**Chapter 2: Literature Review**

**Introduction**

Neuropsychological studies of neurocognitive deficits related to cocaine and methamphetamine (MA) abuse have demonstrated that vulnerabilities, treatment and relapse differ by sex (Anker & Carroll, 2011; Bobzean et al., 2014; Fattore et al., 2014; Kennedy et al., 2013; Ramoa et al., 2013). The Department of Justice (DOJ) and the National Institute on Drug Abuse (NIDA), from their recent national data indicate that abuse and dependence on cocaine and MA has risen significantly among women in the United States (DOJ, 2013; NIDA, 2013). Psychological studies of drug addiction further demonstrate that the experiences of women in drug-seeking, abstinence and relapse are significantly different than those experienced by addicted men. Adverse changes in brain structures related to cognitive and executive function are especially detrimental to decision making and critical thinking processes in cocaine and MA addicted women (Becker et al., 2012; Wetherington, 2010; Winhusen et al., 2013; Verdejo et al., 2013). Chronic impairments in these neural systems are also implicated in the increasingly risky, violent and life-threatening behaviors that women are willing to endure in order to continue drug abuse (Becker, 2012; Bisagno & Cadet, 2014; CDC, 2010; NIDA, 2014).

This chapter begins with a comprehensive review of the literatures of classical and operant conditioning theories of cocaine and MA addiction specific to gender. Next, a cursory review of the neurochemistry of cocaine and MA is provided. Afterwards, an in-depth examination of literatures related to neuropsychological processes of cocaine and MA addiction and gender differences is offered. In addition, relevant studies of cognition and executive function related to neuropsychological performance and gender are examined. A final aspect of the literature reviews explores salient evidence to support new empirical studies of greater inclusion in all aspects of the psychological experiences of cocaine and MA addiction in women.

**Research Strategies**

A thorough review of the literatures for this study was acquired by examining secondary sources published between 2006 to the present. Related terminologies for this study include but are not limited to: *addiction, substance use, substance abuse,* *cocaine, methamphetamine, neurocognitive interference, cognition, executive function, gender, sex,* *learning and memory,* *neuropsychology, neurocognition, neuroscience, and neuropsychological tests*. Information for the literatures was obtained from the following databases: EBSCOHOST, MEDLINE, NCBI, NIDA, and PSYCHINFO. Additional information was found on credible internet sites that included, the American Psychological Association (APA), Center for Behavioral Health Statistics and Quality (CBHSQ), Centers for Disease Control (CDC), Department of Justice (DOJ), National Institutes of Health (NIH), European Monitoring Center for Drugs and Addiction (EMCDA), National Center for Biotechnology (NCBI), the Office of National Drug Control Policy (ONDCP) and the Walden University Library.

**Theoretical Foundation**

**Classical and Operant Conditioning**

Classical (Pavlovian) and Operant (Instrumental) conditioning learning theories support the view that neuroadaptations of brain systems affected by illicit drugs subsequently produce conflicting events--tolerance as well as avoidance behavior in males and females (Everitt, 2014; Yager & Robinson, 2014). Contemporary drug addiction theories are heavily based in classical and operant conditioning theories (Goddard et al., 2013). The rationale for examining an addiction model of classical and operant conditioning theories is two-fold; (1) brain behaviors in addiction are contingent on conditioned learning associations of drug-seeking and drug-taking as for female addicts, and (2) cognition and executive function impairment are predicated on gender differences as positive and negative reinforcements in treatment and relapse.

Ivan Pavlov’s work with animals in classical conditioning provided strong evidence that an event when paired with a stimulus can predict future behaviors based on previous experience (Milton & Everitt, 2012; Jasinska et al., 2014; Pinel, 2011). Milton and Everitt (2012) contend that in both drug-seeking and drug-taking behaviors, “Pavlovian or non-contingent behavior (stimulus-response) occurs with extensive training associations between the drug-conditioned stimulus and the of drug-seeking and taking (stimulus-response actions or S-R associations” (p. 1120). Hence, through Pavlovian conditioning, drug associated stimuli become wanted and preferred, grab attention and produce a variety of physiological and psychological responses for the user (Goddard et al., 2013). Should this repetitive cycle continue unchecked in the user, then drug-taking can move beyond voluntary and controlled to involuntary, and uncontrolled; this process becomes the transitory mechanism in forming new brain behavior associations leading to drug addiction (Goddard et al, 2013).

Classical conditioning in animal studies involving drug-seeking tasks have demonstrated that dependence vulnerability is strongly connected to cocaine and MA related cues rather than pharmacological effects; inferring that when these cues are no longer present; drug-seeking is significantly reduced and only reoccurs when these cues are re-introduced (Everitt, 2014; Lejeuz et al., 2007; Koob & Volkow, 2010). Addiction theories contend that while any user is susceptible to progressive drug use after initial administration, there are some notable differences in how drug-seeking behavior, frequency and reward mechanisms deviate in terms of gender (Todd et al., 2014, Zuloaga et al., 2015). Studies of substance abuse also suggest that women are more prone to develop cue-induced drug cravings and are more likely to remain or relapse into a cycle of dependence (Kerstetter et al., 2013; Potenza et al., 2012). In this respect, the continued response to cocaine or MA ( stimulus) reinforces the probability of repeating drug- seeking and drug-taking behaviors (Milton & Everitt, 2012).

Volkow et al., (2011) compared brain metabolism and drug cravings through the use of Positron Emission Tomography (PET) in female and male cocaine addicts. This study hypothesized that females would demonstrate greater reactivity when presented with various drug cues which could explain their high probability to relapse to cocaine use. The researchers found that although responses did not differ by gender in self-reported drug cravings when viewing cocaine-cued videos; gender differences were noted in whole brain metabolism changes with females exhibiting decreased metabolism, whereas metabolic rates increased among male participants. This research concludes, as in other studies of cue conditioning, that gender differences exist in vulnerabilities to continued drug use and in relapse susceptibility (Andersen et al., 2012; Dalla & Shors, 2009; Potenza et al., 2012: Volkow et al., 2011). Classical conditioning studies of gender based cue-conditioning find that females tend to manifest greater risk taking in drug-seeking because brain regions that are most reinforcing to continued drug use are also the same systems that are resistant to drug abstinence (Mitchell & Potenza, 2013; Balconi & Finocchaiaro, 2015).

The perception in conditioned response research is that if drug cues are not available then instances of drug-seeking actions are radically lessened and the behaviors only recur once cues are reinstated (Goddard, 2013; Todd et al., 2014). Classical conditioning studies suggest that long-term drug abuse leads to adverse changes in prefrontal cortex (PFC) neuronal structure in rats and prominent modifications in the “functional activation of the orbito-frontal cortex (oPFC) in cocaine addicts which could have recovery effects on drug-taking and drug-seeking behaviors” (Everitt, 2014, p.132). Conditioning models demonstrate the complexities of neuropsychological processes in female addiction, including drug susceptibilities, and repetitive relapse behaviors even after an extended absence of drug-taking (Kennedy et al., 2013; Najavits et al., 2008; Ramoa et al., 2013).

Although neural response studies have been more inclusive of the experiences of female addicts, previous research has failed to examine associations between stress, drug cues and craving among women in comparison to men (Potenza et al., 2012). To further illustrate gender differences in relationship to stressors and drug induced cravings; Potenza et al. (2012) used Functional MRI measures to evaluate drug/alcohol imagery and brain-relaxing images for 30 cocaine abstinent participants. Functional MRI was used to assess responses to individualized scripts for stress, drug/alcohol cues and neural relaxing imagery conditions in 30 abstinent cocaine-dependent men and women (n=16 women, n=14 men). This group was compared to 36 healthy (sporadic drinking) participants (n=18 women, n=18 men) (Potenza et al., 2012, p.406). Functional MRI results revealed prominent three way communications visible in a number of brain regions including “the striatum, in multiple brain regions including the striatum, insula, and the anterior and posterior cingulate” (p. 406). The researchers found that while drug-induced craving cues were positively associated with increased corticostriatal-limbic brain activity in both male and female participants; females experienced greater hyperactivity in this region of the brain when stress-inducing cues were introduced compared to cocaine-dependent males. In cocaine dependence, corticostriatal-limbic hyperactivity appears to be linked to stress cues in women, drug cues in men, and neutral-relaxing conditions in both (Gallop et al., 2007; Ide et al., 2014).

Adding to the vulnerabilities of addiction is the reality of risk associated in seeking illicit drugs (BOJ, 2013; Moeller et al., 2010, Tolliver et al., 2012; Tull et al., 2011). In their studies of cocaine dependent individuals (n=42), Mahoney et al., (2010) found that women report more psychotic symptoms, including paranoid and grand delusions, perceptual disturbances and auditory, tactile and olfactory hallucinations more frequently than men. These findings are consistent with other psychological studies hypothesizing that increases in psychotic symptoms in women is attributed to their use of greater quantities of their drug of choice per day and for longer periods than men (Anker et al., 2011; Fox et al., 2014; Volkow et al., 2011b).

Motivation to drug-seeking behavior in laboratory animals is associated with behaviors that produce positive outcomes (the reduction of pain and hunger) these motivational behavior processes are similar for humans (Gould, 2010). While Pavlov’s classical conditioning studies offer some explanation of the cue conditioning and reward in drug abuse behaviors, it does not explain why the behavior continues Instrumental (operant) conditioning originates from the work of E.L. Thorndike in which he theorized that conditioning in learning depends upon the consequences of an action to modify the likelihood of that same action happening in the future (Milton & Everitt, 2012). This assessment that learning depends on the consequences of an individual’s actions differs from Pavlovian conditioning in which “contingency between the CS (conditioned stimulus) and US (unconditioned stimulus) is dependent on the individual’s behavior,” and the motivation to continue the instrumental response relies on whether the action results in a positive or negative consequence (Milton & Everitt, 2012, p.1123. In instrumental or operant conditioning in drug abuse, the reinforcing mechanisms that now deeply involve the dopamine and limbic systems providing the “reward effects of drug use” (positive reinforcement) also provide little incentive to avoid drug use as stopping the use of cocaine and MA can bring on painful and aversive withdrawal symptoms, therefore the choice for many female abusers is to continue drug-seeking and drug-taking (Milton & Everitt, 2012, Pinel, 2011).

Due to the strength of these reinforcing cues, Clark (2006) notes that the use of stimulant drugs, their ingestion and use, can become even more powerful than the body’s natural rewards including appetite, drinking and sexual activity and can alter the satisfaction of these rewards in order to continue drug use. The learning and conditioning response processes associated with these behaviors have been examined in the context of reinforcement in laboratory animals (Pinel, 2011). In general, psychoactive drug research, laboratory animals (when permitted) learned to self-administer all drug types with the exception of LSD (Clark, 2006; Everitt, 2014). These studies emphasize that conditioning in drug-seeking cues in laboratory animals are greatly influenced by motivation and reward, much like drug-seeking in humans is motivated by reward processes (Gould, 2010; Moeller et al., 2012). One element of consequence known to affect behavior is positive reinforcement. In experimental settings, laboratory animals such as rats learn to press a level to obtain food, or a dog follows verbal commands to obtain a treat (Gould, 2010).

The subsequent dependence on drugs wakens the motivational systems in this realm of human behavior, the drug is the cue or reward and the repetition of use links the association between cue, response and rewards becomes stronger upon subsequent administration (Milton & Everitt, 2012). Clark (2006) suggests that this model of addiction can be viewed in terms of a particular path that involves the development of habitual behavior pattern independent of cognitive processes. In this respect the impulses to continue the addictive behaviors can be so robust that they overpower the desire of the addicts to restrain themselves (Clark, 2006).

In their study Mahoney et al. (2010) found that the continued abuse of cocaine and MA can lead to the onset of psychotic symptoms. Forty-two cocaine and MA dependent individuals (n=27 males, n=15 females). All study participants reported MA or cocaine as their preferred drug of choice. Participants responded to survey questions from the Psychotic Symptom Assessment Scale which listed an assortment of psychotic symptoms experienced during use. These researchers concluded that in the “while abstinent” situation, cocaine addicted women reported experiencing auditory hallucinations more frequently, while men conveyed delusions of grandeur; amid MA addicts, in the “while abstinent” condition, women were more likely to report that they felt that something was not right with the way a body part looked. In each group (whether MA or cocaine) all users reported various psychotic symptoms (auditory and olfactory hallucinations) as being more intense in the “while high” stages of drug abuse (Mahoney et al., 2010). Women dependent on cocaine express more cravings when exposed to cocaine cues, and experience a heightened vulnerability to the physical, psychiatric and social consequences of substance use (Winhusen et al., 2013b). Several studies have now documented basal neural differences in cocaine dependent men and women, including a relative absence of cerebral perfusion defects, less frontal cortex neuronal loss, and better white matter blood flow in women relative to men. Women dependent on cocaine also differ from similarly dependent men in their neural response to cue-induced cravings and stress (Mahoney, 2010; Mitchell & Potenza, 2015).

In neuroscience studies of the relevance of cue association provides neural based evidence that the amygdala and the Ant Cing have been consistently shown to be activated in the functional imaging studies of cocaine and MA addicts when they are exposed to drug cues that elicit craving (Colzato et al., 2009; Ersche et al., 2006). In a study of gender and MA abuse, Zuloaga et al. (2014) proposed that alterations in the hypothalamic-pituitary-adrenal axis can result in cyclical use in that continued drug abuse no longer occurs for their desirable but rather to counter the heightened levels of stress and anxiety induced when the effects of the drug are no longer present. In women, this is especially problematic because the rate of MA abuse is high in women of childbearing age and follow up studies indicate that stress-induced cortisol levels were significantly higher in MA exposed infants (Zuloaga et al., 2014). Complicating the cyclical nature of chronic drug abuse among women especially in treatment, are the multiplicity of factors involved in drug-seeking and new problems that arise when women move from experimentation to full addiction.

The importance of studies in cue association support other studies evidencing that the amygdala and the Ant Cing have been consistently shown to be activated in functional imaging studies of cocaine and MA addicts when they are exposed to drug cues that elicit craving (Colzato et al., 2009; Ersche et al., 2006). Empirical studies of drug-seeking and maintenance behaviorsreveal that addictive behaviors are not “normal” occurrences that can simply happen at the will of the abuser, drug-seeking is a task that often requires secrecy and great need to avoid detection. In this respect, addiction behavior involves a multiplicity of tasks that must be accomplished especially in obtaining drugs; thus the reward of the affect must have more importance to the female abuser than the constant risks that must be overcome to secure these drugs (Everitt, 2014; NIDA, 2014).

**Cocaine and Methamphetamine: Neurochemistry**

Cocaine is an alkaloid ester and a tropane alkaloid naturally grown and prepared from the leaves of the coca bush found primarily in Peru, Bolivia and Columbia (EMCDA, 2016; Jonkman & Kenny, 2013). The processed impure residue derived from pure cocaine is known as “crack cocaine” (Pinel, 2011). Cocaine in its capacity as a central nervous system (CNS) stimulant, involves numerous neurotransmitter systems in the brain with specific interactions producing the most profound effects (Koob & Volkow, 2010). Two of these systems are the dopamine and limbic reward systems in which cocaine interactions produce some of its most pleasurable and positively reinforcing effects, including feelings of euphoria, well-being, self-confidence, alertness and a decreased desire for food and sleep (Bell et al., 2014; Ballard et al., 2015; Gould, 2010). One of cocaine’s most important roles in the dopamine system is to prevent the synaptic reuptake of dopamine (Rothman et al., 2008). Unlike other drugs, cocaine does not exactly stimulate the dopamine system, however, it allows neural components of the system to be stimulated by blocking dopamine reuptake transporters ability to evacuate from the intracellular space (Rothman et al., 2008). Studies of cocaine addiction in women find that cocaine can modify communication pathways between neurons (synaptic plasticity) which could provide a new pathway to a persistent and maladaptive drug-stimulus relationship (Garavan et al., 2008; Rothman et al., 2008; Moeller et al., 2014).

Cocaine abusers tend to go on binges also known as “cocaine sprees” in which extremely high levels of intake are maintained for a day or two (Goldstein & Volkow, 2011; Pinel, 2011). During the intake period, users become increasingly tolerant to the euphoria producing effects of cocaine (Nephew & Febo, 2012; NIDA, 2013). Adverse effects of cocaine sprees include bouts of sleeplessness, tremors, nausea, hyperthermia and psychotic behavior; however more severe reactions can result in a loss of consciousness, heart attack, stroke or death (Pinel, 2011). Although tolerance develops to most effects of cocaine (e.g., to the euphoria) repeated exposure to the drug sensitizes subjects (makes them more responsive) to its motor and

convulsive effects (Potenza et al., 2011). Cocaine and MA use during pregnancy is especially risky to the fetus and can cause complications including placental abruption, pre-term labor and delivery, and maternal seizures (Bhuvaneswar et al., 2008). Pregnant women might also experience other serious problems as a consequence of insufficient medical or pre-natal care mediated by continued drug use during pregnancy (Malek, 2012).

**Methamphetamine**

Methamphetamine (MA) is a derivative of a class of CNS stimulant drugs known as amphetamine and is usually administered orally in its more potent form called d-amphetamine (Taylor et al., 2013). Since the 1990’s the attractiveness of d-amphetamines was surpassed by several of its highly dominant relatives; 3, 4-methylenedioxy methamphetamine (MDMA or ecstasy), which is consumed orally; and methamphetamine or “meth,” typically taken in a smokable, crystalline form known as “crystal” or “ice” (Pinel, 2011). Methamphetamine can be produced from a wide variety of materials and methods. The ability to cheaply and quickly manufacture MA has increased potential for abuse and financial attraction for both users and manufacturers (NIDA, 2013; Rusyniak, 2013). Methamphetamine’s psychological effects, like those of cocaine include a heightened sense of euphoria or well-being, elevated alertness, increased vigor, decreased food intake and decreased sleep time (Bell et al., 2014; Taylor et al., 2013). The course of addiction and neurological effects in MA is believed to be similar to that of cocaine, however the withdrawal effects might be more intense due to the length of the drug’s duration in the body (Pinel, 2011; Shaobin et al., 2015).

Methamphetamine and cocaine exhibit similar physiological effects in administration, including a rise in respiratory rate, increases in dilation of the pupils, elevated heart rate and irreparable damage to small blood vessels in the brain (Pinel, 2011). In addition, critical body system overload such as uncontrolled spikes in temperature and seizures are indications of an MA overdose and if immediate medical treatment is not administered, death can occur (Pinel, 2011; Rusyniak, 2013).

In neuroscience studies of chronic methamphetamine use in humans and animals, high doses were associated with frequent irritability, aggressive behaviors, excitement, auditory hallucinations, delusions and paranoia (Shaobin, 2015). In prolonged use of MA (as with cocaine), tolerance develops and in repeated exposure may produce desensitization requiring more frequent and increased quantities of the drug (Andersen et al., 2012; Baicy, 2007; Rusyniak, 2013).

**Cocaine and Methamphetamine: Differences**

The probability for female cocaine and MA abusers to relapse after treatment is significant in terms of their drug of choice (Fridberg et al., 2013; Volkow et al, 2011). Although it is not the goal of this study to analyze the independent contributory effects of cocaine or MA in cognitive or executive function impairments, there are some critical distinctions in terms of their neurologic effects for female users (Fridberg et al., 2013; Mahoney et al., 2012). Methamphetamine is viewed as an aggressor in the pre-synaptic discharge of dopamine in the mesolimbic reward system (Pinel, 2011, Shaobin, 2015). Secondly, current neuroscience research demonstrates higher neurotoxic effects in animals and in humans, thereby adding to the risk of addiction and adverse physiological events (Herbeck & Brecht; 2013; Siegel et al., 2010).

Unlike cocaine, MA does cross neuronal cell membranes and enters into the microscopic sacs (called vesicles) where neurons store dopamine (Shaobin, 2015). Methamphetamine is believed to damage the storage sacs and the neuron’s axonal endings such that dopamine leaks uncontrollably into the synapse (Everitt, 2014). Methamphetamine can also cause neurotoxicity indirectly by mobilizing dopamine out of the safe storage vesicles within the neuron and into the neuron’s cytoplasm (the inner core of matter), there it is changed to noxious and volatile chemicals (Everitt, 2014). Once administered MA is speedily absorbed by plasma and tissue enzymes, however, the body processes MA more gradually in male and female users frequently resulting in prolonged ‘desirous’ state although the probability of dangerous neurotoxic effects of the drug are more likely (Bushra et al., 2014).

Although the half–life (effective duration of action) of cocaine is 1-2 hours, a single dose of MA may produce an effect for 8-12 hours (Shaobin, 2015). The abuse of MA can also carry significant health risks to pregnant women and their unborn children. Pediatric studies support evidence that MA abuse during pregnancy is associated with increased stress, lower birthweight and more developmental problems in babies born to MA abusing mothers (Pinel, 2011).

**Prevalence**

National data reports estimate that in 2012, more than 22.2 million people over the age of 12 were categorized as substance abusers or substance dependent in the United States (NIDA, 2013). These data also demonstrate the significance of gender in the examination of substance abuse patterns including, drug of choice, onset, and frequency of use (Bobzean et al., 2014; Du et al., 2013: Greenfield et al., 2012). A report from the National Survey on Drug Use and Health (CBHSQ, 2015) found that rate of illegal drugs, including cocaine and MA among males were higher (11.5 percent) than for females (7.3 percent), however females showed more frequent use and higher relapse behaviors (Bisagno et al., 2014). Addiction research suggests that while men are more likely to abuse cocaine and MA, women are 3 to 4 times more likely to become addicted within 24 months of initial use (Becker, 2012; Kerstetter, 2013; Volkow et al., 2011).

Although nation-wide data suggests that overall abuse of cocaine has decreased slightly for women, annual health studies as recent as 2015 report that the rate of abuse of methamphetamines have significantly increased (CBHSCQ, 2015). These studies also indicate the rise in MA use among pregnant women has risen from 8% to over 24% in the past decade leading investigators to infer that MA is the most commonly abused drug for which pregnant women seek help (Greenfield, 2010; NIDA, 2014). Complicating the full scope of cocaine and MA prevalence is the frequent and simultaneous use of multiple drugs, including alcohol, marijuana and prescription drugs, thereby adding to the difficulty in the identification of and treatment planning for female abusers. One of the compounding factors in neuropsychological research involves multi-addiction or multi-drug use that complicates the ability to separate the distinguishing effects of cocaine and MA addiction (Goldstein & Volkow, 2011; Gould, 2010). Another complication of female cocaine and MA addiction involves a multitude of brain pathways systems that serve to interrupt, modify and severely damage cognition and executive functions (Everitt, 2014; Thakkar et al., 2014).

The increasing use of MA in the general population is evidenced in part by the following; (a) increased emergency room visits have doubled since 2002, admissions to drug abuse treatment programs for multiple forms of amphetamine use have grown almost 200% from 1994 to 2004 with a record number of states (44 out of 45) reporting epidemic increases; (b) criminal activity, imprisonment and high economic and social costs include higher rates of suicides and accidental deaths due to consumption, distribution and production of MA (DOJ, 2015; NIDA, 2013). The rampant use and distribution of MA has resulted in federal legislation in an attempt to curb the growing problem of MA demand in the United States. The Comprehensive Methamphetamine Control Act of 1996 and the Methamphetamine and Club Drug Act of 2000 were enacted to specifically address the need to curb this epidemic (Salo et al. 2010).

Gender studies of stimulant drug addiction make clear that prevalence of abuse is only one measure of gender differences, there are many factors that must be considered, from the first experience of cocaine and MA use to the transition to full addiction. These studies also demonstrate that females are more likely to start using stimulant drugs (cocaine, MA) at an earlier age than men, the rate of drug abuse escalates faster than for men, and women report higher cravings and upon entering treatment they have usually consumed greater quantities of these drugs than men (Becker, 2011; Greenfield et al., 2010; Taylor et al., 2013).

**Drug Addiction: Definition**

Neuropsychological studies employ multiple terminologies in defining drug addiction, include the terms “substance use disorder” and “substance abuse” (Gould, 2011). The generally accepted definition of drug addiction is a “chronic, relapsing brain disease that is characterized by compulsive drug-seeking and use, despite harmful consequences” (NIDA, 2013 p.1). This definition characterizes drug addiction in this manner because of its ability to interrupt, reconfigure and modify critical structures in the brain (Pinel, 2011). Evidence in drug addiction studies posits that changes in the brain can have adverse short and long-term consequences resulting in dangerous and self-destructive behaviors that can lead to irreversible physical damage, harm or death (NIDA, 2013; Pinel, 2011).

**Neuropsychology of Addiction**

Psychological studies of addiction indicate that only a small portion of individuals (less than 20%) who use illicit drugs, including cocaine and MA will actually become addicted (Badiani, et al. 2013; Becker et al. 2012). Evidence suggests that progression from sporadic to chronic substance abuse depends on a number of factors, including the sex of the individual. In their research, Becker et al. (2012) contend that while males have higher risk factors for MA abuse, cocaine addiction is equally as likely for females as for males, and in a number of cases addiction rates are higher for females (Bell et al., 2014; Bobzean et al., 2014).

Psychologists have documented more than 70 risk factors for substance use and dependence including poverty, physical, sexual or emotional abuse or other social dysfunction that can impact an individual’s decision to initiate the use of cocaine or MA (DOJ, 2015; NIDA, 2013). Studies of drug dependence reveal that although men report similar risk factors associated with early use, the decision to continue use is commonly related to gender. Women are more likely to report physical and sexual abuse, earlier use of alcohol, taking drugs with a spouse or partner, or experiencing co-morbidity behaviors (for example, chronic depression) as likely reasons to commence or continue drug use (Becker et al., 2012; Greenfield et al., 2010, NIDA, 2015). These explanations provide some insight in terms of initial drug-taking behaviors, however they do not fully answer the question of why increasing numbers of women continue their illicit drug use despite complications that substance abuse adds to their lives. Furthermore, these rationalizations do not adequately address why women are more likely to express persistent drug related cravings or why they are more likely to return to drug abuse even after treatment (Becket et al., 2012).

Neuropsychological studies propose that all illicit drugs, including cocaine and MA, while targeting different molecular structures, all carry the same action potential of escalating dopamine (DA) neurotransmission in the nucleus accumbens (NAcb) particularly in the mesolimbic system of the brain (Connolly et al., 2012; Koob & Volkow, 2010; Everitt, 2014). The frequency and predictability of these actions have led to widely held views that the DA system is directly responsible in reinforcing drug-seeking behaviors and the motivation to avoid the effects of withdrawal in addicted individuals (Everitt, 2014).

A review of the neuropsychological literatures reveals that risk factors for drug-seeking, potential addiction and relapse vulnerabilities in females are closely related to conditioning cues associated with brain behaviors in drug abuse (Greenfield, 2010; Fattore, 2014). In addition, theories of brain behavior related to cognitive and executive impairments underscores important sex differences. Although neuroscience studies evidence that the path to cocaine and MA addiction, while similar for males and females, reveal specific differences in neural processes for female addicts (Connolly et al., 2011; Dalla et al., 2009; Greenfield et al., 2010). Studies of treatment attrition and relapse also substantiate that females demonstrate greater enhancement of the dopamine systems during initial drug exposure which might impact their ability to maintain abstinence after treatment (Du et al., 2013; Kennedy et al; 2013; Shrestha et al., 2015).

There are many studies concerning the role of neural systems in the development and sustenance of cocaine and MA addiction, and while there are fewer studies specific to women and addiction, these studies overwhelmingly support that sex differences exist in terms of how neural systems patterns of organization and activation undergird pathways to drug addiction (Becker et al., 2012). According to Becker et al. (2012), differences in neural pathways are also useful in understanding how these systems might contribute to higher risk factors of addiction for women. Evidence from neuroscience research demonstrates that the mesolimbic dopamine system, comprised of the ventral tegumental area (VTA) and nucleus accumbens (NAc) is the brain’s most important reward pathway (Bell et al., 2014; Rusyniak, 2013). The VTA and NAc circuit is a primary sensor of rewarding stimuli in humans (Bell et al., 2014)

Under normal operating conditions, the VTA and NAc regulates an individual’s response to natural rewards, such as food, social interactions and sex, and plays a primary role in motivation and incentives (Goddard et al., 2013). In more simple terms, activation of the circuit instructs an individual to repeat the action that brought about the reward (Goddard et al., 2013).

The mesolimbic system also informs the brain’s memory centers to “pay particular attention to all features of the rewarding experience, so that it can be repeated in the future” (Goddard et al., 2013).

The VTA is the site of dopaminergic neurons, which informs the individual whether an environmental stimulus (natural reward, drug of abuse, stress) is rewarding or aversive (direct cite neuroscience NIDA). The NAc, also called ventral striatum, is a principal target of VTA dopamine neurons. This region mediates the rewarding effects of natural rewards and drugs of abuse (Gould, 2010; Volkow et al., 2011). The amygdala is particularly important for conditioned forms of learning (Milton & Everitt, 2012). It helps an individual establish associations between environmental cues and whether or not that particular experience was rewarding or aversive (Pinel, 2011). The hippocampus is critical for declarative memory, the memory of persons, places or things. Along with the amygdala, it establishes memories of drug experiences which are important mediators of relapse (Pinel, 2011; Rusyniak, 2013).

The limbic reward system (also known as the dopamine or brain reward system) is thought to be the most significant component in terms of the neurological reinforcement structure (Rusyniak, 2013). In addition, every known substance of abuse including, cocaine, methamphetamine, nicotine, alcohol, and heroin in some way produces an effect on the limbic system (Goddard et al., 2013). These drugs in turn produce changes in the nucleus accumbens by signaling an increase in the neurotransmitter dopamine, which assists in pleasurable feelings of euphoria and ease (Pinel, 2011). Dopamine is responsible for assistance in the brain’s ability to control movement, executive and cognitive function, and motivation and reward processes (Lucantonio et al., 2012; Pinel, 2011). Increases in dopamine levels are known to encourage short term highs in emotions, moods and motor activity, however abnormally elevated rises in dopamine can produce adverse effects including high anxiety, aggressiveness, anger, and paranoia, hallucinations and inappropriate behaviors (Volkow et al., 2011). The role of dopamine and its salient effects on the limbic reward system, including its role in reinforcement and motivation are considered the common the link to the abuse so much so that dopamine has been labeled as the “master molecule of addiction.” (Hegarty et al., 2013; p.124).

Terminologies associated with drugs such as cocaine and methamphetamines involve a vast array of psycho-physiological effects that most commonly include changes in brain behavior, cardiovascular events, mood swings and sleep disturbance (Rothman et al., 2008). In cases of extensive use and increasingly high dosages can be manifest in more serious events including psychotic actions or fractured thought patterns. In tests of chronic duration, laboratory testing indicates that the propensity for frequent self-administration is a result of highly reinforcing properties of these drugs (Ballard et al., 2015; Rothman et al., 2009).

Researchers have theorized that the same neural pathways responsible for natural reinforcers such as food, drink, and sex activate also provide powerfully rewarding effects drug-seeking behaviors for males and females (Balconi et al., 2015; Gould, 2010; Seigel et al, 2010, Taylor et al., 2013). In the case of abuse or addiction to cocaine and MA (as with other drugs) the desirable effects provoked by these substances can become even more powerful than natural reward, thereby increasing the likelihood of use and accidental overdosing (Pinel, 2011). Chronic use of cocaine and other stimulant drugs increases modifications in the normal neurochemistry including changes in “the y-amniobutryic acid and glutamate systems and brain circuitry via synaptic plasticity processes” (Rothman et al., 2008, p.459). Neuropsychological studies found that withdrawal from stimulant drugs are related to deficiencies in DA and 5-HT functioning systems (Everitt, 2014; Moreno-Lopez et al., 2012; Moeller et al., 2010).

Over a very short period of time, stimulant drugs are most effective in interrupting or bringing about modification of normal communications between reward circuits and neurons in the brain (Moeller et al., 2014; Pinel, 2011). In terms of specific stimulant drugs such as cocaine and MA, when administered, targeted disruptions are provoked in the dopamine neurotransmitter system. These interruptions occur when the post synaptic neurons become hyperactive by immediately elevating dopamine levels in the synaptic area, by allowing excessive presynaptic releases or preventing the normal pattern of reuptake of dopamine (Koob et al., 2010). For the drug user, these extracellular DA levels and reward systems dysfunctions typically leads to pleasurable mood changes (feeling of satisfaction, ease and calmness) and enhanced motor activity.

The psychological effects of cocaine are distinct from that of MA in terms of duration; the effects of cocaine are much shorter than that of MA, and for females this shorter duration becomes problematic when frequency of administration must occur more often to achieve the initial feelings of euphoria (Gould, 2010; Everitt, 2014). Neuropsychological studies of addiction in women report that the probability of becoming addicted actually begins with increasing rates of frequency and elevated tolerance for drug repetition in the mesolimbic reward systems of the brain (Du et al., 2013; Taylor et al., 2013). Generally the repetition of drug use is expected if first use is deemed pleasurable (rewarding), this can lead to dependence, however, more recent studies have revealed that drug addiction is highly complicated and extends well beyond the mesolimbic reward system, and in this regard, repeated drug use causes the neurocircuitry reward and associative learning systems, thereby causing the user to become increasingly sensitive to the both the drug and drug associated cues, which can result in pathological drug-seeking or “wanting.” (Taylor et al., 2013, p.30).

**Cognition and Executive Function**

Complicating the cocaine and MA problem for female addicts is verification that as a psychostimulant drug, MA poses a neurotoxic effect to dopaminergic frontal areas of the brain and invokes neural deficits in mechanisms of cognition and selective attention (Salo et al., 2010). Cognitive deficits demonstrated by MA users have been linked to neurotoxic events involving numerous neurotransmitter structures located throughout the cortex (Pinel, 2011; Salo et al., 2009). Harm involving the frontal areas of the brain proceeding MA abuse to frontal striatal areas of the brain such as the stratum, prefrontal cortex, anterior cingular cortex and amygdala have been observed to contribute to a vast array of cognitive defects in humans (Baicy, 2007). Methamphetamine dependent individuals have also demonstrated cognitive deficits in relationship to increased performance problems specifically on tasks that entail the withholding of extraneous information, decision making and working memory (Rusyniak, 2011; Salo et al., 2010).

Everitt (2014) notes that while many of the commonly known drugs including

cannabis, alcohol and heroin have a range of different molecular goals they do have similar propensities in increasing dopamine (DA) transport in the nucleus accumbens (NAcb) region of the brain. Neuropsychological studies have indicated that in addition to damage to the mesolimbic system which are vital to dopamine and serotonin neurotransmission, deficits in cognition and executive function are also evident in male and female addicts (Everitt, 2014).

**Neuropsychological Tests of Cognitive and Executive Function**

Neuropsychological studies have determined that chronic cocaine and methamphetamine abuse poses significant threats to cognitive and executive functions in neural processes of humans and animals (Kiluk et al., 2011; Siegel et al., 2010). These specific areas of the brain are largely responsible for learning, memory, decision-making, complex task execution and other critical information processes (Herbeck & Brecht, 2013). Cocaine and MA substance dependent individuals have demonstrated deficits in the domain of executive functioning. Executive function “involves the ability to plan, judge, and weigh several options, to make complex decisions, to have an accurate perception of one’s own abilities, and to implement, organize, and control other cognitive functions such as memory” (van der Plas et al., 2009; p.706).

One of the major concerns in terms of interrupted cognitive and executive function is related to the increased likelihood that these impairments will reinforce a cycle of sustained use in the abuser even in after treatment intervention (Ballard et al., 2015). Among the most studied characteristics associated with cognitive and executive function is the disruption of “normal” learning and memory schemas and the development of new learning and memories precipitated by chronic drug use in males and females (Ballard, 2015). Neuroscience studies add that stimulant drugs such as cocaine and MA not only exhibit temporary disruptions, they can modify short and long term memory by establishing strong associations between drug cues and drug reward mechanisms (Herbreck & Brecht, 2014). Once these cues and drug reward mechanisms activate, these associations are not easily broken, thus rendering the user less control over drug-seeking and use (Winhusen et al., 2013).

Studies comparing the performance of cocaine and MA addicted males and females on neuropsychological tests of executive function found that females were significantly more likely to be demonstrate impairments (Van der Plas et al., 2009). These researchers compared the performance of alcohol-dependent individuals (n=33), cocaine dependent individuals (n=27), and MA dependent individuals (n=38) with healthy controls (matched by sex) (n=36) on various measures of complicated decision making tests using the Iowa Gambling Task, functional memory, (Tic Tac Toe), cognitive elasticity, (the Wisconsin Card Sorting Task), response inhibition (the Stop Signal-RT). Results revealed that cocaine and MA males and females were impaired in every category of memory and decision-making, except for response inhibition. In addition, cocaine and MA dependent women demonstrated significantly more impairment than men who were addicted to these same drugs. Taken together, these findings suggest that sex and drug of choice exhibit different effects on executive functions (Van der Plas et al., 2009).

The Iowa Gambling Task (IGT) is an experimental decision making task that requires the integration of different aspects of executive functioning in order for successful completion. The IGT is used frequently in cognition and executive function research as a means of measuring how well a participant can utilize complex decision making skills that require clarity, quick thinking and the ability to delay gratification when presented with various rewards (Verdejo-Garcia et al., 2007). One of the most prominent aspects of the IGT is the requirement that participants give up immediate rewards (“play” money) for delayed profit. In similar studies of addiction and executive impairment, females were more likely than males to make decisions to select temporary rewards over the long term rewards even at the risk of losing all profits (Van der Plas et al., 2009, Morie et al., 2014).

The consistency in which women cocaine and MA addicts were found to have poorer performance on various tests of executive function has been brought about new questions regarding reward and punishment mechanisms and if those reward systems in the brain operate differently for women addicts compared to male addicts. Adinoff (2006) contends that neuroimaging tests reveal that there are indeed differences in how reward and punishment mechanisms differ by sex. An important region involved in processing many types of reward and punishment in response to environmental changes is the orbitofrontal cortex (OFC), in particular the ventral and medial prefrontal cortex (VMPFC) (Moreno et al., 2012; Shrestha et al., 2015).

Van der Plas et al. (2009) addressed sex differences in substance use disorders. These researchers found that cocaine and MA addicted women exhibited serious impairments in decision making abilities compared to cocaine and MA addicted men. In light of their study, the research indicated that the PFC functioning differs by sex. Other neuropsychological studies concur that differences in brain activation patterns by sex could be related to reward versus punishment, thus reinforcing problems associated with a woman’s decision making ability to discontinue drug use (Dalla & Shor, 2009; Bushra et al., 2013; Volkow et al., 2011).

Van der Plas et al. (2009) further suggests that biological vulnerabilities in OFC systems could further explain the “telescoping” syndrome, a concept in which females are believed to progress more quickly to drug dependence even after a fairly late onset (p. 716).As evidenced in their study, Adinoff et al. (2006) demonstrated that addicted individuals were significantly more likely to show reduced activity in the OFC when performing on the Iowa Gambling Task when compared to non-addicted subjects. In addition, women demonstrated greater memory deficits than addicted men in terms of decision making and working memory. Studies suggest that working memory is impaired in testing in both males and females, however women experienced significantly greater dysfunction The functional integrity of the OFC, however, relies on neural systems that serve memory, in particular working memory (Adinoff et al., 2006).

Working memory is defined as the process of storing and online manipulation of information and includes short term storage, rehearsal, and the executive processes that operate on the contents of memory (Adinoff et al, 2006; Bickel et al., 2011). The dorsolateral prefrontal cortex (DLPFC) is thought to sub-serve working memory and appears particularly important for the executive processor of mnemonic operations.

Studies with substance abusing females suggest that deficits in the working memory domain are not purely due to a mnemonic impairment. Rather, impairments may be due to an executive control problem (Ide et al., 2014). Specifically, van der Plas et al. (2009) found that individuals addicted to alcohol, cocaine, or methamphetamine performed below normal levels on the working-memory task, but increasing the memory load did not influence performance. The task used in this study. Although stress and drug cue exposure each increase drug cravings and contribute to relapse in cocaine dependence, no previous research has directly examined the neural correlates of stress inducted and drug induced cravings in cocaine dependent women and men relative to comparison subjects (Streeter et al., 2008).

Fridberg et al., (2013) administered a neuropsychological test of decision making (the Iowa Gambling Task; IGT) for males and females (n=74, 24 females) with substance dependence and a history of childhood conduct disorder (HCCD) compared to healthy controls (n=152, 84 female) to assess working memory load. A primary role in working memory in executive function mediates the ability to sustain or suppress information and to resist distraction. Lower working load memory is associated with increases in impulsive decision making in healthy adults. Substance dependent males with HCCD completed fewer advantageous decisions than IGT control men. Working memory capacity was reduced more significantly for substance dependent women with HCCD than for substance dependent men with HCCD men (Fridberg et al., 2013).

Worhunsky et al., (2013) administered a Stroop task as part of an exploratory study to examine systems of functional connectivity supporting cognitive control in cocaine addiction. Independent Component Analysis (ICA) was utilized in fMRI data to assess whether regional activations supporting cognitive control activities operate in functional systems in terms of performance and treatment outcome in cocaine dependent participants. The study compared the performance of participants (n=20) on a Stroop task during fMRI before entering treatment and were compared to a control group (n=20). Cocaine addicted males and females demonstrated differences in three out of five networks: reduced involvement of a fronto-cingular network contributing to conflict management in treatment retention, increased engagement of two bottom up subcortical and ventral prefrontal networks linked to cue-elicited motivation correlated with abstinence during treatment (Worhunsky et al., 2013).

**Summary and Discussion**

The reviews of literatures that have evaluated cognitive and executive function in cocaine and methamphetamine use supports the existence of gender differences in onset, maintenance and treatment outcomes (Anker et al., 2011; Bobzean et al., 2014; Fattore et al., 2013). National health data provided statistical information regarding current use and addiction rates among women in the United States, with an emphasis on the detrimental personal and societal costs (NIDA, 2013).

Classical and operant theories of drug abuse support that women are more likely respond to the desirable effects of cocaine and MA in the reward systems of the brain and to avoid withdrawal thereby increasing their likelihood to continue their cycle of abuse (Goddard et al., 2013). Neuropsychological studies of cognition and executive function demonstrate in tests of decision making, cognition, error-processes, and complicated skills tasks that women are significantly impaired in key regions of the OFC in the brain (the region that controls complex decisions and error processing) (Everitt, 2014). These problems signal that women neural processes in terms of learning and memory affect differences have demonstrated that that the association between new learning and reward reinforcement complicate treatment and add to the vulnerability of drug relapse (van der Plas, 2013).

The literatures contained in this chapter overwhelming contend that the experiences of addicted females are not plentiful and create more challenges in that, 1) women are not included as often in neuropsychological studies, 2) issues unique to women are not widely addressed and, 3) treatment planning often locates the addiction of women in relation to those of male addicts, thus ignoring specialized and relevant treatment to improve outcomes.

The studies presented in this chapter attempt to address some of these issues of onset, maintenance, withdrawal and relapse and the research offers valuable information regarding sex differences across a spectrum of neuropsychological issues including learning and conditioning, propensity to develop cocaine and MA addictions, the problems manifest in cognitive and executive functioning that may negatively impact treatment and encourage relapse. While prior research on gender differences consistently failed to include or marginalized the participation of female cocaine and MA addicts, current research does not go far enough to investigate unique situations that are specific to women in terms of their diversity of experiences, the efforts that are required to curb the rise in abuse and more extensive research in the area of PET and FDG assessments and evaluations (van der Plas, 2011; NIDA, 2014).

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