors: normal impulsivity, anxious impulsivity, and P-constraint. Normal impulsivity relates to a stronger BAS over the BIS paired with an overactive NAS. On the other hand, anxious impulsivity is associated with a stronger BIS paired with an overactive NAS. P-constraint within this context refers to a specific characteristic observed in psychopathic individuals' responses towards competing reward and punishment conditions (Lynam, 1996).

Two dimensional theory of impulsivity. Dickman's behavioral theory differentiates between two types of impulsivity, functional and dysfunctional (Dickman, 1985). Functional impulsivity is defined as an impulsive action in a situation where impulsivity would be beneficial because the risks of negative consequences are low and potential rewards are greater. On the contrary, dysfunctional impulsivity is seen as the type that is often studied by theorists and refers to an impulsive action in any environment where impulsive behaviors are disadvantageous and likely punished by negative consequences. In his work, Dickman suggested that these two types of impulsivity are not strongly correlated, are highly situationally specific, depending on situational demand characteristics, and that each can possess distinct associations with

specific personality traits. Dickman's approach was entirely behavioral and he does not address the effect of personality structure per se.

Impulsivity as a personality trait. Taking into account the complexity of this construct, for the purpose of this study, impulsivity was defined as a personality trait that is characterized by a susceptibility to react to external and internal stimuli in a quick and spontaneous matter. These impulsive reactions are made without consideration for any negative outcome that might result (Moeller et al. 2001). As such, impulsivity is understood to be "a higher order personality variable composed of more primary components" (Patton & Stanford, 2012). That is, impulsivity covers certain factors that match with several aspects of behavior. These factors may be orchestrated by different biological mechanisms. Because of this, multiple measures need to be employed to account for every impulsivity sub-component. Furthermore, an adequate measure should also aid in the differentiation between impulsivity per se and behaviors that might be influenced by impulsivity, like drug use or aggression (Evenden, 1999).

Impulsivity Measures

The array of theoretical and operational definitions of impulsivity reported in the literature has influenced the number of existing impulsivity assessment measures. Self-report measures are often used to assess trait-like impulsivity because they allow the researcher to collect large amounts of specific data on impulsive behaviors (Moeller et al., 2001). Clinically relevant data gathered from self-report measures can shed light on a subject's or client's long-term pattern of personality traits (Dougherty, Mathias, Marsh, & Jagar, 2005). However, this type of assessment relies on the subject's ability to recognize

and accurately report their own behavioral patterns, which can be especially difficult for substance-dependent individuals (De Wit, 2009). Another disadvantage of self-report measures in clinical settings would be their inadequacy for repeated use on the same subject (Moeller et al., 2001).

Other assessment methods commonly used to measure impulsivity are operational/behavioral tasks. These tasks excel at measuring state-dependent changes in impulsivity levels, therefore they can only account for certain aspects of impulsivity (Dougherty et al., 2005). However, by employing behavioral tasks researchers may avoid subjective bias effects usually seen with self-report measures. Each task may possibly reflect a different impulsivity feature and therefore perhaps a distinct underlying process. Impulsive decision making (sometimes referred to as impulsive choice) and behavioral disinhibition (sometimes referred to as impaired inhibition) are the two most commonly identified processes measured by behavioral impulsivity tasks (De Wit, 2009). Delay discounting paradigms are commonly used to measure impulsive decision-making by offering subjects two payoff contingencies, from which a subject must choose only one. Depending on the choice made each subject can either receive a small reward immediately (e.g. $1 now) or a bigger reward after some specific time has passed (e.g. $10 in a month). On the other hand, behavioral inhibition processes are usually measured using go/no-go tasks where each subject has to stop (inhibit) a response after initiating it (Perry & Carroll, 2008). Behavioral measures of impulsivity can be used repeatedly, across interesting situations, and they can be adapted for use in animal studies. However, they currently lack the social component of impulsivity and the capacity to assess stable personality traits over a long period of time (Moeller et al., 2001). Many studies have

found significant correlations between self-report measures of impulsivity but the results from correlational studies between behavioral and self-report measures are mixed and have often been inconsistent. Patton and colleagues attempted a comprehensive study and found almost no relationships between self-report and behavioral measures (Gerbing et al., 1987). Recently, Reynolds and colleagues sought to clarify this again by studying the relationship between behavioral and self-report measures of impulsivity (Reynolds, Ortengren, Richards, & de Wit, 2006). Four commonly used behavioral impulsivity tasks and three widely recognized self-report impulsivity measures were administered to 70 adult subjects. All self-report measures were highly inter-correlated, but none of them were correlated to any behavioral task, similar to research in Patton's lab twenty years before, and since. These results suggest that behavioral and self-report measures most likely reflect different types or aspects of the impulsivity personality trait (Gerbing et al., 1987; Reynolds et al., 2006).

Another line of research has focused on developing physiological measures of impulsivity. Of these, event-related potentials (ERP's) have been most commonly studied. An ERP refers to a specific waveform that can be detected using electroencephalogram (EEG) recordings while the subject is responding to an imperative stimulus. One specific task, the positive 300 (P300) waveform, is seen 300ms after the presentation of a target stimulus has been made (Moeller et al., 2001). Unfortunately, ERP effects or changes are associated with many psychological disorders and therefore they cannot be used specifically as impulsivity measures on their own. Along with ERP's, frontal resting EEG activity has also been used to study individual differences in personality traits (Lake, Stanford, & Patton, 2014). Specifically, frontal EEG

asymmetries (during resting state and state-dependent activation) have been known to be associated with emotional state alterations and trait-dependent emotional responding (Coan & Allen, 2003). The usefulness of physiological measures of impulsivity stems from the direct association between the specific measure and neural function which reflects cognition (Moeller et al., 2001).

Based on this review, it seems that the best impulsivity measure (state and/or trait) is one that combines multiple forms of assessment.

Impulsivity and Substance Abuse Disorders

Impulsivity is a stable personality trait and can be observed to function within the limits of normal behavior but it is also commonly associated with psychopathology when excessive. The Diagnostic and Statistical Manual (DSM) does not include a general impulsivity disorder, however many disorders list certain aspects of impulsivity within their diagnostic criteria. Out of these the most commonly associated with impulsive behaviors are impulse control disorder, attention deficit and hyperactivity disorder (ADHD), and substance use disorder (Evenden, 1999). The last version of the Diagnostic and Statistical Manual (American Psychiatric Association, 2013) merges two previously separated categories: substance abuse and substance dependence. This new category is scaled on a spectrum that goes from mild to severe symptoms depending on the specific criteria for each substance. According the to the DSM-V a substance use disorder can be diagnosed when the use of a specific substance causes impairments related to the person's health, work and/or family responsibilities, or any social impairment.

The relationship between impulsivity and substance abuse has been studied extensively across the years and several hypotheses have been repeatedly proposed.

There is sufficient evidence to state that impulsivity plays multiple roles in addiction. Several authors have proposed two distinct primary processes related to impulsivity observed in any drug abuse trajectory: impulsive decision making and impaired inhibition (Perry & Carroll, 2008). Impulsive decision making often refers to a spontaneous choice a person makes in order to obtain an immediate reward. On the other hand, impaired inhibition occurs when a person fails to stop or avoid a possible negative outcome. Initially, drug abuse is conceptualized around the idea of an impulsive choice being made (to use a drug) in order to receive an immediate reward (drug effects) instead of choosing a larger or more important but delayed reward (e.g. personal well-being) (De Wit, 2009). Once a pattern of abuse is established, the person makes a compulsive choice (impaired inhibition) to keep using said substance in order to avoid the negative withdrawal symptoms and cravings that would occur if drug use is stopped.

Within this framework, the relationship between impulsivity and substance abuse has been studied from three perspectives: impulsivity leads to substance abuse, substance abuse leads to impulsive behavior, and impulsivity is related to drug abuse via a third unknown variable. Various animal and human studies have found evidence suggesting impulsivity to be an antecedent of drug use. In a 2008 animal study (Perry, Nelson, & Carroll, 2008) rats categorized based on baseline impulsivity levels (High vs. Low) were compared on self-administrated cocaine intake. High impulsivity rats acquired self-administration faster and self-administered higher quantities of drug compared to rats rated as low impulsivity. In humans this effect is typically measured using a delay discounting task. For this task participants are asked to make a choice between two options: one that results in a small immediate reward and a second choice that results in a

larger delayed reward. In a 2003 study, college students' scores on a delay discounting paradigm revealed an association between discounting values and several substance use variables. College students that discounted delayed rewards at a higher rate had been exposed to drugs earlier in life and had experiences with more drugs (Kollins, 2003). On the other hand, many authors have argued that impulsivity also plays a role as a consequence of chronic drug use. In one animal study (Simon, Mendez, & Setlow, 2007) rats were administered cocaine for two-weeks followed by a three-week withdrawal period. Subsequently, the rats were exposed to a delay discounting paradigm in which each had to choose between a lever that delivered one food pellet immediately and one that delivered four food pellets after a delayed period. Compared to controls, rats exposed to cocaine had a higher rate of choosing the immediate over the delayed reward. However, in humans the findings have provided mixed results. A 1999 study (Bickel, Odum, & Madden, 1999) using a delayed discounting paradigm sought to investigate impulsive choice tendencies in non-smokers, current smokers, and ex-smokers. The results suggested a significant increase in discounted values for delayed rewards in current smokers. No significant difference was found between non-smokers and ex-smokers. On the other hand, a similar study using a delay discounting paradigm with heroin, cocaine and alcohol users and a control group yielded different results. An increased discount for delayed rewards was observed for cocaine and heroin users but not for alcohol users or control subjects (Kirby & Petry, 2004). These results suggest that the effect of increased impulsivity (as measured by the delay discounting paradigm) following a pattern of drug abuse might be dependent on the type of substance being abused. Moreover, baseline levels of impulsivity could also be affecting these results.

Based on these findings several authors have proposed that impulsivity levels in drug abusers might be able to predict treatment outcomes, and relapse rates (Weafer, Mitchell, & De Wit, 2014). These findings suggest the consideration of impulsivity as a predictor in the treatment plan for drug abusers as a potential way of minimizing relapse rates.

A third line of research has focused on the influence of a third, unknown variable that could mediate the relationship between impulsivity and drug abuse. This research is built on the assumption that other factors, such as genetic or environmental vulnerabilities, along with impulsivity may have an impact on future drug abuse (Perry & Carrol, 2008). For example, negative early-life experiences have been found to be related to subsequent drug abuse. An association between negative early-life experiences and impulsivity has also been found (for review, see Olmstead, 2006). Sex has also been found to influence several drug-abuse factors like self-administration and escalation of drug use. Several studies have found that females are more likely to display drug-seeking behaviors compared to men (for review, see Lynch, Roth, & Carroll, 2002). Notably, studies measuring sex differences in impulsivity levels have yielded mixed results. A study assessing impulsive choice using a delay discounting task found that females discounted delayed rewards at a higher rate than men when using hypothetical rewards (Heyman & Gibb, 2006). However, when using real reinforcers the aforementioned effect was reversed.

In any case, no matter the predisposing factors, substance abuse is a problem that continues to plague our society. The situation begs for research attention.

Phases of Addiction

Any drug abuse trajectory can be conceptualized as being divided into several stages: 1) Acquisition, 2) Maintenance, 3) Escalation, 4) Abstinence, and 6) Relapse. In order to better understand the relationship between drug abuse and impulsivity it is imperative to consider each stage separately. The first stage, acquisition, is typically understood as being the turning point where the person switches from using a drug for the first time to using it routinely. As stated before, impulsivity plays an important role during this phase where impulsive individuals are more likely to initiate drug self-administration. The second phase of drug addiction, maintenance, is characterized by a steady and regular pattern of drug use. To this date, this stage has not been found to exhibit a significant relationship to impulsivity (Perry & Carroll, 2008). The third phase, escalation, is characterized by a dysregulation of drug use that leads the person to go from a steady maintenance of drug use to a "binge-like" degree of intake. Studies have found impulsivity to be involved in two ways within this stage of addiction. On one hand, high baseline impulsivity has been shown to reduce the time between maintenance and escalation. On the other hand, escalation of drug use has been found to also increase impulsivity levels in drug abusers (Weafer, Mitchell, & De Wit, 2014). The last two phases, abstinence and relapse, are also influenced by impulsivity. Studies have found that highly impulsive drug-dependent individuals are more likely to quit treatment and relapse (Weafer, Mitchell, & De Wit, 2014). The treatment/abstinence phase of addiction is the main focus of the current study.

Neural Correlates of Drug Abuse and Impulsivity

Behavioral tasks that measure impulsivity most often do not correlate with each other, suggesting that performance on each task is associated with distinct underlying neural mechanisms (Jentsch et al., 2014). However, frontal brain regions and circuits have consistently been implicated in impulsive decision-making and inhibition processes, with distinct frontal locations associated with specific measures of impulsive behavior. For example, performance in response inhibition tasks has been associated with activation of right frontal lobe regions (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003) as observed by magnetic resonance imaging. On the other hand, delay-discounting processes have been associated to the orbitofrontal cortex and the ventromedial pre-frontal cortex (Boettiger et al., 2007). Additionally, performance on tasks measuring risk-taking behaviors has been associated with activation of left regions of the frontal lobe (Floden, Alexander, Kubu, Katz, & Stuss, 2008).

The frontal cortex is most commonly associated with executive function. Not surprisingly, loss of gray matter in this area has been linked to the development of many disorders involving executive dysfunction (Anderson, Baldridge, & Stanford, 2011), including substance abuse and impulsivity disorder (Bellis et al., 2005; Boes et al., 2008). Imaging studies of human addicts have mostly focused on the involvement of mid-brain dopamine circuits on reward-related behaviors. However, recent human clinical studies have suggested an important role for frontal brain regions in the development, maintenance, and relapse of drug addiction (Goldstein & Volkow, 2011). Furthermore, impulsivity-related neural circuits have also been implicated in drug addiction (London, Ernst, Grant, Bonson, & Weinstein, 2000).

Frontal Asymmetry and Impulsivity

The existence of brain asymmetries and their functions have long been the source of controversy within the neuroscience field. Anatomical and functional asymmetries are found across many animal species, including humans. However, contrary to popular beliefs, there are no definitive differences between brain hemispheres accounting for "left or right brain personalities". Nevertheless, some asymmetrical brain components do exist (Toga & Thompson, 2003). Specifically, a line of research has focused on the role of the left and right frontal lobes in the expression of emotion and emotional responses to various stimuli (Reid, Duke, & Allen, 1998). One of the first findings involving frontal asymmetry was suggested by Harmon-Jones and Allen (1997). In their study, they proposed that EEG frontal asymmetry is associated with approach/withdrawal-related motivation and emotion. Specifically, the left-hemisphere was associated with increased approach-related behaviors while activation of the right hemisphere was associated with withdrawal-related behaviors. These findings follow Davidson's initial diathesis-stress hypothesis (Davidson, 1993), where relatively less left frontal activation would correlate with a predisposition towards negative affect, depressive symptoms, and increased emotional reactivity. However, this thesis has had only mixed support. In a 2006 study, relative increases in left frontal activity were found to be associated with patterns of disruptive behaviors in aggressive children and adolescents (Rybak, Crayton, Young, Herba, & Konopka, 2006). It is worth noting that for this sample, clinical severity was based on number of past diagnoses and not based on current assessments. Moreover, the majority of adolescents in the sample were being treated with various medications that could be mediating frontal activation. Considering the right side, several measures of

anxiety and anxiety disorders have been associated with increased relative right frontal activation (Thibodeau, Jorgensen, & Kim, 2006). Furthermore, impulsive aggression and trait anger have also been associated with increased relative right cortical activation during a resting-state EEG paradigm (Jaworska et al., 2012; Lake, Stanford, & Patton, 2014).

As mentioned earlier, activation of the right frontal hemisphere has been observed during behavioral tasks measuring inhibitory control in substance-dependent individuals (Tsujii, Sakatani, Nakashima, Igarashi, & Katayama, 2011). However, when measuring decisional impairments and risk-taking this activation pattern is reversed, with increased relative activation observed in the left frontal lobe (Balconi, Finocchiaro, & Canavesio, 2014; Black et al., 2014). These findings suggest that the relationship between substance dependence and frontal asymmetry might be mediated by a third variable. As mentioned earlier, past research has suggested a strong comorbidity between anxiety, depression and drug addiction (Grant et al., 2004; Kreek, Nielsen, Butelman, & LaForge, 2005). To date, no studies have assessed the relationship between resting EEG frontal asymmetry in substance-dependent individuals and impulsivity controlling for anxiety and depression symptomatology. Resting frontal EEG indexes might possibly be employed to assess risk factors and disorder severity as well as serve as an additional physiological marker that could aid in choosing a personalized treatment strategy.

Conclusions

Impulsivity is a multi-dimensional higher-order personality trait that can be expressed across a wide variety of behavioral classes and situations. Impulsive behaviors have been used as markers or symptoms of various disorders, including substance abuse and dependence. Additionally, various assessments of impulsivity have been related to distinct aspects of drug addiction, suggesting a complex relationship between impulsivity per se, and/or impulsive behavior and substance abuse. Self-report measures of trait impulsivity contribute to an understanding of this relationship because they assess long-term personality patterns that are likely less susceptible to changes in temporal emotional state or specific situation. Physiological measures of impulsivity have also been used to help investigate and characterize the relationship between drug abuse and impulsivity. One example are measures or changes in cortical activation as they relate to the individual's performance on specific behavioral tasks. Given the complex relationship between impulsivity and substance abuse, as well as recent findings on frontal asymmetry related to certain aspects of both, I hypothesized that trait impulsivity (as measured by self-report), would correlate with asymmetrical frontal activity. Specifically, highly impulsive substance-dependent individuals would have increased frontal activation in the right hemisphere relative to the left. Furthermore, this relationship would persist even after assessing general aggression, and anxiety/depression symptomatology.

CHAPTER TWO

Methods

Recruitment Process and Inclusion Criteria

Participants

Substance dependent males (n = 24) were recruited from a local residential treatment program which incorporated Christian principles in its treatment strategy. The residents were mostly referred to the program by court order, while others referred themselves for treatment. The program consisted of an initial drug and Axis I disorder screening process, followed by a three phase period that typically lasted from 3 to 6 months. The treatment program was not free of charge although there was a donor fund for qualifying participants. The fees provided for room and board, program materials, and therapeutic activities (e.g. individual and group counseling, Bible study, case management, and 12 step community meetings). During the last phase of the program residents were also provided with computer training, GED classes, retention skills, and job seeking resources. Furthermore, the residents were in charge of all house-related tasks including: cleaning, cooking, and working in the garden. Out of the initial 24 participants, three were unsuccessfully discharged during the study and are not included in our analyses because their data is incomplete or inaccurate. An unsuccessful discharge from the treatment program was given to any resident that did not comply with the program's "cardinal rules". These included: No use or possession of any drug, no violence, stealing, or breaking the law. Data analysis therefore included 21 subjects.

To be invited to participate in our study residents were required to have the approval of the program's director and to be absolutely drug-free for at least three weeks (21 days) prior. Participants were provided with a 25$ gift card that was given to the treatment program administrators to make sure that the funds were not used inappropriately by the resident. Subjects were also provided with snacks during their time in the lab. Participants were brought individually to our lab located at the university. Each participant would arrive at 8:00 in the morning and leave between 11:00 am and 12:00 pm. The lab visit consisted of two parts: EEG recordings were first obtained followed by administration of self-report questionnaires. Transportation to and from the university was provided by the treatment program. All experimental procedures were approved by the Institutional Review Board at Baylor University and all participants were required to provide informed consent.

Participants were between 21 and 62 years old (M = 34), and approximately 62% (*n* = 13) identified as white, non-Hispanic. Five other participants (24%) identified as black non-Hispanic; two other (10%) as white-Hispanic; and one (5%) as black-Hispanic. Six participants from the initial group were not included in the asymmetry analyses due to left-handedness (Propper, Pierce, Geisler, Christman, & Bellorado, 2012).

Procedures

Electrophysiology

Participants' scalp and mastoids were prepared using isopropyl alcohol to eliminate excess oils and then a slightly abrasive gel (NuPrep) was applied to increase conduction. Furthermore, each participant was fitted with a Neuroscan Quick-Cap with 64 tin electrodes following the international 10-20 system. Each head cap included standard and intermediate positions that were referenced to the mastoids (M1 and M2 channels). In addition, four electrodes were added around the eyes to record horizontal and vertical eye movements that would allow artifact and eye-blink data removal. EEG data was recorded at a sampling rate of 1000 Hz and was further amplified using SynAmps² amplifiers. Participants were provided with headphones (SONY: MDR-NC60 noise cancelling) and seated in a padded chair in a light and sound controlled, radio-frequency shielded chamber. The distance between each participant and the computer screen (Dell 2007-FP, 16 x 12 inches) was kept constant at approximately 3.6 ft.

Resting Asymmetry

The resting EEG paradigm used had a duration of 8 minutes where participants were instructed to keep their eyes open or closed for 1-minute blocks with 15 seconds in between blocks. In the eyes-open condition participants were instructed to focus on a 1.25 x 1.25 in. plus sign (+) presented at the center of the screen for one minute. For the eyes-closed condition the plus sign was not presented. Participants were instructed to close their eyes until they heard a "beep" sound (100 dB) through their headphones

cueing them to re-open them. The order of the 1-minute blocks was counterbalanced between conditions (eyes-open, eyes-closed).

Data Cleaning and Analysis

An off-line program, NeuroScan® 4.3 was used to filter and eliminate frequencies below 0.1 Hz and above 50 Hz (both at 12 dB/oct). Additionally, a spatial filter was used to filter out eye blinks by isolating epochs from -200 ms to 600 ms post-stimulus. Subsequently, each continuous recording was re-referenced to the mastoids and further inspected to manually remove contaminated epochs. Finally, time domain EEG epochs were converted to frequency domain using a Fast Fourier Transformation (FFT) algorithm. This process separated artifact-free data into frequency bands with a Hamming window of 1 s and a 50% overlap. Before the analysis, the average alpha power at each electrode site was then natural log transformed to avoid the positive skewness typically observed with untransformed power values. As is common, alpha power values were interpreted as an inverse of cortical activity (Davidson, 1988).

Psychological Assessments

Barratt Impulsiveness Scale-brief (BIS-brief). The BIS-brief (Steinberg, Sharp, Stanford, & Tharp, 2013) is an 8-item scale developed to be a shorter, unidimensional version of the BIS-11 (Patton & Stanford, 1995). A total impulsivity score can be obtained by adding up the responses to the eight items. Participants responded to items on a 4-point scale, where 1 = *Rarely/Never*, 2 = *Occasionally*, 3 = *Often*, 4 = *Almost Always/Always*. Steinberg and colleagues reported good reliability estimates using Cronbach's alpha as an indicator (a = .78). Moreover, construct validity estimates were

reported for adults who met criteria for Borderline Personality Disorder (BPD) (*a* = .81), an adult domestic violence sample (*a* = .74), and an adolescent and young adult inpatient sample (*a* = .83). Significant correlations were reported between BIS-brief, BIS-11, and Buss-Perry Aggression Questionnaire (BPAQ) (Steinberg et al., 2013).

Life History of Impulsive Behaviors (LHIB). The LHIB questionnaire (Coccaro & Schmidt-Kaplan, 2012) was designed to estimate the frequency of "real life" impulsive behaviors from a historical perspective as a compliment to self-report assessments. The questionnaire consists of 20 items that include an array of behaviors that could be observed in different environments, taking into account motivational, attributional, and emotional factors of impulsivity (Coccaro & Schmidt-Kaplan, 2012). This shorter version of the original LHIB-Q53 (Schmidt, Fallon, & Coccaro, 2004) calculates an overall impulsivity score. Internal reliability estimates are good for subjects with or without an Axis I or II disorder (*a* = 0.92) as is test-retest reliability (*r* = 0.79). Concurrent validity with BIS-11 impulsivity is *r* = 0.51. The LHIB requires participants to respond to items on a 6-point scale, where 0 = *Never happened*, 1 = *Happened only once*, 2 = *Happened 2-3 times*, 3 = *Happened 4-9 times*, 4 = *Happened more than ten times*, 5 = *Happened too many times to count*.

Buss-Perry Aggression Questionnaire (BPAQ). The BPAQ is a 29-item measure that evaluates individual components of aggression as well as an overall aggression score (Buss & Perry, 1992). Buss and Perry identified these components as: Physical Aggression (α = .84), Verbal Aggression (α = .80), Hostility (α = .83), and Anger (α =

.76). Participants responded to items on a 5-point scale, where 1 = *Extremely uncharacteristic of me,* and 5 = *Extremely characteristic of me*.

Drug Abuse Screening Test (DAST-20). The DAST consists of 20 *Yes* or *No* items and in this study was administered to assess severity of substance abuse in the last 12 months (Skinner, 1982). A higher score on the DAST reflects a higher abuse severity. The DAST has yielded generally solid reliability and test-retest estimates as well as adequate estimates of validity and specificity (Yudko, Lozhkina, & Fouts, 2007).

Alcohol Use Disorders Identification Test (AUDIT). The AUDIT was developed to identify when alcohol intake has become harmful to a person's health. The test was developed by Saunders and colleagues in 1993 (Saunders, Aasland, Babor, De la Fuente, & Grant, 1993) and it encompasses several aspects of alcohol use like consumption frequency, detrimental problems associated with alcohol use, and drinking behaviors. Subjects responded to 10 items on a 5-point scale where values were dependent on the nature of each question. This instrument is widely used in alcohol research (J. P. Allen, Litten, Fertig, & Babor, 1997; Reinert & Allen, 2002, 2007).

Depression Anxiety Stress Scales (DASS-21). The DASS scales were developed to differentiate between core symptoms of anxiety, depression, and stress (P. F. Lovibond & Lovibond, 1995; S. Lovibond & Lovibond, 1993). Depression and anxiety disorders have been known to show comorbidity with substance abuse disorders (Grant et al., 2004). In our study, we administered the DASS-21 scale to assess depression and anxiety symptomatology within our sample and their relationship with impulsivity and substance dependence. Subjects responded to items on a 4-point scale, where 0 = *Did not apply to*

me at all, 1 = *Applied to me to some degree, or some of the time*, 2 = *Applied to me to a considerable degree, or a good part of time*, 3 = *Applied to me very much, or most of the time.*

Statistical Analysis

Following examples from past research, difference scores (ln(Right) – ln(Left) alpha power) were calculated as a way of summarizing relative asymmetric activity in each hemisphere (J. J. Allen, Coan, & Nazarian, 2004; Coan & Allen, 2003). Hemispheric asymmetry indices provide a degree of correction for overall power because they represent the difference between natural-log transformed values, thus providing a natural-log transform of the ratio of two specific values (Coan & Allen, 2003). When using these asymmetry indices a score of zero would presumably define frontal symmetry between hemispheres. A higher score would indicate increased left frontal activation relative to the right hemisphere and a lower score a relative increase in right-hemisphere activation. Asymmetry indices were included in correlational analyses and t-tests with measures of individual differences (self-report assessments). To explore the specific contribution of activity in each hemisphere we computed a mixed-design ANOVA. Using a median split, subjects were divided based on their scores on impulsivity measures (BIS-brief and LHIB) and arranged in either a High Impulsivity (HI) group or a Low Impulsivity (LI) group. Region (mid-frontal and lateral-frontal) and hemisphere (left and right) were included as within-subjects variables and group (HI or LI) was included as the between-subjects variable.

CHAPTER THREE

Results

Initially, 24 participants were recruited but data from *n = 3* were excluded because the participants dropped out of the treatment program. Additionally, data from *n* = 3 other participants was excluded due to incomplete or invalid self-report assessments. A total of *N = 18* participants (high impulsivity = 10) were included in the statistical analyses. An initial group analysis (see Table A.1) using both impulsivity scales (LHIB and BIS-brief) as grouping variables revealed higher scores for the high impulsivity group (HI) on general aggression scores using the BPAQ. Interestingly, scores on the DAST-20 and AUDIT were differently associated to high or low impulsivity depending on the grouping variable used. Using the LHIB scores, higher AUDIT scores were associated with LI, and higher DAST-20 scores were associated with HI. On the other hand, using BIS-brief scores, higher AUDIT scores were associated with HI, and higher DAST-20 scores were associated with LI. None of these group differences were statistically significant. However while no significant differences were found using LHIB and DASS-21 scores [$t(16) = 0.05$, $p = 0.96$, $d = 0.02$], using trait impulsivity as measured by the BIS-brief. The HI group scored higher on depression and anxiety (as measured by the DASS-21) [$t(18) = -2.45$, $p = 0.03$*, $d = 1.13$] compared to the LI group.

To analyze asymmetry according to Coan and Allen's model (J. J. Allen et al., 2004) asymmetry indexes for medial and lateral frontal regions were entered in t-tests with either LHIB or BIS-brief scores as grouping variables. Using the asymmetry index

(*ln*[right] – *ln*[left]) at mid-frontal (F3/F4) and lateral-frontal (F7/F8) sites and total BIS-brief scores, no statistically significant effect was found between high and low impulsivity groups [F3/F4: $t(18) = 0.17$, $p = 0.87$, $d = 0.08$; F7/F8: $t(18) = 0.39$, $p = 0.70$, $d = 0.17$]. However, using LHIB total scores and asymmetry indices, HI individuals showed a trend towards increased right cortical activity during the resting state compared to those in the low impulsivity group at mid-frontal electrode sites [F3/F4: $t(16) = 1.83$, ***p* = .08**, $d = .836$; F7/F8: $t(16) = 1.64$, $p = 0.12$, $d = 0.76$]. No significant group difference or trend was found at lateral-frontal sites.

To further analyze the contribution of activity in each hemisphere a mixed-design ANOVA was computed with Region (mid-frontal and lateral-frontal) and Hemisphere (left and right) as within subjects variables and Group (high impulsivity vs. low impulsivity) using LHIB total scores, as between-subjects variable. Because there was no relevant difference between asymmetry indexes and BIS-brief scores no ANOVA was computed for these data. There was a significant region main effect [$F(1,16) = 108.367$, $p < .0001$, $\eta^2 = 0.17$], with more activity at mid-frontal relative to lateral-frontal electrode sites in both groups. Furthermore, there was a trend towards a Group X Hemisphere interaction effect [$F(1,16) = 3.558$, $p = .078$, $\eta^2 = .009$] with more left alpha power, thus more right activity for the HI group (MLeft = 2.14, SD = .65; MRight = 2.08. SD = .65) compared to the LI group (MLeft = 1.84, SD = .65; MRight = 1.92. SD = .71).

CHAPTER FOUR

Discussion

Trait impulsivity and impulsive behaviors have both been studied in relation to psychopathology. Distinct and overlapping facets of impulsivity have been associated with different stages of a drug abuse trajectory. For instance, increased baseline impulsivity levels have been associated with likelihood of initiation of drug use as well as escalation and relapse. Concurrently, drug abuse and especially dependence has been suggested to increase impulsive behaviors, which can further influence future drug use. In addition, mood and anxiety disorders have been found to be associated with substance use disorders. Studies on frontal asymmetry in relation to substance dependence have yielded mixed results, with relative increased activation in the left or right frontal hemisphere while performing inhibitory control or delay-discounting tasks, respectively. Moreover, increased left frontal activation has been associated with depression and negative affect. On the other hand, increased right frontal activation has been related to anxiety disorders, impulsive aggression, and dysfunctional anger. However, studies examining resting frontal activity in drug abusers have reported increased right cortical activation in poly-substance abusers and alcoholics (Hayden et al., 2006; Roemer, Cornwell, Dewart, Jackson, & Ercegovac, 1995).

In our sample, the only significant group difference between impulsivity and self-report variables was observed with BIS-brief (trait impulsivity) scores and DASS-21, where higher impulsivity was associated with higher levels of depression, anxiety, and

stress. This result is in agreement with past research that has suggested an association between impulsivity levels and anxiety disorders (Mathersul, Williams, Hopkinson, & Kemp, 2008). The lack of significant differences between impulsivity groups and other self-report variables could be due to the small sample number. Future research should address this using a larger sample. Multiple t-tests revealed no significant differences between asymmetry indices and self-report measures. However, a trend was observed towards increased right frontal cortical activity in the high LHIB compared to the low LHIB scoring group. These results are in partial agreement with my original hypothesis, stating that impulsivity in substance dependence would likely be reflected as increased right frontal activity. Note that the LHIB scale measures an individual's history of impulsive behavior as opposed to trait impulsivity. Therefore, a case could be made for recorded impulsive behaviors being a consequence of drug abuse, at least during the abstinence/treatment phase of addiction. The contribution of hemispheric activity was assessed using a mixed-design ANOVA. Results suggested an overall increase in activation in mid-frontal as opposed to lateral-frontal electrode sites for both groups (high and low LHIB). This result could suggest an association between activation within medial regions of the frontal cortex and substance abuse independent of impulsivity levels. Further research should explore this possibility. Moreover, the ANOVA results further reflected the aforementioned trend towards increased right frontal activation (mid-frontal region) in the high LHIB scoring group. This result is in agreement with findings from impulsive aggressive individuals, where right frontal activation was found to be associated with increased levels of impulsive aggression (Lake et al., 2014). In our sample higher levels of general aggression were observed in both high-impulsivity

groups (BIS-brief and LHIB). However, these group differences were not statistically significant. Right frontal activation has been associated in the past with controlled inhibition (Goldstein & Volkow, 2011), and impaired inhibition has been documented in substance dependent individuals (De Wit, 2009). Thus, this result could suggest a possible rehabilitation-induced therapeutic effect reflected as an up-regulation of inhibitory systems associated with inferior regions of the right frontal cortex (Jaworska et al., 2012; Jentsch et al., 2014).

I encountered several limitations that could account for the lack of significant results. First, due to unexpected subject loss and limited sample pool, the sample size was likely too small to yield adequate power values. In the future, replicating this experiment with a larger sample might possibly result in significant results in the same direction we report: higher levels of impulsive behaviors and/or trait impulsivity in substance dependent individuals leads to increased right frontal cortical activation during resting state. Another limitation of this study is the lack of a control group without any history of drug abuse. A control group for this study should have included subjects matched on age, socioeconomic status, and personality assessments. Because the sample used for this study was composed of substance-dependent males receiving rehabilitation treatment in a residential facility completing a study such as this one turned out to be a difficult task. If a large treatment population were to exist, in order to further explore the relationship between frontal asymmetry and impulsivity across the drug-dependence trajectory, the design should include subjects experiencing each addiction stage.

Future studies might also benefit from including separate depression and anxiety self-report assessments. This would allow for an analysis of the individual contribution of

each variable that is not possible with the DASS-21 because it gives an overall anxiety/depression/stress score. Additionally, the lack of significant differences between trait impulsivity and frontal asymmetry scores could be due to the fact that the BIS-brief might not be representing the multidimensionality of the impulsivity construct. The BIS-brief lacks the differentiation between specific impulsivity factors, thus only providing a brief, unidimensional measure of trait impulsivity (Steinberg et al., 2013). Future studies might also include behavioral tasks used in impulsivity research to see if any relate to resting EEG paradigms. Studies examining drug abuse and performance on delay discounting or go/no-go tasks have yielded confusing results and no reported study has included behavioral tasks measured alongside resting frontal EEG paradigms and self-report measures of impulsivity.

In spite of these limitations the results reported here add to the existing evidence supporting the use of frontal asymmetry as a biological marker for psychopathology. To the extent of our knowledge, this study is the first to associate self-reported impulsivity to resting frontal asymmetry in relation to substance abuse. Future research in this area is warranted.

APPENDIX

APPENDIX A

Table A.1 Group differences in self-report measures

	LHIB					**BIS-brief**				
Measure	*Low impulsivity M (SD)*	*High impulsivity M (SD)*	*t (df)*	*p*	*Cohen's d*	*Low impulsivity M (SD)*	*High impulsivity M (SD)*	*t (df)*	*p*	*Cohen's d*
BPAQ	79.75 (25.45)	90.44 (17.46)	-1.02(15)	0.32	0.49	76.33 (16.11)	89.30 (24.14)	-1.36(17)	0.19	0.63
DASS21	20.63 (15.38)	20.30 (14.33)	0.05 (16)	0.96	0.02	11.22 (8.99)	25.18 (15.03)	-2.45(18)	**0.03**	1.13
DAST20	10.43 (6.18)	14.40 (4.09)	-1.60(15)	0.13	0.76	14.14 (4.88)	11.80 (5.57)	0.90 (15)	0.38	0.45
AUDIT	24.50 (13.66)	13.78 (11.13)	1.78 (15)	0.09	0.86	12.17 (10.89)	22.45 (13.34)	-1.61(15)	0.13	0.84

Note. Lifetime History of Impulsive Behaviors (LHIB; Coccaro & Schmidt-Kaplan, 2012), Barrat Impulsiveness Scale - Brief version (BIS-brief; Steinberg et al., 2013), Buss-Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992), Depression Anxiety Stress Scales (DASS-21), Drug Abuse Screening Test (DAST-20), Alcohol Use Disorders Identification Test (AUDIT; World Health Organization, 1982).

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