UCLA
UCLA Electronic Theses and Dissertations

Title

Examination of the Effects of Methamphetamine Use Severity on Executive Functioning and Impulsivity

Permalink

https://escholarship.org/uc/item/5bm9n0q1

Author

Correa, Nathasha Roya Moallem

Publication Date

2016

Peer reviewed|Thesis/dissertation

eScholarship.org Powered by the California Digital Library
University of California

UNIVERSITY OF CALIFORNIA

Los Angeles

Examination of the Effects of Methamphetamine Use Severity on Executive Functioning and Impulsivity

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Psychology

by

Nathasha Roya Moallem Correa

2016

ABSTRACT OF THE DISSERTATION

Examination of the Effects of Methamphetamine Use Severity on Executive Functioning and Impulsivity

By

Nathasha Roya Moallem Correa

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2016

Professor Lara Allison Ray, Chair

Background: Abuse of psychostimulants, including methamphetamine (MA), has been linked to cognitive deficits. However, there is ongoing debate that evidence for the relationship between MA and cognitive deficits is limited. While previous research has demonstrated neurocognitive differences between MA users and non-substance users, less is known about variability in cognitive functioning within MA users and whether the severity of MA-related problems predicts cognitive functioning within individuals who regularly use MA.

Objective: This study aims to elucidate neurocognitive deficits, specifically impulsivity and executive functioning, as a function of MA use severity. This study used a multivariate approach that simultaneously accounts for clinical variables (e.g., frequency of use, craving, and diagnostic symptoms) as well as outcome variables related to impulsivity and executive function.

Method: Non-treatment seeking individuals who reported regular MA use (n = 177) completed an impulsivity battery comprised of self-report (Barratt Impulsivity Scale-II (BIS)) and behavioral measures (Stop Signal Task (SST), Delay Discounting Task (DDT)) and a sub-sample

(n = 63) completed an in-depth neuropsychological battery. A structural equation modeling (SEM) approach was used to (1) test the relationship between the MA-use problem severity and measures of impulsivity; and (2) examine the association between MA-use problem severity and tests of executive functioning.

Results: The final SEM model of impulsivity and MA use problems revealed that greater MA use severity was associated with greater self-reported impulsiveness (ß = 0.51 and ß= 0.42), but no relationship was found between MA use severity and the behavioral measures of impulsivity (SST and DDT). Analyses of neuropsychological functioning suggested that MA use severity was not significantly associated with either executive functioning factor; however follow-up analyses revealed that gender and frequency of MA use may moderate the relationship between MA use severity and measures of executive functioning.

Conclusions: The current findings extend previous research by providing additional evidence that MA use is associated with greater self-reported impulsivity and highlights the importance of evaluating impulsivity as a multidimensional construct. The lack of relationship between MA use severity and executive functioning suggest that individual differences in MA use may not be directly related to neuropsychological functioning, although previous literature has shown performance on neuropsychological tests can differentiate between MA users and non-substance users. Future studies should expand on the current findings by comparing neurocognition across substances and by utilizing the MA Use Severity factor in longitudinal and biologically informative approaches, such as genetic and neuroimaging studies.

The dissertation of Nathasha Roya Moallem Correa is approved.

Adriana Galvan

Rena L. Repetti

Steve J. Shoptaw

Lara Allison Ray, Committee Chair

University of California, Los Angeles

2016

Table of Contents

Curriculum Vitae ..... **ix**

Introduction **1**

Methamphetamine use is highly prevalent in the U.S. and worldwide **1**

Methamphetamine has widespread effects **2**

Methamphetamine use disorders are brain disorders **5**

Methamphetamine neuromodulates the dopaminergic system **8**

Drug use and neurocognitive deficits: Cause, consequence, or both **11**

Methamphetamine use affects neurocognitive functioning **13**

Many criticisms of the current literature remain **21**

Methamphetamine and impulsivity **23**

The Dissertation **27**

Specific aims and hypotheses **27**

Methods **28**

Participants **28**

Procedures **29**

Measures **29**

Data Analysis Plan **32**

Results **35**

Descriptive statistics **35**

Aim 1 SEM model results **36**

Aim 2 SEM model results **41**

Discussion **46**

Strengths and Limitations **59**

Conclusion **62**

References **96**

List of Tables and Figures

Table 1 ..... **67**

Table 2 ..... **68**

Table 3 ..... **69**

Table 4 ..... **71**

Table 5 ..... **72**

Table 6 ..... **73**

Table 7 ..... **75**

Table 8 ..... **76**

Table 9 ..... **77**

Table 10 ..... **78**

Table 11 ..... **79**

Table 12 ..... **80**

Table 13 ..... **81**

Figure Captions **82**

Figure 1. ..... **84**

Figure 2. ..... **85**

Figure 3. ..... **86**

Figure 4. ..... **87**

Figure 5. ..... **88**

Figure 6. ..... **89**

Figure 7. ..... **90**

Figure 8. ..... **91**

Figure 9.....92

Figure 10.....93

Figure 11.....94

Curriculum Vitae

Nathasha Roya Moallem Correa

Education

2010 - 2011	Master of Arts, Clinical Psychology University of California, Los Angeles Thesis Title: *Dimensions of impulsivity among heavy drinkers, smokers, and heavy drinking smokers: singular and combined effects.* Advisor: Lara Ray, Ph.D.
2004 - 2008	Bachelor of Arts, Psychology (Magna Cum Laude) University of San Diego

Honors and Awards

2011-2014	Student Merit Award, Research Society in Alcoholism Conference
2012	National Science Foundation, Honorable Mention
2010-2011	Distinguished University Fellowship

Peer-Reviewed Publications

Ray, L.A., Bujarski, S., Courtney, K.E., **Moallem, N.R.**, Lunny, K., Roche, D., Leventhal, A., Shoptaw, S., Heinzerling, K., London, E.D., & Miotto, K. (2015). *The effects of naltrexone on subjective response to methamphetamine in a clinical sample: A double-blind, placebo-controlled laboratory study.* Neuropsychopharmacology 40(10):2347-56. PMID: 25801501

Roche, D.J.O., Bujarski, S., **Moallem, N.R**., Guzman, I., Shapiro, J.R., & Ray, L.A. (2014). *Predictors of smoking lapse in a human laboratory model.* Psychopharmacology. 231(14):2889-97. PMID: 24500677.

Bujarski, S., Roche, D., Lunny, K., **Moallem, N.R.,** Courtney, K.E., Allen, V., Hartwell, E., Leventhal, A., & Ray, L.R. (2014). *The relationship between methamphetamine and alcohol use in a community sample of methamphetamine users.* Drug Alcohol Depend. 142:127-32. PMID: 24975477.

Moallem, N.R., Courtney, K.E., Bacio, G.A., & Ray, L.R. (2013). *Modeling alcoholism severity: An integrative structural equation modeling approach*. Frontiers Psych. 4:75. PMID: 23908635.

Ray L., Lunny K., Bujarksi S., **Moallem N.,** Krull, J., & Miotto K. (2013). *The effects of varenicline on stress-induced and cue-induced craving for cigarettes*. Drug and Alcohol Dependence. 131:136-142 PMID: 23298651.

Courtney, K.E., Ashenhurst, J., Bacio, G., **Moallem, N.,** Bujarski, S., Hartwell, E. & Ray, L.A. (2013). *Craving and subjective responses to alcohol administration: Validation of the desires for alcohol questionnaire in the human lab.* Journal on Studies of Alcohol and Drugs. 74(5):797-802. PMID: 23948540.

Moallem N.R. & Ray L.A. (2012). *Dimensions of impulsivity among heavy drinkers, smokers, and heavy drinking smokers: singular and combined effects.* Addictive Behaviors, 37(7):871-4.

Moallem N.R. & Ray L.A. (2012). *Quetiapine improves response inhibition in alcohol dependent patients: a pilot study.* Pharmacology, Biochemistry, and Behavior. 100(3):490-3.

Brown A., Mandelkern M.A., Farahi J., Robertson C., Ghahremani D.G., Sumerel B.**, Moallem N.R.**, & London E.D. (2012). *Sex Differences in Striatal DopamineD2/D3 Receptor Availability in Smokers and Nonsmokers.* Int JNeuropsychopharmacol. 16:1-6.

Manuscripts under Review

Hartwell, E.E.; **Moallem, N.R**.; Courtney, K.E.; Glasner-Edwards, S.; & Ray, L.A. *Gender differences in the association of internalizing symptoms and craving in methamphetamine users.* Journal of Addiction Medicine. (Under review).

Grant Funding

Completed Research Support

T32 DA024635 London (PI) 07/2011-09/2013
NIDA
Research Training in Translational Neuroscience in Drug Abuse
Mentor: Lara Ray, PhD

Graduate Summer Research Mentorship 06/2012-08/2012, 06/2011-08/2011
UCLA Graduate Division; Mentor: Lara Ray, PhD

Graduate Summer Research Mentorship
Distinguished University Fellowship 08/2010-06/2011
UCLA Graduate Division; Mentor: Lara Ray, PhD

Professional Presentations (selected from 9)

Moallem, N.R.* & Ray, L.A. (2014). *Nicotine dependence severity mediates the relationship between alcoholism severity and working memory.* Presented at the 37th Annual Scientific Meeting of the Research Society on Alcoholism, Bellevue, WA.

Moallem N.R.*, Courtney, K.E., Bacio, G., & Ray L.A. (2013). *Modeling alcoholism severity: An integrative structural equation modeling approach.* Presented at the 36th Annual Scientific Meeting of the Research Society on Alcoholism, Orlando, FL.

Moallem, N.R.* & Ray L.A. (2012). *Dimensions of impulsivity among heavy drinkers, smokers, and heavy drinking smokers: singular and combined effects.* Presented at the 35th Annual Scientific Meeting of the Research Society on Alcoholism, San Francisco, CA.

Moallem, N.R.* & Ray. L.A. (2011). *Effects of quetiapine on alcohol craving, subjective intoxication, and neurocognition in alcohol dependence: a double-blind, placebo controlled study.* Presented at the 34th Annual Scientific Meeting of the Research Society on Alcoholism, Atlanta, GA.

*Indicates presenter

Select Research Experience

2010 - 2016 **Graduate Research Associate**, Department of Psychology, University of California, Los Angeles
UCLA Addictions Lab
Investigator: Lara Ray, Ph.D.

2008 - 2010 **Research Associate**, Department of Psychiatry & Biobehavioral Sciences, University of California, Los Angeles
Laboratory of Molecular Neuroimaging (Funding: NIDA)
Investigators: Edythe London, Ph.D., Amira Brown, Ph.D.

Select Clinical Experience

2015- Present **Intern**, VA Greater Los Angeles Healthcare System, West Los Angeles

Introduction

Methamphetamine use is highly prevalent in the U.S. and worldwide

Methamphetamine (MA) is a popular stimulant used in the United States and across the globe. In 2007, MA was considered one of the fastest growing illicit drugs in the world and was recognized as a major public health concern, globally and in the United States (Rawson & Condon, 2007). The 2013 National Survey on Drug Use and Health (NSDUH) report found that rates of MA use in the past month were similar to 2012 and 2011, as 0.2 percent of the United States population (approximately 595,000 people) reported using MA (Substance Abuse and Mental Health Services Administration, 2014). These estimates rose from 2010 where 0.1 percent of the population reported using MA in the past month. In 2012, approximately 1.2 million people (0.4 percent) reported using it in the past year (Substance Abuse and Mental Health Services Administration, 2013).

There are regional differences of MA use in the United States. More specifically, MA use and MA related problems are more prevalent in the West and parts of the Midwest United States (National Institute on Drug Abuse, Revised 2013). Despite the trend of higher usage in specific regions of the nation, MA use has been shown to have a significant economic cost nationally. In 2005, MA was estimated to cost the United States approximately $23 billion (Nicosia, Pacula, Kilmer, Lundberg, & Chiesa, 2009). Not only is MA associated with major fiscal cost, it was also estimated to cause approximately 900 deaths in 2005 and a loss of 44,000 total adjusted quality-of-life years (Nicosia et al., 2009).

MA use has also been associated with a host of negative public health outcomes such as decreased quality of life, serious health issues, psychiatric comorbidity, risky sexual behavior, and losses in everyday functional ability (Henry, Minassian, & Perry, 2010; Shoptaw, Peck,

Reback, & Rotheram-Fuller, 2003; Walter et al., 2012). Henry and colleagues (2010) found that individuals diagnosed with MA dependence performed worse than control participants on tasks associated with functions of daily living (e.g., comprehension and planning, financial acumen, communication ability, medical management, and navigation of travel). This suggests that MA use may have a significant negative impact on overall functional ability and quality of life. In a large sample of MA users (N = 350), Brecht et al. (2004) found that MA use was associated with increased crime (93% had been arrested at least once and approximately half, 51%, had multiple arrests). Participants also reported high rates of negative MA consequences such as health (e.g. dental problems, weight loss), legal, economical, work, and psychological problems (e.g., hallucinations, paranoia, sleep disruption, increased violence). In brief, MA remains a significant public health concern nationally and, across the globe, as it has been associated with a host of negative outcomes such as, fiscal costs, decreased health and functioning, and even death.

Methamphetamine has widespread effects

MA is a stimulant drug whose mechanism of action lies in increasing activation of the central nervous system through the release of multiple neurotransmitters, including dopamine (DA), noradrenaline, adrenaline, and serotonin (Seiden, Sabol, & Ricaurte, 1993; World Health Organization, 2004). The mechanism of action that has been most implicated in the rewarding effects of MA is in the release of DA in the striatum (Volkow et al., 2001a; Volkow, Fowler, Wang, Baler, and Telang, 2009). This increase in extracellular DA is associated with the rush or "high" experienced following acute MA use (Volkow et al., 2009). Acutely, MA use leads to a range of physiological and subjective effects such as increased heart rate, increased energy, decreased appetite, feelings of euphoria, decreased fatigue, elevated blood pressure and other

physiological arousal symptoms. With increased dosage, users may also experience effects such as paranoia, hallucination, confusion, and panic attacks (Ciccarone, 2011).

The molecule that creates the powerful stimulating effects of MA is *d*-methamphetamine (Ciccarone, 2011; Cruickshank & Dyer, 2009). *D*-methamphetamine has between 3-5 times more stimulating effect of the central nervous system activity than the other molecule that methamphetamine exists in, *l*-methamphetamine (Ciccarone, 2011). Although time to reach peak plasma MA concentration varies based on route of administration (intravenous: 6 ± 11 minutes; inhalation: 150 ± 30 minutes; oral: 180- 30 minutes; intra-nasal: 169 ± 8 minutes), the half-life of MA is approximately 10 hours and remains similar across types of administration (Cruickshank & Dyer, 2009). Peak subjective effects and cardiovascular changes occur within approximately 5-15 minutes of using the drug, while subjective effects typically last approximately four hours (Cruickshank & Dyer, 2009). In comparison, MA maintains in the system longer and diminishes slower than another well-known stimulant, cocaine, which declines rapidly following use and has a half-life of approximately one hour (Freye, 2010). The extended duration of the subjective and physiological effects of MA increases its appeal as an alternative to shorter half-life stimulants such as cocaine, thus adding to the abuse liability of MA.

MA comes in various forms, such as pill, powder, and crystalline, and can be administered in a number of ways. The most popular routes of administration include oral ingestion (e.g., swallowing, drinking, eating MA), snorting/sniffing, injecting, and smoking the substance; however other more uncommon routes of administration include inserting the substance rectally or vaginally (Degenhardt et al., 2007). MA administration through smoking and injecting allow for the quickest "high" due to the immediate absorption into the bloodstream and up to the brain, possibly contributing to greater addictive potential (National Institute on

Drug Abuse, Revised 2013). Regardless of preferred route of use, MA is considered to have high potential for abuse and has been found to have some medical benefit according to the U.S. Drug Enforcement Administration. As such, it is listed as a Schedule II controlled substance.

In discussing the potential for drug abuse, it is useful to review the criteria used to diagnosis a substance use disorder. Substance use disorder is a complex behavioral disorder characterized by compulsive drug use, the development of tolerance and withdrawal, and overall functional impairment (American Psychiatric Association, 1994). In the *Diagnostic and Statistical Manual of Mental Disorders IV-TR* (DSM-IV-TR) substance use disorder was split into two categories: abuse and dependence. To meet criteria for a substance abuse diagnosis, one or more of the following criteria had to be met: (a) recurrent failure to fulfill major role obligations; (b) recurrent use of the substance in situations in which it might be hazardous; (c) recurrent substance-related legal problems; and (d) continued substance use despite having persistent or recurrent social or interpersonal problems. A substance dependence diagnosis was met if three or more of the following criteria were fulfilled: (a) tolerance; (b) withdrawal; (c) using larger amounts or over a longer period of time than intended; (d) a persistent desire or unsuccessful efforts to cut down or control use; (e) spending a great deal of time obtaining, (f) using or recovering from the effects of the substance; (g) reducing or giving up important activities due to substance use; and (h) persistent physical or psychological problem that are likely due to or exacerbated by the substance.

With the revised edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) there has been a shift from the traditional categorization of addiction as substance abuse and/or dependence to a more dimensional model that combines the diagnostic criteria from both “abuse” and “dependence” into a singular disorder. The criteria for diagnosis remains

relatively the same in the DSM-5 with a few changes such as the removal of "recurrent legal problems" criteria, the addition of "craving or a strong desire to use the substance," and the threshold for diagnosis has been revised to include positive identification with two or more criteria. The shift from a categorical to a more dimensional approach exemplifies the evolving conceptualization of addiction in the field. This dimensionality better captures the clinical progression of substance use disorder as has been described in neurobiological theories and is consistent with the approach of the current project which used a severity model to capture the variability of MA use addiction on an individual basis.

Methamphetamine use disorders are brain disorders

From a clinical neuroscience framework, addiction is considered to be a brain disorder. In order to provide support for this conceptualization as a brain disorder, prominent neurobiological theories of addiction are reviewed here. In particular, these theories emphasize the progression from initiation of substance use to addiction and the neurological changes observed during this progression. The changes particularly of interest are the neurocognitive deficits associated with the neuromodulation following substance use. The neurobiological mechanisms underlying addiction serve to inform the questions examined in the current study, specifically the association between MA use disorder and cognitive functioning.

In observing the development of a drug addiction, Everitt and Robbins (2005) and Goldstein and Volkow (2002) hypothesize that addiction is the result of the shift from goal-directed actions to habits and ultimately, to compulsive drug-seeking and taking. This transition from deliberate drug use to habitual responding has been hypothesized to reflect a neural shift from prefrontal cortical activation to striatal regions and from ventral to dorsal subregions (Everitt & Robbins, 2005). The neuroadaptation associated with the various stages toward

addiction may also affect executive control over behavior, further serving to increase habit-forming behavior (Everitt & Robbins, 2005). Neuroimaging studies provide evidence for the involvement of the frontal cortex in the cyclical stages of addiction, including the increased salience of drug cues, possibly at the expense of other rewarding stimuli (Goldstein & Volkow, 2002; Kalivas & Volkow, 2005).

However, the theories that explain addiction as simply the result of a shift from goal-directed behavior to habit do not fully capture the "compulsive" nature of addiction. Previous literature has suggested that increased incentive sensitization of the drug may help explain this aspect of addiction. Incentive sensitization refers to the increased biases of attentional processing towards drug-associated stimuli which result in compulsive motivation and desire for the drug (Robinson & Berridge, 1993). In this way, substance use leads to neuroadaptation in which the brain circuitry becomes hypersensitive to drugs and drug-associated cues, thus increasing craving and the use of the drug (see reviews by Robinson & Berridge, 2001, 2008). Incentive sensitization has been examined through studying psychomotor stimulation in preclinical studies. Interestingly, animals remain hypersensitive to psychomotor or rewarding effects of the drugs for months or even years following exposure (Paulson, Camp, & Robinson, 1991; Robinson & Becker, 1986; Valadez & Schenk, 1994). These findings suggest that neural sensitization may play a critical role in relapse and re-initiation to drugs of abuse, due in part to cravings as a product of the sensitization to drug-cues.

Another prominent neurobiological theory explains the compulsive nature that is a hallmark of substance use disorders. According to Koob (2003), drugs of abuse lead to changes in the brain reward circuitry that contributes to the development of addiction or to the compulsive desire for the drug. Addiction has also been conceptualized as a progression of

allostatic changes in which the addicted individual is able to maintain stability but at a pathological set point (Koob, 2003). In this model, addiction is conceptualized in three cyclical stages: preoccupation, binge, and withdrawal. This cycle highlights the delicate balance of positive and negative reinforcement associated with drugs of abuse. Satisfying the state of preoccupation of the drug with a binge is positively reinforcing due to the experience of a "high" while the drug is onboard. Following a binge or intoxication, individuals experience withdrawal symptoms that are only alleviated through subsequent drug use or with extended abstinence. In this way, the reduction of withdrawal symptoms negatively reinforces the drug taking behavior. This cycle is thought to intensify over time with the primary motivation for drug use switching from the initial positive effects of the drugs to the elimination of withdrawal symptoms. In other words, with the progression of addiction, a shift is observed from positive reinforcement to negative reinforcement. Thus, it is the increasing motivation to alleviate withdrawal symptoms that leads to the "compulsiveness" associated with addiction.

Incentive salience theory highlights the role of learning in the development and maintenance of addiction. This theory suggests that the ability of a drug to sensitize neural pathways is modulated by learning and conditions associated with the drug administration (Robinson, Browman, Crombag, & Badiani, 1998). Hyman (2005) argues that in fact, drugs of abuse lead to a pathological change to the mechanisms underlying learning and memory. Others have discussed the improbability of addiction being simply a function of learning, as there is a motivational component to the disorder, at least initially (Robinson & Berridge, 2008). Although the magnitude of the role learning may play in the development of an addiction is debated, it remains recognized that some amount of learning and conditioning is involved in the progression from drug initiation to disorder.

Although the neurobiological theories reviewed briefly above have their differences, taken together, it may be the case that each represents a part of the process of addiction. Neuroscience has provided a variety of theories and evidence for the development, maintenance, and severity of addiction from a biological standpoint with the ultimate goal being to translate preclinical research to clinical. To that end, the dissertation aimed to examine clinical phenomenology utilizing the neurobiological theories as a foundation of the research. Through our understanding of neurobiological models of addiction, particularly those which highlight the switch from goal-directed actions to compulsive drug-seeking and –taking (Everitt & Robbins, 2005) and the neuromodulation that occurs in the progression from drug initiation to addiction, we aimed to capture how cognitive functioning may vary as a function of MA use disorder severity within a well-characterized sample of MA use disorder individuals.

Methamphetamine neuromodulates the dopaminergic system

Previous research has shown that drugs of abuse act on the same neural circuits as do other things that we find naturally rewarding (e.g. sex, food, etc.; Ray, 2012). It has been well established that dopamine (DA) plays a role in reward and learning. DA pathways in the central nervous system project from the ventral tegmental area (VTA) to the prefrontal cortex (PFC) and the limbic system, including the nucleus accumbens (NAc) and has been established as the reward pathway of the brain (Koob, 1992). It is believed that the increase of DA from the VTA to the NAc is what leads to the addictive and rewarding properties of drugs of abuse (Volkow, Wang, Fowler, & Tomasi, 2012). Drugs of abuse tend to trigger a much larger release of DA in this pathway than do natural rewards, thus leading to potential development of disease (for a review of clinical neuroscience of addiction see Ray, 2012).

Interestingly, preclinical studies have found an increase of DA in the NAc not only following the intake of drug but in anticipation of the drug (Schultz, 2010; Schultz, Dayan, & Montague, 1997). In support of the neurobiological theory of incentive salience, drugs become paired with conditioned stimuli or cues, which consequently become overly sensitized to the individual. Both preclinical and clinical studies have found these cues can induce craving and even drug use (Monti et al., 2004; Weiss et al., 2001) as well as have been found to evoke a DA "spike" that occurs during the conditioned stimuli rather than the actual intake of the drug (Schultz et al., 1997). These findings highlight the power of the drug and overly salient nature of drug-related people, places, and things. This is clinically relevant as this sensitization to drug cues identifies a potential vulnerability to relapse given the neuromodulation of the DA system following chronic drug use.

Similar to other drugs of abuse, upon acute use of MA, individuals experience a rush or "high" which is associated with an increase of DA in the brain (Mark, Soghomonian, & Yamamoto, 2004; Volkow, Fowler, Wang, Baler, & Telang, 2009). Over time, chronic use of MA leads to the modulation of the DA system. Previous studies have found a significant loss of dopamine transporters following MA administration as well as decreased D2 receptor availability (McCann et al., 1998; Seiden & Sabol, 1996; Volkow, Chang, Wang, Fowler, Ding, et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001). Importantly, preclinical research has found reductions in DA transporter availability following both a binge dose regimen of MA (Izquierdo et al., 2010) and a chronic, escalating regimen of MA (Groman et al., 2012). Additionally, Groman and colleagues (2012) found decreased D2-receptor availability in the striatum following chronic exposure to MA in non-human primates.

Previous research has found mixed results regarding whether MA abuse leads to permanent DA transporter loss. Some have found that deficits of the dopamine transporters continue to be observed into long-term abstinence (at least 11 months; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001) and previous studies suggested that dopamine transporter loss as a consequence of MA use was irreversible (Harvey, Lacan, & Melegan, 2000; McCann et al., 2008). However, a positron emission tomography (PET) study which measured changes in striatal dopamine transporters during protracted abstinence (12-17 months) found a significant recovery of dopamine transporter function among five MA abusers who were tested twice during short-term abstinence (< 6 months) and protracted abstinence (Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001). Despite the mixed findings regarding the reversibility of the deficits of DA transporters, it remains well supported that chronic MA use leads to a loss of DA transporters in the brain. Additionally, this modulation of the dopaminergic system has been associated with cognitive deficits among MA users, which was the focus of the current study.

There is evidence to suggest that the neurocognitive deficits observed in MA users may be linked to the neuromodulation of the dopaminergic system that occurs following repeated MA use. Volkow and colleagues (2001) found that MA abusing participants exhibited a significant reduction of DA transporters in the striatum, which was also associated with poor motor and memory performance. In a study examining protracted abstinence, performance on tests of motor and memory function did not improve with time or with recovery of DA transporters (Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001). This suggests that although there may be a recovery in the brain, the individual may still experience cognitive deficits. These findings highlight the importance of examining the relationship between chronic MA use and neurocognition.

Drug use and neurocognitive deficits: Cause, consequence, or both

Previous research has examined the increased risk of initiation of substances during adolescence. Multiple factors have been identified as being associated with increased risk of substance use during this period of development including individual differences (e.g., impulsivity, negative affect, aggression, decreased harm avoidance, low motivation for achievement, etc.), biological (e.g., family history, genetic predisposition, etc.), and environmental factors (e.g., high levels of stress, peer influences, availability of substances, trauma experiences, parental control and support, etc.) (e.g., Bates & Labouvie, 1997; Fergusson, Boden, & Horwood, 2008; Kilpatrick et al., 2000; Nation & Heflinger, 2006). While the factors listed above have been linked to increased risk for substance experimentation and continued use, the role pre-morbid deficits in cognition and impulsivity play are of most relevance to the dissertation study. One longitudinal study examining high-risk (father with a diagnosed substance use disorder) and low-average-risk (father did not meet criteria for substance use disorder or any Axis I disorder) boys across a two year period found poorer executive functioning performance among the high-risk group as well as increased liability to developing a substance use disorder (Aytaclar, Tarter, Kirisci, & Lu, 1999). Tarter et al. (2003) examined a construct of neurobehavioral inhibition, made up of indicators of affect, behavior, and cognition, in a longitudinal study of high-average risk and low-average risk boys. The authors found that neurobehavioral inhibition distinguished between the high- and low-risk groups, significantly predicted substance use at age 19, and was a stronger predictor of substance use disorder than consumption frequency (Tarter et al., 2003). Further, in participants with a family history of alcohol use disorders, tests of executive functioning were found to predict alcohol consumption at a three-year follow-up (Deckel & Hesselbrock, 1996). Conversely, another longitudinal study

found deficits in neurocognition, namely executive functioning, did not predict consistent substance use disorders in adolescents but rather executive functioning impairments were observed following consistent cigarette use (Wilens et al., 2011). Previous literature examining the relationship between pre-morbid cognitive functioning and substance use disorders remains mixed; however, increasing evidence suggests cognitive impairments may be associated with an increased liability to substance use and addiction, particularly among individuals deemed high-risk due to positive family history of addiction.

Following initiation and repeated substance use, previous studies have found brain abnormalities among adolescents (see review by Squeglia, Jacobus, & Tapert, 2009). Additionally, substance use during adolescence has been associated with impairments in cognitive functioning. A longitudinal study examining substance-using adolescents' neuropsychological functioning in comparison to non-using adolescents found that heavy use of alcohol, marijuana, and/or stimulants were associated with increased learning, retention, and attentional difficulties (Tapert, Granholm, Leedy, & Brown, 2002). Specifically, stimulant use in mid-adolescence to early adulthood predicted performance on measures of attention and processing speed at an 8-year follow-up (Tapert et al., 2002) and are consistent with studies of MA dependent adults (Scott et al., 2007; Simon et al., 2000; Simon et al., 2002). Additionally, a cross-sectional study found that the MA-using adolescents performed significantly worse on a number of measures of executive functioning as compared to non-drug using counterparts (King, Alicata, Cloak, & Chang, 2010). Taken together, previous literature suggests that although multiple biological, environmental, and individual differences factors may play a role in substance initiation and repeated use, MA may further compound any pre-morbid deficits in cognition and lead to increased impairments in cognitive functioning.

In addition to individual differences associated with neurocognitive functioning, neural changes occurring in the adolescent brain may also be playing a role in susceptibility to addiction. Previous research has provided initial evidence for a hyper-responsive striatal reward system during this developmental period which may serve as a risk factor for increased reward-seeking, such as through substance use (see review by Galvan, 2010). Additionally in a comparison of children, adolescents, and adults, Galvan and colleagues (2006) captured a neural developmental shift as the adolescent brain exhibited similar activation and reward-sensitivity in the accumbens as adults but their orbital frontal cortex activity more closely resembled the brain of a child. The authors postulate that perhaps it is the differential rates of neurodevelopment in these areas that lead to increased reward-sensitivity and risk-taking. To that end, brain changes during adolescence may further increase the likelihood of risky decision-making and impulsive behavior.

In sum, both behavior and brain studies combine and suggest that there are pre-morbid deficits, such as neurocognition and impulsivity, which may predispose individuals to substance use. But importantly, repeated drug use may serve to worsen existing deficits thus placing individuals at a greater risk of experiencing impairments of daily functioning and quality of life. Importantly, MA in particular has been linked to neurocognitive deficits, thus making it the focus of the current study.

Methamphetamine use affects neurocognitive functioning[1]

Repeated MA use has been linked with deficits in neurocognitive functioning (Scott et al., 2007). Of particular interest is the role MA may play in affecting executive functioning, as loss of executive control has been implicated in playing a role in the progression of addiction

[1] All literature reviewed here are comprised of cross-sectional studies unless otherwise noted. Additionally, unless otherwise noted, all studies reviewed are comparison between clinical and non-clinical populations.

(Everitt & Robbins, 2005). Executive functioning has traditionally been conceptualized as "higher-order cognition" and has been described as being responsible for our goal-directed behaviors, decision-making, and planning (Alvarez & Emory, 2006; Jurado & Rosselli, 2007). Although operationalizing executive functioning has posed a problem, previous literature suggests that inhibitory control, working memory, and cognitive flexibility are three components of executive function (see review by Diamond, 2013). Others have conceptualized inhibition and switching, attention, and working memory as the functions underlying executive functioning (see review by Alvarez & Emory, 2006).

The current project merged both conceptualizations such that executive functioning will be operationalized as: (a) working memory, (b) attention, and (c) cognitive flexibility. Working memory involves the ability to attend to a stimulus while manipulating the information (Baddeley, 1992; Baddeley & Hitch, 1994), and can be split into two distinct types: spatial/visual working memory and verbal working memory (Diamond, 2013). Working memory allows us to make connections in everyday life and is critical to comprehension and reasoning. Attention entails inhibiting irrelevant stimuli in order to maintain focus. This ability to concentrate and maintain awareness allows us to center in on important tasks and assists in our working memory processes in order to identify relevant information and ignore unimportant stimuli. Lastly, cognitive flexibility builds on both working memory and attention to allow individuals to switch between tasks, perspectives, and ways of thinking (Diamond, 2013). Cognitive flexibility has also been found to develop at later ages (Davidson, Amso, Anderson, & Diamond, 2006; Garon, Bryson, & Smith, 2008) as it is one of the more complex components of neurocognition. Cognitive flexibility allows us to adapt our behavior to changes in the environment and our thinking in relation to others. Largely, all three components of executive function work together

to allow for maximal daily functioning. However, the ability to parse apart these facets of executive functioning are crucial as they offer insight to specific deficits and importantly, areas of potential improvement through cognitive remediation or pharmacology. It is in these specific areas that we aimed to examine among a MA dependent population in order to inform future interventions for MA users who experience impairments in cognitive functioning.

The current literature has convincingly shown that MA dependent individuals perform worse than non-drug using controls on a variety of cognitive measures. A review by Baicy and London (2007) suggests that alterations to the brain and neurotoxicity due to MA use may contribute to cognitive impairments. Neuroimaging studies have found MA users during early abstinence (4-7) exhibit decreased activity in cortical areas of and performed worse on the Stroop Test (increased errors and response time) than did their healthy control counterparts (Nestor, Ghahremani, Monterosso, & London, 2011). Other studies have found impairments among MA dependent individuals in perceptual speed, cognitive flexibility, memory, attention, and the ability to manipulate information (Simon et al., 2000; Simon et al., 2002). Further, preclinical studies have shown that binge dose regimen of MA caused deficits in reversal learning in rats (Izquierdo et al., 2010) and chronic MA exposure has been shown to impair performance on reversal learning in non-human primates (Groman et al., 2012). Importantly, a meta-analysis confirmed the results found in prior studies that implicate the role of chronic MA use in contributing to neurocognitive deficits (Scott et al., 2007). Cognitive deficits among chronic MA users were found in multiple domains but those with the largest effect sizes were executive functioning (d = -0.63), learning (d = -0.66), memory (d = -0.59), and processing speed (d = -0.52; Scott et al. 2007). Scott and colleagues (2007) were able to demonstrate an overall medium effect size for the relationship between MA use and neurocognition. In contrast,

previous meta-analyses examining the relationship of other substances and cognitive deficits, such as cocaine (d = -0.35; Jovanovski, Erb, & Zakzanis, 2005) and marijuana (d = -0.15; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003), have found much smaller effects. From previous findings, not only does there appear to be a clear cognitive difference between MA users and non-substance users, but also according to meta-analyses, MA appears to have a more substantial effect on neurocognitive functioning than other drugs of abuse, such as marijuana and cocaine. This highlights the importance of understanding the relationship between MA and cognitive functioning.

Impaired cognitive functioning has also been observed during abstinence. Kalechstein and colleagues (2003) found MA dependent individuals performed worse on a range of neurocognitive domains as compared to controls during short-term abstinence (5-14 days). Similarly, during longer-term abstinence (2-4 months), MA dependent individuals exhibited greater difficulty with cognitive inhibition than did healthy control individuals (Salo et al., 2002). Although some have found a recovery of DA transporters and changes in the brain with abstinence from MA in a longitudinal design, cognitive performance of tests of motor and memory did not improve (Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001).

In a longitudinal study, Iudicello and colleagues (2010) administered a neurocognitive battery to individuals with MA dependence and to a healthy control group. At baseline testing, consistent with prior studies, those who used MA performed significantly worse on global neuropsychological tasks than the control group. At a one-year follow-up, some individuals with MA dependence had remained abstinent (25 out of 83) while the rest had resumed MA use. The authors found that the abstainers and the healthy control individuals performed similarly on neuropsychological tests, while those who had returned to using MA continued to perform

significantly worse than the comparison group. These findings suggest that following a year of abstinence there may be some rebound of cognitive functioning (Iudicello et al., 2010).

While previous research has demonstrated neurocognitive differences between MA dependent individuals and non-drug using controls, less is known about variability in cognitive functioning within MA users. Differences within MA users driven by clinical variables are arguably most relevant to informing treatment at the individual and group levels. In this way, treatment for a MA use disorder can be individualized based on the specific deficits or needs. To address this gap in the literature, the current study aimed to elucidate cognitive deficits within individuals with a MA use disorder using a multivariate approach that simultaneously accounts for clinical variables such as age of onset, frequency of use, and MA use disorder symptoms. Current literature suggests there is little association between MA use parameters (e.g., years of MA use, total grams used, frequency of use, etc.); however there are mixed findings (Dean, Groman, Morales, & London, 2012). A meta-analysis examining 17 cross-sectional studies found no association between duration of MA use and neurocognition (Scott et al., 2007), although one study found years of MA use was correlated with poorer performance on the Stroop test (Salo et al., 2009), a task capturing cognitive flexibility. This suggests that duration of MA use may affect specific domains of neurocognition, but not others and highlights the importance of an integrative model that can capture multiple dimensions of MA use severity simultaneously.

Mixed findings have also emerged for frequency and recent amount of MA use, with some studies finding negative correlations between MA use amount and frequency and performance on neurocognitive tests (Simon et al., 2000) and some finding no relationship (e.g., King et al., 2010; Monterosso, Aron, Cordova, Xu, & London, 2005; Rippeth et al., 2004). In a primary analysis, Cherner et al. (2010) compared neuropsychologically impaired and non-

impaired MA dependent individuals on various indices of MA use and found they did not differ. However, conclusions from this study are limited by the small sample size and lack of analyses of the continuous, versus dichotomous, association between MA use and neurocognition. The current study aimed to address these issues by including a large, well-characterized sample of individuals with a MA use disorder and to examine the relationship between MA use and executive functioning within a multidimensional and integrative framework.

As for addiction severity, one study of amphetamine found an association between amphetamine dependence severity and decreased performance on tests of memory and attention (McKetin & Mattick, 1998). A longitudinal neuroimaging study found the rate in which there was a recovery of dopamine transporters was negatively correlated with the severity of MA abuse prior to abstinence and positively correlated with the time between evaluations (days abstinent; Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001). Conversely, Hoffmann and colleagues (2006) found no relationship between addiction severity and cognitive deficits. These mixed findings highlight an area in need of continued research. As such, this study examined neurocognition in the context of MA addiction severity through MA use parameters through the utilization of a number of self-report measures and interviews meant to capture MA use disorder on a multidimensional level.

Importantly, the relationship between MA use severity and neurocognition may be playing an important role in treatment outcomes and highlights the clinical significance of the dissertation project. Currently there are no robust psychosocial or pharmacological treatments for stimulant dependence, with cognitive therapy remaining the leading treatment for stimulant use disorders; however cognitive deficits associated with MA use may be deleterious to treatment goals and outcomes (Vocci, 2008). In general, substance users with cognitive impairments have

been shown to be less engaged in treatment and discontinue treatment earlier (e.g., Aharonovich et al., 2006; Aharonovich, Nunes, & Hasin, 2003; Katz et al., 2005; Teichner, Horner, Roitzsch, Herron, & Thevos, 2002). Previous research has found that cocaine users who dropped out of treatment performed poorer on cognitive measures assessing attention, memory, spatial ability, perceptual speed and accuracy, global functioning, and cognitive proficiency than did completers (Aharonovich et al., 2006). Another study among cocaine users found performance on the Stroop better predicted treatment retention than did a measure of depression, with poorer performance on the Stroop being associated with greater rates of discontinuation of treatment (Streeter et al., 2008). Additionally, substance users (alcohol and drug) with cognitive impairments were found to have increased treatment drop-out rates; however both cognitively impaired and intact participants benefited from treatment and made significant treatment gains (Teichner et al., 2002). Taken together, previous literature suggests that deficits in neurocognition may act as potential obstacles to treatment.

In regards to MA, previous research has noted that individuals with MA use disorders may experience worsened cognitive functioning during short-term abstinence (Simon, Dacey, Glynn, Rawson, & Ling, 2004), in addition to the neurocognitive deficits that have been linked with MA use. This poses another major barrier to recovery as many patients seek treatment during the crucial period of early abstinence. Neurocognitive assessments prior to treatment have already been suggested in order to facilitate the identification of potential impairments and ways in which interventions may be most beneficial (Tapert, Brown, Myers, & Granholm, 1999; Tapert, Ozyurt, Myers, & Brown, 2004). By elucidating the specific ways in which MA use parameters predict cognitive functioning and impulsivity during short-term abstinence, treatments may be developed, for example cognitive remediation and medication development

(Vocci, 2008), such as the targeted use of cognitive enhancers (e.g., modafinil). Cognitive training and remediation have been shown to be efficacious in other clinical populations, such as schizophrenia and traumatic brain injury, and such strategies have been suggested to be suitable for substance using populations as well (see review by Ersche & Sahakian, 2007).

All in all, the field appears to be recognizing the importance of making cognitive processing a target of treatment and suggests that pharmacological agents that enhance cognition may be a viable option (Sofuoglu, 2010; Sofuoglu, DeVito, Waters, & Carroll, 2013). Previous research has shown evidence that modafinil improved learning among MA users in comparison to placebo (Ghahremani et al., 2011) while in a separate study, it was found to improve cognition among high-frequency users of MA (Dean et al., 2011). Thus, this study is highly relevant as it addresses a high priority research area and focuses on a major barrier to treatment engagement and sustained recovery, namely cognitive deficits. Through detailed examination of cognitive deficits associated with MA use and by addressing many remaining gaps in the literature, the goal of the dissertation is to translate the findings from the project to real-world, clinical applications. In this way, treatment-seeking individuals may have an increased chance of benefiting from treatment, either through an initial trial of cognitive remediation prior to skills-building and cognitive behavioral protocols, or through medication management.

In sum, previous literature suggests that a relationship exists between MA use and cognitive deficits. Because cognitive differences have been well established between MA users and non-substance users, the dissertation expanded on this research by focusing solely on the individual differences within a population of MA users. Additionally, because previous research findings on MA use parameters and neurocognition are so mixed, this study examined these variables simultaneously in a multidimensional model. Further exploring the relationship

between MA and neurocognitive functioning is significant as it holds implications for treatment of this disorder in the future, as growing evidence suggests that addressing cognitive impairments may contribute to treatment efficacy and outcomes.

Many criticisms of the current literature remain

Although there appears to be substantial evidence that MA use is associated with cognitive deficits, gaps remain in the existing literature. In a critical review of the association between MA and cognition, Hart and colleagues (2012), argue that studies to date have failed to provide concrete evidence indicating a true relationship between MA use disorder and neurocognitive deficits. The dissertation aimed to address many of these criticisms as described below. For example, Hart et al. (2012) discuss one of the key issues with the current literature regarding previous findings of cognitive impairment among MA users lies within the definition of "impairment." According to Hart et al. (2012), "impairment" has been primarily defined by previous studies as occurring when there is a significant difference between control participants and the MA individuals, even if the drug-using group performed within the normal range on a task. Conversely, the review suggests that a more appropriate definition of "impairment" should include difficulty or loss in functioning as captured by performance on cognitive tasks outside the normal range. To address this issue, the current study considered cognitive impairment to be present based on the latter definition of "impairment" when interpreting the clinical relevance of our findings. Therefore, we assessed performance based on normative scores and considered deficits to exist only when performance is outside the normal range. This is important because the dissertation aimed to capture an actual relationship between MA use severity and neurocognitive deficits. By considering deficits to be performing outside of the normal range, we are ensuring that we are truly capturing neurocognitive deficits.

An additional weakness in the literature is the tendency for previous studies to draw conclusions regarding a specific cognitive domain (e.g., memory, attention, etc.), from an individual's performance on a single task (Hart et al., 2012). In other words, it is not safe to assume that performance on only one task aimed at measuring working memory fully captures an individual's ability to manipulate information and attend to novel stimuli. To that end, the dissertation utilized multiple tasks to measure a single domain of executive functioning (e.g., working memory, attention, and cognitive flexibility). In this way, we can be more confident that impairment in a specific domain truly exists, as we were able to measure performance across multiple tasks capturing the same cognitive domain.

Further critiques of the current literature include: limited examination of comprehensive neuropsychological batteries in favor of a few select tests, demographic and drug use variables differ greatly across studies, and the research examining MA use parameters or addiction severity on cognition have predominately found null results, most likely because self-reported drug use histories are rarely accurate and difficult to obtain (Dean et al., 2012; Hart et al., 2012; Scott et al., 2007). This study included a full comprehensive battery aimed at capturing a near-complete picture of cognitive functioning. However, specifically, the research question focuses on executive functioning and the components thought to make up this cognitive domain, such as working memory, attention, and cognitive flexibility.

Lastly, in order to address the potential inaccuracy associated with self-reported drug use history; the study used a severity factor score that would include multiple self-reported MA use variables (e.g. years using, average days of use per month, etc.), self-reported measures of clinical variables associated with MA use (e.g., withdrawal, craving, etc.), and MA use disorder symptom count taken from a semi-structured diagnostic interview (Structured Clinical Interview

for the DSM-IV; SCID). To our knowledge, this is the first study to combine multiple measures of MA addiction into a singular MA use severity factor, which is thought to better capture the dimensionality of the disorder. In sum, utilization of an integrative model, in a large, well-characterized sample of MA use disorder individuals, allows for us to be in a promising position to capture true cognitive impairments in this at-risk population while simultaneously addressing several gaps in the existing literature.

Methamphetamine and impulsivity

In a review of neurocognition and MA, Scott and colleagues (2007) highlight an area in need of research lies in the examination of the relationship between MA use and impulsivity. There is relatively less literature focused specifically on the relationship between impulsivity and MA in comparison to the research on neurocognition and MA; which is surprising given more recent models of addiction have placed impulsivity at the center of addictive behavior (Harrison, Coppola, & McKee, 2009). The role impulsivity may play as an underlying mechanism in MA use is of particular interest due to emerging evidence of it being a critical component across multiple forms of addiction (Goldstein & Volkow, 2002; Jentsch & Taylor, 1999). The DSM-IV-TR and the more recently revised, DSM 5, both place a failure to control one's impulses for MA despite negative consequences as a criteria for diagnosis of MA dependence/use disorder, thus suggesting that MA abusers may have generalized problems with impulse control. Therefore, the dissertation study examined the relationship between MA use severity and facets of impulsivity.

Impulsivity is traditionally defined as acting suddenly and without plan to satisfy an immediate desire (Kreek, Nielsen, Butelman, & LaForge, 2005) and has been implicated in addictive behaviors (Lawrence, Luty, Bogdan, Sahakian, & Clark, 2009). Impulsivity is not considered to be unidimensional (De Wit, 2009; Fernie, Cole, Goudie, & Field, 2010), but can be

examined through several constructs including, but not limited to, response inhibition, and delay reward discounting. In a recent review, Jentsch and colleagues (2014) suggest that although the individual constructs of impulsivity (i.e. delay reward discounting and response inhibition) may be distinct and separate aspects of impulsivity, they share common mechanisms in key frontostriatal circuits. Importantly, the authors highlight that the relationship between impulsivity and substance use disorders is robust and deficits in various constructs of impulsivity have been linked with clinical and preclinical populations either as a consequence or predating substance use (Jentsch et al., 2014). All in all, impulsivity plays a significant role in regards to the initiation of drug use, continued use despite negative consequences, and potential to relapse.

In order to prevent initiation of substance use as well as throughout periods of abstinence to avoid relapse, self-control is critical. Response inhibition is an individual's ability to inhibit his/her thoughts or behaviors and is an adaptive strategy that healthy individuals develop in order to control their behaviors. Some have suggested that inhibition can be separated into two parts: response inhibition (the ability to stop a pre-potent response) and attentional inhibition (the ability to ignore extraneous information); however both factors have been found to be highly correlated and share similar neural pathways (see review by Diamond, 2013). Thus, the concept of inhibitory control has also been conceptualized as a component of executive functioning as it requires higher-order processes to hinder a response or action (Diamond, 2013).

In addition to difficulties with response inhibition, failing to value rewards in the future may also explain continued drug use despite negative consequences and relapse during periods of abstinence. Delay reward discounting involves the individual's tendency to devalue a reward as time increases before the reward becomes attainable (see review by Jentsch & Taylor, 1999). Impulsively choosing a smaller, immediate reward over a larger, delayed reward, is the basis of

the delay-discounting model of impulsiveness (Kirby, Petry, & Bickel, 1999). Poor delay reward discounting can be translated into the addiction model as substance users may be less capable of rejecting the immediate high in order to experience better health in the future. In a meta-analysis examining delay reward discounting across the addiction literature, MacKillop and colleagues (2011) found that clinical samples (groups exhibiting addictive behavior, e.g., gambling, tobacco, alcohol, stimulant, opiate, or mixed substance use) had significantly larger effect sizes (d = .61) than did non-clinical samples (d = .45). These findings suggest that addicted individuals have increased delay reward discounting than non-substance users.

As with neurocognitive deficits, increased impulsivity may be associated with neuromodulation of the dopaminergic system following MA use. Previous research has found deficits in striatal D2/D3 receptors were related to increased self-reported impulsivity among MA dependent individuals (Lee et al., 2009). Conversely, previous research has also suggested that an inhibitory control deficit may be risk factor for stimulant-dependence rather than a consequence of substance use as one study examining stimulant-dependent individuals and their biological siblings with no long-term drug use history found deficits in response inhibition among both groups (Ersche et al., 2012). Additionally, a neuroimaging study found fMRI activation during a response inhibition task among adolescents predicted substance use 18 months later, above and beyond drug and alcohol use history (Mahmood et al., 2013). Taken together, growing evidence suggests that impulsivity is both a predisposition for addiction and a consequence of substance use (see review by Jentsch et al., 2014).

In a large-scale study (N = 385) examining self-reported impulsivity among MA users, Semple and colleagues (2005) found higher impulsivity was associated with greater MA consumption and increased reports of MA "binges." Binges were defined as using large amounts

of MA in a period of time until the individual no longer had any left or physically could not continue use. Additionally, higher impulsivity was associated with younger, less educated individuals, increased risky sexual behavior (e.g., a large number of sexual partners, unprotected sex, etc.), and higher self-reported depression. In fact, higher self-reported depression had the strongest relationship with impulsivity ratings. Other studies have found individuals with MA use disorder exhibited greater difficulty with response inhibition (Monterosso et al., 2005) and discounted delayed rewards more steeply (Hoffman et al., 2006) than healthy control individuals. Preclinical studies have also found that following chronic MA administration (4 mg/kg daily for two weeks) rats valued a delayed reward (water) less as compared to saline administration, suggesting increased impulsivity with chronic MA use (Richards, Sabol, & de Wit, 1999).

Although previous studies provide initial evidence of increased impulsivity among stimulant users in comparison to healthy control participants, the current study addressed a limitation in the literature by examining the relationship between MA use disorder severity and impulsivity, response inhibition, and delay discounting. Specifically, we administered the following behavioral and self-report measures: (a) the Stop Signal Task (SST) which consists of a "Go", "No-Go" task in which participants must perform quickly on "Go" signals, but withhold their response during the "No-Go" signal to measure response inhibition (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003); (b) the Delay Discounting Task (DDT) a measure of preference for smaller immediate rewards to larger, delayed rewards to assesses for delay reward discounting; and (c) the Barratt Impulsivity Scale-11 (BIS), a self-report measure of impulsivity. Given the conceptual overlap between impulsivity and executive functioning, it is important to examine the relationship between MA use severity and impulsivity for a more comprehensive picture of the widespread effects of MA.

The Dissertation

Specific aims and hypotheses

The dissertation study aimed to examine two areas of deficits previously associated with MA use: neurocognition and impulsivity. This study examined cognitive deficits in individuals who met criteria for a MA use disorder at early abstinence in a large and well-defined sample. While many studies have failed to find differences in MA use parameters and degree of cognitive impairment (e.g., Cherner et al., 2010), a few studies have found associations between the two (see review by Dean et al., 2012). The dissertation project examined this relationship during early abstinence, which is critical because it is most closely related to the beginning of a treatment episode, when adjustments for cognitive impairments must be made so that treatments can be tailored or adapted to meet patients' needs (Vocci, 2008). Cognitive deficits in MA dependence represent a major barrier to treatment engagement and sustained recovery, thus elucidating clinical features associated with neurocognitive impairments has great potential to directly inform treatment planning. Additionally, understanding the association between MA use severity and impulsivity, response inhibition, and delay discounting is highly significant given the conceptual overlap between executive functioning and impulsivity as well as the need to identify unique deficit areas that can inform etiology and treatment, and that can serve as treatment targets.

The dissertation study built upon the neurocognitive and impulsivity assessments collected as part of Dr. Ray's completed R21 (Ray et al., 2015). By extending upon the data collected by the candidate during the chair's R21, the current study was adequately powered to examine cognitive deficits in MA dependence. The dissertation study provides a comprehensive and multivariate evaluation of the relationship between MA addiction severity and

neurocognitive deficits, including (a) impulsivity, and (b) executive functioning, in a large and well-characterized sample of MA users. Specific Aims:

Aim 1: **To evaluate the relationship between MA use severity and measures of impulsivity (Barratt Impulsivity Scale), response inhibition (Stop Signal Task), and delay reward discounting (Delay Discounting Task) among current MA users.** It was hypothesized that greater MA addiction severity will be associated with greater impulsivity, poorer response inhibition, and increased delay discounting.

Aim 2: **To examine whether MA use severity, measured in a multivariate model, predicts cognitive deficits in attention, working memory, and cognitive flexibility during early abstinence (4-7 days without use of MA).** It was hypothesized that those who exhibit greater MA addiction severity will display the greatest cognitive deficits across all domains.

Methods

Participants

Non-treatment seeking individuals who currently use MA were recruited from the Greater Los Angeles area. Inclusion criteria consisted of the following: (1) must meet current DSM-IV criteria for MA abuse and/or dependence; (2) be fluent in English; (3) be between the ages of 18 and 50; (4) produce a MA positive urine prior to study entry; and (5) agree to abstain from MA during the study, as evidenced by a MA-negative urine upon the morning of the neuropsychological battery. Exclusion criteria included the following: (1) currently in treatment for MA dependence or a history of treatment in the 30 days before enrollment or are treatment seeking; (2) have a current (last 12 months) DSM-IV diagnosis of drug dependence (other than MA); (3) report a lifetime DSM-IV diagnosis of schizophrenia, bipolar disorder, or any psychotic disorder; (4) have current major depressive disorder with suicidal ideation; and (5)

current use of psychoactive drug, other than marijuana and MA, determined by toxicology screen.

Procedures

Participants were recruited from the community through radio, Internet, and newspaper advertisements. Interested individuals called into the laboratory and completed a brief phone screen to assess for eligibility. Following the phone screen, eligible individuals were invited to the lab to complete an in-person screening. During the behavioral screen, we obtained information regarding medical history and individual differences, administered the SCID, and collected a urine sample for toxicology. During this visit, participants also completed behavioral measures to capture impulsivity (Aim 1). Eligible participants then returned to the lab 4-7 days since the time of last MA use to complete the neuropsychological battery (Aim 2). At this visit, once participants tested negative for all drugs (with the exception of marijuana), they completed the neuropsychological battery. Refer to **Table 1** for the study appendix. Participants were continuously assessed as to their wish to enter drug treatment and were provided with treatment referrals accordingly. Participants received $50 for participating in the in-person screening interview and $60 for completing the neuropsychological battery.

Measures

Methamphetamine Use Severity: MA use disorder and other psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First, Spitzer, Gibbon, & Williams, 1995) in order to determine inclusion based on diagnostic criteria. DSM-IV symptoms of MA abuse and MA dependence were recorded for a total of 11 possible symptoms (4 of abuse and 7 of dependence) comprising of the indicator variable SX_Count. Additionally, from the SCID, age of first MA use comprised the indicator variable Onset and the total years of using

MA were calculated to comprise the indicator variable Yrs_Use. MA withdrawal was assessed using the MA Withdrawal Questionnaire (MAWQ), a self-report questionnaire of physical, emotional, and functional symptoms of MA withdrawal (Srisurapanont, Jarusuraisin, & Jittiwutikan, 1999a, 1999b). A total score was tabulated for each participant to comprise the indicator variable MAWQ. The MA Urge Questionnaire (MAUQ) was used as a self-report measure of craving and a total score will be tabulated for each participant to comprise the indicator variable MAUQ. Frequency of MA use over the past 30 days was calculated from the 30-day TLFB interview which obtained baseline of quantity and frequency of MA and served to comprise the indicator variable Frequency (Sobell, Brown, Leo, & Sobell, 1996; Sobell & Sobell, 1980). Thus, the indicator variables that make up the MA use severity latent construct included: (i) SX_Count, (ii) Onset, (iii) Yrs_Use, (iv) MAWQ, (v) MAUQ, and (vi) Frequency.

Impulsivity Battery: The following measures were collected during the behavioral visit in order to capture aspects of impulsivity: (1) The Barratt Impulsivity Scale -11 (BIS), a brief, self-report, 30-item measure that assessed participants for trait impulsivity; (2) The Stop Signal Task (SST) is a computer task which captures both inhibitory and activational responding and requires participants to respond to go signals while stop signals will occasionally appear informing subjects to inhibit their response; and (3) The Delay Discounting Task (DDT) captures participants ability to delay rewards as it requires participants to choose between and immediate, smaller monetary gain and a larger, delayed gain. The indicator variables comprising of the impulsivity latent construct included: (i) total score from the BIS (BIS), (ii) the stop signal delay ladder 1 and ladder 2 extracted from the SST task (SSD1 and SSD2), (iii) the mean go reaction time extracted from the SST task, and (iv) the preference for smaller, immediate over larger

delayed rewards as indexed by three *k* values (Small k, Medium k, and Large k) calculated from the DDT task.

Attention: Subtests from the Delis Kaplan Executive Function System (D-KEFS) and the Weschler Adult Intelligence Scale (WAIS-IV) were used to assess for attention. Specifically, Trails Visual Scanning, in which the examinee is presented with a series of numbers and letters and must identify every "3" as quickly and accurately as possible, was utilized. In the Tower Test, the examinee must build target towers by moving disks across three pegs in the least amount of moves possible. The Digit Span Forward is a subtest of the Weschler Adult Intelligence Scale (WAIS-IV) and requires the examinee to repeat back numbers the examiner has just listed. Thus, the indicator variables extracted for the attention latent construct included: (i) Trails: Visual Scanning, (ii) Tower, and (iii) Digit Span Forward.

Cognitive Flexibility: Subtests from the DKEFS were used to assess for cognitive flexibility. Trails Letter-Number Switching entails the examinee to switch between number and letters in ascending order as quickly and accurately as possible. In the Verbal Fluency Test, examinees must switch between naming objects from two distinct categories (fruits and pieces of furniture) in a 60 second period. Lastly, in Color-Word Interference, the examinee is presented with a list of words printed in different colored ink and are instructed to say the color of the ink the words are printed in, not read the word. The three indicator variables which comprise the cognitive flexibility latent construct were: (i) Trails: Letter-Number Switching, (ii) Verbal Fluency, and (iii) Color-Word Interference.

Working Memory: Subtests from the WAIS-IV and the Rey-Osterrieth Complex Figure (REY-O) will be used to measure working memory. Digit Span Backward requires the examinee to repeat the number presented by the examiner but backwards. In the Coding Test, the examinee

must copy symbols that are paired with distinct numbers in 120 seconds. Lastly, the REY-O Complex Figure Delay requires the examinee to recall and re-draw a figure they copied at least 30 minutes prior. Thus, the three indicator variables comprising of the working memory latent construct were: (i) REY-O, (ii) Digit Span Backward, and (iii) Coding. See **Table 2** for a summary of the neuropsychological measures.

Additional Individual Differences Measures: (1) A Demographics Questionnaire was used to collect information on age, sex, marital status, socioeconomic status, occupation, income, education, and ancestry; (2) Current smoking was assessed by the Fagerstrőm Test for Nicotine Dependence (FTND), a measure used to assess nicotine dependence severity (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991); and (3) The Beck Anxiety (BAI) and Beck Depression (BDI) Inventories were used to assess for physical and cognitive symptoms of anxiety and depression, respectively.

Data Analysis Plan

Descriptive Data Analysis: Prior to analysis of the specific aims, several steps were taken to ensure data accuracy and to determine associations within predictors and outcomes in the study. Two descriptive statistics tables (Mean, SD, Frequency) were constructed for demographic and MA use variables according to Aim (see **Tables 3** and **6**). Descriptive statistics tables of outcome variables separated by Aim were also constructed (see **Tables 4, 7**, and **8**). Additionally, correlation matrices were created for study predictors, outcomes, and the intersection for the two by Aim (see **Tables 5** and **9**). This allowed for the identification of significant relationships between clinically relevant variables. The overarching goal of this set of analysis was to become familiar with the data and to build parsimonious latent factors that were later used to test the proposed structural equation models (SEM). In addition, careful analysis of

descriptive and correlational data allowed us to refine study variables and generate hypotheses for additional analyses.

Analyses of Specific Aims: Consistent with the study goals of evaluating the relationship between MA use disorder severity, impulsivity, and executive functioning, a multivariate structural equation modeling (SEM) approach was used in order to simultaneously capture associations between these constructs. The latent constructs included observed variables as described in the measures section. Modeling analyses were conducted using the EQS version 6.1 for Windows SEM program (Bentler, 1995). Robust statistical estimates were used due to the non-normal distribution of the MA indicator variables. Statistical model fit was assessed with the Satorra-Bentler scaled chi-squared fit index (Satorra & Bentler, 2001). A relative estimate (ratio of chi-square to degrees of freedom) was also calculated, as the use of the chi-squared likelihood ratio to assess the model fit has been deemed unsatisfactory for numerous reasons (Tanaka, 1993). Values < 2 on the relative chi-square indicate adequate model fit (Byrne, 1989). Descriptive model fit was assessed with the robust versions of the comparative fit index (CFI; Bentler, 1990) and the root mean square error of approximation (RMSEA; Browne & Cudeck, 1993). Both the CFI and the RMSEA are sensitive to model misspecifications and are minimally affected by sample size (Hu & Bentler, 1995). The CFI ranges from 0 to 1, with values above 0.90 indicating acceptable fit (Bentler, 1990). The RMSEA ranges from 0 to 8, where fit values < 0.05 indicate close fit and values < 0.10 indicate reasonable fit (Steiger, 1990).

A two-step approach using the Bentler-Weeks model was taken (Bentler & Weeks, 1980). First, we specified an a priori measurement model for each of the constructs as described below. This step allowed us to examine how well the indicator variables informed the latent constructs. We evaluated the critical ratios, which are distributed as z-values to determine the fit

of individual indicator variables. Practical fit of the standardized indicator variable loadings were examined and variables were trimmed accordingly to produce the most parsimonious latent constructs. Secondly, paths between the constructs were defined as described below. This defined the structural model for each aim. Please note that SEM models changed as a function of the optimal factors for both predictors and outcomes.

Study Aim 1: MA Use Severity and Impulsivity: To test the hypothesis that there was an association between MA use severity and impulsivity among MA dependent individuals, such that those exhibiting the greatest severity will also be more impulsive, a multivariate structural equation modeling (SEM) approach was used. Specifically, we constructed an outcome latent factor for Aim 1 (impulsivity) that included the indicator variables as described in the measures section (see **Figure 1**). Secondly, we built a MA Use Severity latent construct for predictor variables in the study comprised of indicator variables as described in the measures section. A path was drawn between these constructs in order for MA Use Severity to be estimated as predicting Impulsivity.

Study Aim 2: MA Use Severity and Neurocognition: To test the relationship between MA Use Severity and measures of attention, cognitive flexibility, and working memory, multiple latent constructs of executive functioning were constructed for each neurocognitive domain. The latent constructs (MA Use Severity, Attention, Working Memory, and Cognitive Flexibility) included observed variables as described in the measures section (see **Figure 2**). The MA Use Severity construct was modeled as predicting the latent constructs of executive functioning. Further, consistent with the literature, it was hypothesized that there would be significant inter-factor correlations between the three neurocognitive latent constructs (e.g., attention, working

memory, and cognitive flexibility), hence interfactor paths were estimated between these domains.

Exploratory Analyses: In addition to the models proposed above, we tested associations across variables for the two outcome latent factors, namely, impulsivity (Aim 1) and executive functioning (Aim 2). Additionally, exploratory analyses investigated the group differences between sub-populations of MA users, namely gender and high frequency users [clinical cut-off for MA use (15+ days of use per month)] (Hillhouse, Marinelli-Casey, Gonzales, Ang, & Rawson, 2007).

Results

Descriptive statistics

A total of 203 participants completed the in-person impulsivity assessment battery. Twenty-six participants were removed from the analyses for providing unreliable data, leaving a total of 177 participants (127 men, 50 women). Of these 177 participants, 65% met DSM-IV criteria for both MA dependence and abuse, 19.8% met criteria for MA dependence only, 9.6% met criteria for MA abuse only, 4.5% were diagnostic orphans, and 1.1% did not endorse any symptoms of either MA abuse or dependence. Means, standard deviations, and frequencies of all model variables for completers of the impulsivity battery (Aim 1) are presented in **Table 3**. Means and standard deviations for all outcome measures for Aim 1 are presented in **Table 4**. Correlations across all model variables are presented in **Table 5.**

Of the 117 participants who were eligible following the in-person screening visit, 63 participants (43 men, 20 women) went on to complete the neuropsychological battery. Of these 63 participants, 66.7% met DSM-IV criteria for both MA dependence and abuse, 22.2% met criteria for MA dependence only, and 11.1% met criteria for MA abuse only. Means, standard

deviations, and frequencies of all model variables for completers of the neuropsychological battery (Aim 2) are presented in **Table 6**. Means and standard deviations for all outcome measures for Aim 2 are presented in **Table 7**. Additionally, means and standard deviations of the impulsivity battery outcome measures among participants who completed Aim 2 (n=63) are presented in **Table 8**. Correlations across all model variables for Aim 2 are presented in **Table 9.**

Aim 1 SEM model results

The initial proposed model was not found to fit well descriptively (CFI= 0.694, RMSEA= 0.146) or statistically (S-B scaled χ^2 [63, n = 103] = 291.33; relative χ^2 = 4.62). The CFI ranges from 0 to 1, with values above 0.90 indicating acceptable fit (Bentler, 1990). The RMSEA ranges from 0 to 8, where fit values < 0.05 indicate close fit and values < 0.10 indicate reasonable fit (Steiger, 1990). The following results are based on the standard significance threshold at $p < .05$. The initial model, with standardized coefficients, is presented in **Figure 3**. Importantly, the MA use severity indicator variables, SX_Count (β =.71), MAWQ (β =.53), MAUQ (β =.46), Onset (β = -.28), Frequency (β = .25), and Yrs_Use (β =.29), were all found to load significantly onto the MA Use Severity latent construct, suggesting that all indicators are explaining variance from the same construct. The impulsivity indicator variables, Small k (β = .87), Medium k (β = .89), and Large k (β = .83), loaded significantly onto the Impulsivity factor. However, the other impulsivity indicator variables, BIS (β = .01), SSD1 (β = -.12), SSD2 (β = .04), and MGRT (β = .12) did not load significantly onto the Impulsivity factor. Additionally, the path from MA Use Severity to Impulsivity was not found to be statistically significant (β =.18). Given the poor descriptive and statistical fit of the initially proposed model, multiple iterations of the model were run in order to improve fit.

In the second model examining the relationship between MA use severity and impulsivity, the singular Impulsivity latent factor was separated into multiple latent factors in order to accommodate the indicator variables which had not significantly loaded onto the singular Impulsivity factor. To do so, four latent factors were created based on the task from which the indicator variables were obtained. Thus, the three indicator variables for the Stop Signal Task factor include (i) stop signal delay ladder 1 (SSD1), (ii) stop signal delay ladder 2 (SSD2), and (iii) mean go reaction time (MGRT). The three indicator variables for the Delay Discounting Task factor include (i) Small k, (ii) Medium k, and (iii) Large k. Lastly, the Barratt Impulsivity Scale-11 (BIS) was split into two factors which have been found to better capture domains of impulsivity rather than using a single, total score from the measure (Reise, Moore, Sabb, Brown, & London, 2013). Thus, the indicator variables for the BIS: Cognitive Impulsivity factor include (i) not planful (Item 1), (ii) not planful (Item 7), (iii) no concentration/self-control (Item 8), (iv) no concentration/self-control (Item 9), (v) not a steady thinker (Item 20), and (vi) not a steady thinker (Item 12). The seven indicator variables for the BIS: Behavioral Impulsivity factor include (i) acts impulsively (Item 19), (ii) acts impulsively (Item 17), (iii) changes, moves around (Item 21), (iv) changes, moves around (Item 16), (v) changes, moves around (Item 24), (vi) extraneous/racing thoughts (Item 26), and (vii) extraneous/racing thoughts (Item 6). For a full description of each item, refer to **Table 10**.

The second model was found to fit relatively well descriptively (CFI= 0.875, RMSEA= 0.064) and well statistically (S-B scaled χ^2 [265, n = 103] = 443.14; relative χ^2 = 1.67). The second model is presented in **Figure 4**. Again, the MA use severity indicator variables, SX_Count (β =.67), MAWQ (β =.58), MAUQ (β =.41), Onset (β = -.33), Frequency (β = .21), and Yrs_Use (β =.34), were all found to load significantly onto the MA Use Severity latent

construct. The stop signal indicator variables, SSD1 (β = .85), SSD2 (β = .97), and MGRT (β = .69) loaded significantly onto the Stop Signal Task factor. The delay discounting indicator variables, Small k (β = .85), Medium k (β = .90), and Large k (β = .83) loaded significantly onto the Delay Discounting Task factor. Additionally, all indicator variables of behavioral impulsivity from the BIS loaded significantly onto the BIS: Behavioral Impulsivity factor (β ranging from .42 to .81) and the six indicator variables on the BIS: Cognitive Impulsivity factor loaded significantly (β ranging from .54 to .71).

The paths from both BIS factors (Cognitive Impulsivity and Behavioral Impulsivity) to MA Use Severity were found to be statistically significant (β= 0.42 and β= 0.53, respectively), such that greater MA use severity was associated with increased self-reported behavioral and cognitive impulsivity. The path from Delay Discounting Task to MA Use Severity was also found to be significant (β = 0.17), such that greater MA use severity predicted steeper delay discounting of larger, future rewards. The path from Stop Signal Task to MA Use Severity was not significantly significant (β = -0.07). There was a statistically significant and positive inter-factor correlation between BIS: Cognitive Impulsivity and BIS: Behavioral Impulsivity (*r* = 0.387), such that individuals reporting greater cognitive impulsivity (i.e. difficulty concentrating, planning, keeping on task, etc.) reported greater behavioral impulsivity as well (i.e., acting impulsively, difficulty staying still, etc.). However, the relationships between all other latent factors were not statistically significant. The aim of the second model was to improve fit on the side of the outcomes. This was successfully achieved by splitting the singular Impulsivity factor into four separate constructs: BIS: Cognitive Impulsivity, BIS: Behavioral Impulsivity, Stop Signal Task, and Delay Discounting Task.

In order to further improve model fit, a principal component analysis was conducted to derive factor scores from the MA use severity indicator variables. The principal factor method followed by promax (oblique) rotation revealed the six indicator variables split into two meaningful factors (Eigenvalue = 1.95 and 1.32). Sx_Count, MAUQ, and MAWQ, comprised the first factor while Yrs_Use, Onset, and Frequency made up the second factor, with each index loading on to its respective factor at 0.40 or greater. The third factor fell below the 1.0 cutoff; thus, only two factors were maintained. Factor loadings are presented in **Table 11**.

The third SEM model split the MA Use Severity factor into two factors consistent with the principal component analysis. The third model was found to fit relatively well descriptively (CFI= 0.897, RMSEA= 0.059) and well statistically (S-B scaled χ^2 [260, n = 103] = 406.86; relative χ^2 = 1.56). The third model is presented in **Figure 5**. The MA problems indicator variables, MAUQ (β = .44), MAWQ (β = .64) and SX_Count (β = .67) all loaded significantly onto the MA Use Related Problems factor as did the indicator variables for the MA Use factor, Onset (β = -.65), Frequency (β = .30), and Yrs_Use (β = .68). Additionally, all of the indicator variables loaded significantly onto their respective Stop Signal Task, Delay Discounting Task, BIS: Behavioral Impulsivity, and BIS: Cognitive Impulsivity factors (all βs > .40).

Surprisingly, MA Use did not significantly predict MA Problems (β= -.03). MA Use only significantly predicted BIS: Behavioral Impulsivity (β= 0.27), such that increased MA use was associated with increased self-reported behavioral impulsivity. The paths from both BIS factors (Cognitive Impulsivity and Behavioral Impulsivity) to MA Use Related Problems were found to be statistically significant (β= 0.40 and β= 0.52, respectively), such that greater MA use related problems were associated with increased self-reported behavioral and cognitive impulsivity. Neither paths from Delay Discounting Task nor Stop Signal Task to MA Use Related Problems

were found to be significant (β = 0.15 and β= -.04, respectively). Again, there was a statistically significant and positive inter-factor correlation between BIS: Cognitive Impulsivity and BIS: Behavioral Impulsivity (r = 0.387), while the relationships between all other latent factors were not statistically significant. The third model improved fit on the side of the predictor by splitting the MA Use Severity factor into two separate factors: MA Use and MA Use Related Problems. In order to identify the most parsimonious model, the final model was run to investigate the role of MA use related problems only.

The fourth and final model was found to fit well descriptively (CFI= 0.929, RMSEA= 0.054) and well statistically (S-B scaled χ^2 [199, n = 103] = 294.32; relative χ^2 = 1.48). In order to create the most parsimonious model, the MA Use factor was removed from the final model. The final model is presented in **Figure 6**. Again, the MA problems indicator variables, MAUQ (β = .43), MAWQ (β = .64) and SX_Count (β = .67) all loaded significantly onto the MA Use Severity factor and all of the indicator variables loaded significantly onto their respective Stop Signal Task, Delay Discounting Task, BIS: Behavioral Impulsivity, and BIS: Cognitive Impulsivity factors (all βs > .40).

Finally, the paths from both BIS: Behavioral Impulsivity and BIS: Cognitive Impulsivity factors to MA Use Severity factor were found to be statistically significant (β = 0.51 and β= 0.42, respectively). Consistent with the previous models, the relationship was such that increased MA use related problems predicted increased self-reported behavioral and cognitive impulsivity. The paths from Delay Discounting Task and Stop Signal Task factors to MA Use Severity were not statistically significant (β = 0.12 and β= -.03, respectively). Lastly, as with all previous models, there was a statistically significant and positive inter-factor correlation between BIS: Cognitive Impulsivity and BIS: Behavioral Impulsivity (r = 0.401), while the relationships

between all other latent factors were not statistically significant. In summary, by improving the model on both the predictor and outcome side, we were able to determine that severity of MA use (indexed by craving, withdrawal, and DSM-IV symptom count) was associated with both BIS factors, but not with Stop Signal or Delay Discounting.

Follow-up Analyses: In order to examine the effect of gender on the relationship between the MA Use Severity factor (with indicator variables of the MA use related problems only) and the four impulsivity factors: BIS: Cognitive Impulsivity, BIS: Behavioral Impulsivity, Delay Discounting Task, and Stop Signal Task, correlations were examined across both genders. This approach was selected in lieu of SEM based comparisons because statistical power was not adequate to test between-subjects comparisons within the SEM framework. There were no significant differences of the correlation coefficients between both genders suggesting that the relationship between MA Use Severity and the various impulsivity factors were the same across men and women. Similarly, participants were split into high MA use frequency (≥ 15 days of use per month) and low frequency use (< 15 days of use per month) groups. Again, correlation coefficients were not statistically significant across groups suggesting that the relationship between MA Use Severity and the four impulsivity factors were the same regardless of high or low self-reported frequency of MA use in a one month period.

Aim 2 SEM model results

As with Aim 1, the initial proposed model for Aim 2 was not found to fit well descriptively (CFI= 0.706, RMSEA= 0.108) or well statistically (S-B scaled χ^2 [84, n = 59] = 291.33; relative χ^2 = 3.47). The following results are based on the standard significance threshold at $p < .05$. The initial model is presented in **Figure 7**. The MA use severity indicator variables, SX_Count (β =.86), MAWQ (β =.40), MAUQ (β =.40), Frequency (β = .33), and Yrs_Use (β = -

.38), were all found to load significantly onto the MA Use Severity latent construct, suggesting that these indicators are explaining variance from the same construct. The only indicator variable that did not load significantly onto the MA Use Severity factor was Onset (β = -.28). The attention indicator variables, Trails: Visual Scanning (β = .36), Digit Span Forward (β = .23), and Tower Test (β = .28), loaded significantly onto the Attention factor. Additionally, Verbal Fluency (β = .57), Color-Word Interference (β = .82), and Trails: Letter-Number Switching (β = .66) loaded significantly onto Cognitive Flexibility factor and the three indicator variables on the Working Memory factor loaded significantly (Rey-O, β=.67; Coding, β=.53; Digit Span Backward, β = .49). None of the paths from MA Use Severity to the three executive functioning factors were statistically significant (Attention, β =-.21; Cognitive Flexibility, β = .44; Working Memory, β = .05). There was a statistically significant and positive inter-factor correlation between Attention and Cognitive Flexibility (*r* = 1.0), Cognitive Flexibility and Working Memory (*r* = .97), and between Attention and Working Memory (*r* = 1.8). In order to improve the descriptive and statistical fit of the initially proposed model, multiple iterations of the model were run. To investigate the effects of a simplified MA Use Severity factor with only MA use related problems used as indicator variables, the original theoretical model was re-estimated and was found to be virtually identical to the original model (CFI = 0.818, RMSEA = 0.100; S-B scaled χ^2 [48, n = 59] = 76.76; relative χ^2 = 1.60). In order to maintain consistency with the final model of Aim 1, the MA Use Severity factor for the remainder of the models for Aim 2 was comprised of only the MA use related problems indicator variables (MAUQ, SX_Count, and MAWQ).

Due to the high inter-factor correlations, the second model aimed to examine executive functioning as a singular factor. Again, the second model did not fit well descriptively (CFI=

0.778, RMSEA= 0.105) or statistically (S-B scaled χ^2 [53, n = 59] = 88.08; relative χ^2 = 1.66). The second model is presented in **Figure 8**. All of the indicator variables comprising executive functioning, Trails: Visual Scanning (β = .36), Digit Span Forward (β = .23), Tower Test (β = .28), Verbal Fluency (β = .57), Color-Word Interference (β = .82), Trails: Letter-Number Switching (β = .66), Rey-O (β = .67), Coding (β = .53), and Digit Span Backward (β = .49) loaded significantly onto the Executive Functioning factor. All MA use related problems indicator variables were found to load significantly onto the MA Use Severity factor (SX_Count, β = .82; MAUQ, β = .68; MAWQ, β = .43). The path from MA Use Severity to Executive Functioning was not statistically significant (β = .20). The second model attempted to improve fit by combining all executive functioning variables into a single factor but was unsuccessful. A third model was run in order to improve fit on the outcome variables.

The third model was empirically driven by a factor analysis of the executive functioning variables. A principal component analysis was conducted to derive factor scores from all of the executive functioning indicator variables. Consistent with a factor analytic approach, variables with defused loadings (i.e., significant loadings in multiple factors) were systematically removed from the model and the solution was re-estimated. This resulted in the final solution of six variables indexing psychological tests of executive function. The principal factor method followed by promax (oblique) rotation revealed the remaining six indicator variables split into two meaningful factors (Eigenvalue = 1.90 and 1.18). Verbal Fluency, Digit Span Forward, and Digit Span Backward, comprised the first factor while Trails: Visual Scanning, Color-Word Interference, and Tower Test made up the second factor, with each index loading on to its respective factor at 0.40 or greater. The third factor fell below the 1.0 cutoff; thus, only two factors were maintained. Factor loadings are presented in **Table 12**.

The third, empirically based model, fit well descriptively (CFI= 0.978, RMSEA= 0.032) and well statistically (S-B scaled χ^2 [24, n = 59] = 25.47; relative χ^2 = 1.06). The third model is presented in **Figure 9**. All indicator variables of the MA Use Severity factor loaded significantly (MAUQ, β = .65; SX_Count, β = .84; MAWQ, β = .42). The three indicator variables for Executive Functioning 1 factor were all statistically significant (Verbal Fluency, β = .70, Digit Span Forward, β = .45; Digit Span Backward, β = .58). The second executive functioning factor indicator variables, Trails: Visual Scanning (β = .53) and Color-Word Interference (β = .63) loaded significantly onto the Executive Functioning 2 factor; however Tower Test (β = .30) did not. Similar to previous models of Aim 2, the paths from Executive Functioning 1 factor (β = -.77) and from Executive Functioning 2 factor (β = 1.03) to the MA Use Severity factor were not found to be statistically significant. As expected, there was a statistically significant and positive inter-factor correlation between both executive functioning factors (r = 0.75) suggesting that participants performed similarly across executive functioning tasks. Although the third model greatly improved fit due to improvements on the outcome factors, another model was required in order to address the lack of fit of the Tower Test on Executive Functioning 2.

The final model built upon the empirically driven executive functioning factors. In order to improve the model, the Tower Test indicator variable was added to Executive Functioning 1 factor as suggested by the Wald Test (χ^2 (2) = 4.097). The final model fit well descriptively (CFI= 1.00, RMSEA= 0.000, SRMR = 0.069) and well statistically (S-B scaled χ^2 [24, n = 59] = 23.31; relative χ^2 = 0.97). The standardized root mean square residual (SRMR) is an absolute measure of fit with a value less than .08 considered an indicator of good fit (Hu & Bentler, 1995). The fourth and final model is presented in **Figure 10**. In the final model, all of the MA use severity indicator variables loaded significantly onto the MA Use Severity factor (MAUQ, β

= .62; SX_Count, β = .89; MAWQ, β = .40) as did the two indicator variables for the Executive Functioning 2 factor (Trails: Visual Scanning, β = .53; Color-Word Interference, β = .66). Importantly, the indicator variables comprising of Executive Functioning 1 factor, Verbal Fluency (β = .74), Digit Span Forward (β = .42), Digit Span Backward (β = .56), and Tower Test (β = .37) loaded significantly onto the factor. Consistent with previous models, neither paths from Executive Functioning 1 factor (β = -.62) nor Executive Functioning 2 factor (β = .89) were statistically significant with MA Use Severity factor. Lastly, once again there was a positive inter-correlation between both executive functioning factors (r =.68). In summary, by improving fit on both the predictor and outcome sides of the model, the overall model was found to fit well both descriptively and statistically. However, MA use severity was not found to be related to either executive functioning factor.

Follow-up analyses: In order to examine the effect of gender on the relationship between the MA Use Severity factor (with indicator variables of the MA use related problems only) and the two empirically derived executive functioning factors, correlations were examined across both genders. There was a statistically significant difference between the correlation coefficient of MA Use Severity and Executive Functioning 1 factor across gender (z = -3.32, p < .01). As seen in **Figure 11**, there was a positive, statistically significant correlation between MA Use Severity and Executive Functioning 1 for females (r = .68, p < .01) but the relationship was not significant for males (r = -.15, p =.34).

To examine the effect of frequency of use, participants were split into high MA use frequency (≥ 15 days of use per month) and low frequency use (< 15 days of use per month). A negative, statistically significant correlation was found between MA Use Severity and Executive Functioning 2 among low frequency users (r = -.44, p <.05) but no relationship was found for

high frequency users (r = .18, p =.29). **Figure 12** illustrates a statistically significant difference between the correlation coefficient of MA Use Severity and Executive Functioning 2 factor across frequency group (z = -2.26, p < .05).

Lastly, in order to integrate both aims and investigate the relationship between the impulsivity and executive functioning factors, correlations were conducted to examine the association between the executive functioning factors (Executive Functioning 1 and Executive Functioning 2) and the impulsivity factors (BIS: Cognitive Impulsivity, BIS: Behavioral Impulsivity, Delay Discounting Task, and Stop Signal Task). As expected, there was a significant inter-correlation between the two BIS factors (r = .30); however none of the correlations between factors were statistically significant.

Discussion

MA use continues to be a significant public health problem across the United States. Importantly, abuse of psychostimulants, including MA, has been linked to cognitive deficits (Vocci, 2008). Although some have argued that support for the relationship between MA and cognitive deficits is limited (Hart et al., 2012), recent reviews provide convincing evidence of this association (Dean et al., 2012). Previous studies have identified some specific cognitive deficits for MA dependent individuals, such as reduced cognitive flexibility, attention, working memory, and vigilance (London et al., 2005; Salo et al., 2005; Simon et al., 2000; Simon et al., 2002) with some deficits persisting through short-term abstinence (Kalechstein et al., 2003). A meta-analysis revealed deficits in episodic memory, executive functioning, and information processing speed in individuals with MA use disorder versus controls (Scott et al., 2007). MA dependence has also been associated with increased impulsivity (Vocci, 2008), decreased response inhibition (Monterosso et al., 2005), and poorer delay reward discounting (Hoffman et

al., 2006). Clinical findings are consistent with preclinical studies showing that MA administration increased impulsivity in animal models (Richards et al., 1999).

While the substrates of cognitive deficits are not entirely understood, there is evidence to suggest that the neurocognitive deficits observed in MA users may be linked to the neuromodulation of the dopaminergic system that occurs following repeated MA use. To that end, both preclinical and clinical studies have found a significant loss of dopamine transporters following MA administration (McCann et al., 1998; Seiden et al., 1993; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001). Furthermore, research has found that the decrease of dopamine transporters was also associated with poorer cognitive performance (e.g., motor and memory; Volkow, Chang, Wang, Fowler, Franceschi, et al., 2001; Volkow, Chang, Wang, Fowler, Leonido-Yee, et al., 2001) while striatal D2/D3 receptor deficits in MA dependent individuals have also been linked to increased impulsivity (Lee et al., 2009).

While previous research has demonstrated neurocognitive differences between MA dependent individuals and non-drug using controls, less is known about variability in cognitive functioning within MA users. Differences within MA users driven by clinical variables are arguably most relevant to informing treatment at the individual and group levels. Additionally, given the need for increased research examining the relationship between MA use and impulsivity (Scott et al., 2007) and to address multiple gaps in the neurocognitive literature (Dean et al., 2012; Hart et al., 2012; Scott et al., 2007), the current study aimed to elucidate cognitive/impulsivity deficits using a multivariate approach that simultaneously accounted for clinical variables of MA use, such as age of onset, frequency of use, craving, and diagnostic symptoms, in a large sample of MA users. In order to do so, individuals who reported regularly using MA participated in a two-day study where, at the initial screening visit, they provided a

positive urine toxicology screen for MA, completed a number of questionnaires and interviews to determine eligibility, and completed an impulsivity battery consisting of the Barratt Impulsivity Scale-11 (BIS), a self-report measure of impulsivity, and behavioral measures to capture response inhibition with the Stop Signal Task (SST); and delay reward discounting with the Delay Discounting Task (DDT). Following this screening visit, eligible participants were invited back to complete an in-depth neuropsychological battery consisting of subtests from the D-KEFS, WAIS-IV, and WASI to capture dimensions of executive functioning (i.e., working memory, cognitive flexibility, attention). All participants were required to test negative for MA on the urine toxicology screen in order to participate in the neuropsychological battery.

The aims of the current study were twofold. The first aim was to examine impulsivity, response inhibition, and delayed discounting as it related to MA use severity. It was hypothesized that MA use severity would predict greater self-reported impulsivity, increased difficulty with response inhibition, and greater delayed discounting. Secondly, the study aimed to examine the relationship between MA use severity and three domains of executive functioning: cognitive flexibility, attention, and working memory, as measured by multiple neuropsychological tasks. It was hypothesized that greater MA use severity would be associated with increased deficits across all three executive functioning domains.

In order to examine the relationship between MA use severity and impulsivity, the first aim of the study utilized a structural equation modeling approach. The initial proposed model was not found to fit well. Importantly, although all indicator variables loaded significantly onto MA Use Severity, only three impulsivity variables loaded significantly onto the singular Impulsivity factor. This finding highlights the multidimensionality of impulsivity (De Wit, 2009; Fernie et al., 2010). Despite previous findings that individual constructs of impulsivity share

common mechanisms in key frontostriatal circuits (see review by Jentsch et al., 2014), the current findings offer further support that each construct of impulsivity may be distinct and unique in their clinical presentation. Furthermore, there was no significant relationship between MA Use Severity and impulsivity. This finding is likely due to the poor indicator variable fit on the unidimensional Impulsivity latent factor. As further support of the multidimensionality of these constructs of impulsivity, no significant correlations were found between indicator variables of the different tasks of impulsivity. In other words, the only variables that were significantly correlated were from the same task (i.e., small k and medium k were significantly correlated and both are variables of the DDT).

Following several iterations, the final model consisted of a streamlined version of the MA Use Severity factor containing indicator variables of problems related to MA use (e.g., craving, withdrawal, DSM-IV symptoms of MA abuse/dependence). The MA use indicator variables, specifically age of onset, frequency of days using MA in a one month period, and years of MA use, were removed in order to develop the most parsimonious severity factor and in part because, as previous literature has suggested, self-reported drug use histories are rarely accurate and difficult to obtain (Dean et al., 2012; Hart et al., 2012; Scott et al., 2007). The MA use variables did not add to the examination of MA use severity in prior iterations of the model and overall model fit was greatly improved once they were removed. Similar to the current study, many have found that years of use do not relate to neurocognitive and impulsivity deficits (e.g., Hoffman et al., 2006; Monterosso et al., 2005; Scott et al., 2007) while a few others have found that frequency and/or duration of MA use are associated with impairments (Salo et al., 2009; Simon et al., 2000). While a select number of studies have found a relationship between MA use variables and deficits in cognitive functioning, the majority have not, and the current study

further supports this lack of relationship. It is plausible that self-reports of MA use related problems may be more easily recalled than variables of MA use itself due to the salience of symptoms associated with withdrawal, craving, interpersonal problems, etc. Additionally, the timeframe of reference for self-reported MA use problems may be playing a role in ease of recall as they tend to fall within a shorter, more recent time-span (24-hour period (i.e., MAUQ and MAWQ) to the past several months (SCID)), rather than the months and years required to collect data on historical MA use variables. For these reasons, the final MA Use Severity factor was comprised of only variables of MA use related problems (i.e., craving, withdrawal, and DSM-IV symptom count).

Analyses of impulsivity found that increased MA use related problems were related to greater self-reported behavioral and cognitive impulsivity. These findings provide increased evidence supporting the relationship between MA use severity and higher self-reported impulsivity, specifically as measured by the BIS. Previous literature comparing cocaine dependent and MA dependent individuals examined the relationship between impulsivity as measured by the BIS and craving of drug of choice (Tziortzis, Mahoney, Kalechstein, Newton, & De La Garza, 2011). The study found that although there were no differences in impulsiveness scores on the BIS between cocaine- and MA-dependent individuals, high self-reported impulsivity was associated with increased craving among MA dependent individuals only. Furthermore, Tziortzis et al. (2011) found that craving and impulsivity were related to other drug use variables such as severity of withdrawal and self-reported craving following drug use, among both groups. The current study expands on these findings as multiple MA use related problems, indexed by increased craving, withdrawal, and DSM-IV symptoms, were significantly associated with greater self-reported impulsivity on the BIS.

Previous research has suggested a potential biological mechanism for increased impulsivity among MA users. In a PET study examining striatal D2/D3 receptors and self-reported impulsivity with the BIS among MA users, Lee and colleagues (2009) found deficits in striatal D2/D3 receptors were related to increased self-reported impulsivity among MA dependent individuals as compared to healthy control subjects. Given these findings, it is plausible that the individuals in the current study may be exhibiting similar deficits in striatal D2/D3 receptors and that these deficits may be underlying the relationship between MA use severity and self-reported impulsivity. However, future studies examining MA use severity and impulsivity with the BIS in neuroimaging studies will be best positioned to elucidate the neurobiological mechanisms underlying this relationship.

Importantly, the findings from the current study that greater MA use severity is associated with increased self-reported impulsivity may have implications for treatment. In a recent multi-site treatment study, cocaine- and MA-dependent individuals completed the BIS during outpatient substance use disorder treatment (Winhusen et al., 2013). MA-dependent participants were found to report higher ratings of impulsivity on the BIS than cocaine-dependent individuals. Additionally, a subscale of the BIS, which has been thought to capture acting without thinking, was related to treatment non-completion rates ($d = 0.53$). These findings suggest that although there may be differences in impulsivity between MA- and cocaine-dependent individuals, self-reported impulsiveness on the BIS may be useful in predicting those at risk of treatment dropout among both groups. The current study may inform clinicians as the MA Use Severity factor includes measures that would readily identify potential triggers for relapse or treatment dropout (e.g., self-reported withdrawal and craving). Both the BIS

(Winhusen et al., 2013) and the MA Use Severity factor could potentially be utilized to identify patients at increased risk for not completing treatment.

Interestingly, there was not a significant relationship between MA use severity and the behavioral measures of impulsivity, suggesting that response inhibition and delay reward discounting may not be associated with severity of MA use. These findings are surprising given other clinical and preclinical studies that have shown increased impulsivity among MA users as compared to non-substance users as measured by these behavioral tasks (Hoffman et al., 2006; Monterosso et al., 2005; Richards et al., 1999). These studies have found individuals with MA use disorders exhibited greater difficulty with response inhibition (Monterosso et al., 2005) and discounted delayed rewards more steeply (Hoffman et al., 2006) than healthy control individuals. The current study differs from the aforementioned ones in several ways. First, it does not include a healthy control group comparison but rather examined the relationship between MA use related problems and these constructs of impulsivity within a large, well-characterized sample of MA users. As such, the current findings suggest that MA use severity does not predict either increased difficulty with response inhibition or steeper delay reward discounting; however, it is possible that these measures could differentiate between MA users and non-substance users. In an attempt to evaluate response inhibition in the context of MA use variables, Monterosso and colleagues (2005) had found an association between worsened performance on the SST and recent amount of MA used (in grams), but no relationship with performance and frequency of use in a small group of MA abusers (n = 11). Hoffman et al. (2006) reported that variables of MA use, such as severity of MA use, years of use, and average amount used daily (in grams), were not related to any neuropsychiatric variables, although it is unclear if the authors included the DDT in that analysis as it was not specifically stated. The current findings provide further

evidence in a much larger sample (n = 177) that response inhibition and delay reward discounting are not affected by severity of MA use as captured by MA use related problems.

Lastly, the behavioral measures of impulsivity in the current study were collected during the initial screening visit, when participants tested positive for MA on a urine toxicology screen. In the previous studies (Hoffman et al., 2006; Monterosso et al., 2005), all participants had been abstinent from MA and tested negative at the time of data collection. Of note, Hoffman et al. (2006) found no association between length of abstinence and delayed discounting. In a preliminary analysis of performance on the DDT and SST pre- and post-MA infusion as part of Dr. Ray's completed R21 (Ray et al., 2015), there were no differences in performance on these behavioral measures. Taken together, this suggests that response inhibition and delay reward discounting as captured by behavioral measures may not be sensitive to the acute effects of MA.

In addition to examining the relationship between MA use severity and the constructs of impulsivity, inter-correlations were tested between factors of impulsivity. Because previous research has suggested that despite functioning as separate aspects of impulsivity, these constructs ultimately share common mechanisms in key frontostriatal circuits (Jentsch et al., 2014), it was hypothesized that there would be significant inter-correlations between the factors. However, none of the impulsivity factors were found to be significantly correlated with one another, with the exception of the two factors derived from the BIS (BIS: Cognitive Impulsivity and BIS: Behavioral Impulsivity). A previous study from our laboratory examining dimensions of impulsivity and alcohol use problems among problem drinkers in an SEM framework also found no significant correlation between performance on behavioral measures of response inhibition (SST) and delay reward discounting (DDT) (Courtney et al., 2012). The replication of

these findings among a sample of MA users provides further evidence for the importance of examining and comparing multiple dimensions of impulsivity across substance-using groups.

Summary of Impulsivity Findings: In sum, the current study examined the relationship between MA use severity and dimensions of impulsivity in a multivariate framework. The analyses found that increased MA use severity was associated with greater self-reported cognitive and behavioral impulsivity, but not significantly associated with behavioral measures of impulsivity, specifically the SST and the DDT. The significant relationship between MA use severity and the BIS may be a byproduct of the task as they both capture self-report measures whereas the SST and DDT are thought to capture dimensions of impulsivity behaviorally, without self-report biases. However, previous research has identified a relationship between MA use and greater self-reported impulsivity as measured by the BIS and the current study further supports those findings. Taken together, the current study provides increased evidence of the relationship between MA use and increased impulsivity. Additionally, the findings highlight the importance of evaluating impulsivity as a multidimensional construct. Because there has been less research examining the relationship between MA use and impulsivity, this study advances the current literature as it does so in a large (n=177), well-characterized sample of individuals who use MA regularly. Further research is needed to investigate the role MA use severity may play in predicting treatment outcomes as well as to investigate the biological mechanisms underlying impulsivity and its association to MA use severity.

The second aim of the study utilized the same structural equation modeling approach in order to examine MA use severity and performance on tasks of executive functioning during short-term abstinence (between 4-7 days abstinent). To address multiple gaps in the literature (Dean et al., 2012; Hart et al., 2012; Scott et al., 2007), the current study aimed to elucidate

cognitive deficits within a sample of individuals who met criteria for a MA use disorder using a multivariate approach that simultaneously accounted for MA use severity in relation to performance on a number of measures capturing executive functioning.

The final, empirically based model found that MA use severity was not significantly related to executive functioning. This suggests that in this sample of individuals with a MA use disorder, individual MA differences and MA use problems were not associated with performance on tasks of executive functioning. These findings support previous research, which suggest there is little to no relationship between parameters of MA use and cognitive functioning (e.g., Cherner et al., 2010; Rippeth et al., 2004; Scott et al., 2007). Despite a few studies which have found an association between clinical variables of MA use and neurocognitive deficits (McKetin & Mattick, 1998; Salo et al., 2009; Simon et al., 2000), the current findings in conjunction with existing literature (see review by Dean et al., 2012) provide increased evidence that MA use severity is not associated with neurocognitive functioning, as captured by performance on standard neuropsychological batteries. Of note, although the path coefficients in the model are large, decreased power afforded by the sample size in the present study may be contributing to the non-significance of these relationships. Future studies may find that with a larger sample, there may be a significant relationship between MA use problems and neuropsychological functioning.

Interestingly, in an 8-year longitudinal study, Tapert et al. (2002) found heavy use of alcohol, marijuana, and/or stimulants were associated with increased learning, retention, and attentional difficulties, with stimulant use in mid-adolescence to early adulthood predicting performance on measures of attention and processing speed at the 8-year follow-up. Another study by the same group found heavy alcohol use, marijuana use, and co-use of both substances

were associated with poorer performance on a number of cognitive domains as compared to a healthy control group of adolescents following one month of monitored abstinence (Winward, Hanson, Tapert, & Brown, 2014). A cross-sectional study found that MA-using adolescents performed significantly worse on a number of measures of executive functioning as compared to non-drug using counterparts (King et al., 2010). Although there are obvious differences between these studies and the current one, such as the population (adolescents versus adults) and the comparisons to a healthy control group, the findings in the adolescent literature highlight the importance of examining the relationship between substance use and neuropsychological functioning across development. The previous literature examining adolescent substance use and cognition suggest that neuropsychological functioning may be increasingly vulnerable during this period of adolescence (King et al., 2010; Tapert et al., 1999; Tapert et al., 2002). Indeed, prior studies have found neural changes occurring in the adolescent brain may also be playing a role in susceptibility to addiction (Galvan, 2010; Galvan et al., 2006; Squeglia et al., 2009) and in turn, to potential neurocognitive deficits. Although the current study did not find a relationship between MA use severity and measures of executive functioning among adults, future studies could extend this research by examining MA use severity and neuropsychological functioning during adolescence.

Critically, participants of the current study were found to perform within one standard deviation of the norm on all measures of executive functioning with the exception of the Rey-O Delay task, a measure of memory. Given the recent criticisms of the literature associating MA use with neurocognitive impairments (Hart et al., 2012), these findings suggest that not only do individual differences of MA use parameters not predict performance on tasks of executive functioning, but also individuals with a MA use disorder are testing within normal range on

various neurocognitive measures. One of the leading criticisms of the existing literature has been the definition of impairment, as Hart and colleagues (2012) have pointed out, it is often deemed to occur in previous studies when there was a significant difference between control participants and MA-using individuals, even if the drug-using group performed within the normal range on a task. The current study addresses this critique by assessing performance based on normative scores rather than as compared to non-substance using control participants. The findings that participants performed within the normal range on all but one task measuring memory highlight the importance of evaluating cognitive functioning beyond differences between clinical and non-clinical populations.

Further, the effect of gender and frequency of MA use (< or ≥ 15 days of use in a one month period) on the relationship between MA use severity and the two executive functioning factors were investigated. These follow-up analyses found there was a difference between males and females such that for females, as MA use severity increased, scores on the Executive Functioning 1 factor also increased. There was not a significant relationship between MA use severity and executive functioning for males. These findings suggest that females in this sample may be benefiting from the cognitive enhancement capabilities of the stimulating nature of the drug; however this does not explain the relationship fully as all participants were abstinent a minimum of four days before completing the neuropsychological battery. Future research is needed to better understand how gender may moderate the relationship between MA use related problems and executive functioning.

Follow-up analyses also found there was a difference between frequency groups such that as MA use severity increased, performance on the Executive Functioning 2 factor decreased among the low frequency users (< 15 days of MA use in a one month period). There was not a

significant relationship between MA use severity and executive functioning for high frequency users. It may be the case that low frequency users who report more MA use problems and thus scored higher on the MA Use Severity factor, may represent a more severe group. These findings suggest that despite less frequent MA use, this group is still experiencing impacts to their daily life (i.e., symptoms of withdrawal, craving, and other diagnostic criteria of MA dependence/abuse) which are also associated with decreased performance on measures of executive functioning. Although the present study was underpowered to examine the effects of gender and frequency of use within the SEM framework, these preliminary findings suggest that future studies would benefit from recruiting a larger sample and examining these differences in a multivariate model.

Summary of Neuropsychological Findings: The second aim of the current study examined MA use severity in relation to executive functioning. There has been much debate on whether MA users truly experience neuropsychological impairment (Dean et al., 2012; Hart et al., 2012) and mixed findings on whether individual differences in MA use affect neuropsychological functioning (Dean et al., 2012). It may be the case that performance on neuropsychological tests can differentiate between MA users and non-substance users, but in comparing their performance to normative data, MA users in the current study performed within the normal range on all measures, except for one task of memory (Rey-O). Importantly, both executive functioning factors were not significantly associated with MA use severity, providing further evidence that neurocognitive measures may not be associated with MA use related problems. Future research is needed to further investigate differences in neuropsychological functioning between MA users and healthy controls as well as comparisons across substance using groups. An area in need of investigation is the relationship between MA use severity and

daily functioning, such as attending appointments, paying bills, being on time, etc. Future research should examine the relationship between deficits in day-to-day functioning and neuropsychological functioning in the context of MA use severity. In addition, combining neuroimaging with neuropsychological tasks may also elucidate underlying neural differences in cognitive performance, which may not be detected by overall performance on these tasks. Furthermore, extending the use of the MA Use Severity factor to longitudinal studies and/or adolescent studies will allow for a better understanding of the relationship between MA use problems and neuropsychological functioning across development.

Strengths and Limitations

The findings should be considered in light of strengths and limitations of the study. One limitation of the present study is the lack of a healthy control group, which prevented comparisons of performance on impulsivity and neuropsychological measures between individuals with a MA use disorder and non-substance users. However, the aims of the study were to investigate the effects of MA use parameters on impulsivity and executive functioning as it has been well established that MA users perform worse than non-drug using control participants on a variety of cognitive measures (Dean et al., 2012). Additionally, although the samples of both aims are considered large for the nature of the population, they are not sufficiently powered for moderation analyses of sample characteristics such as the influence of ethnicity and gender within the specified SEM models. Sample size also prevented further investigation of the relationship of the impulsivity factors, executive functioning factors, and the MA Use Severity factor within one integrated, comprehensive SEM model. As there is conceptual overlap between impulsivity and neuropsychological functioning, future studies should aim to investigate the interplay between these constructs in the context of MA use.

Further, this was a cross-sectional examination of regular users of MA, thereby precluding causal inferences about the progression of the disorder within individual participants and about the relationships between MA use severity and outcome variables. Future research might address these limitations by increasing sample size and investigating these relationships in a longitudinal design. Longitudinal studies may be ideal to capture changes in neurocognitive functioning within the individual across the lifespan as previous research has identified certain periods, such as adolescence, to be particularly vulnerable to the effects of substance use on neuropsychological functioning (e.g., Tapert et al., 2002; Winward et al., 2014). Lastly, generalizability of the findings is limited due to the exclusion of treatment-seeking individuals, those who met criteria for a lifetime DSM-IV diagnosis of psychiatric disorders, and current use of psychoactive drugs (other than MA or marijuana). However, as this study was initially part of a larger-scale, MA administration study (Ray et al., 2015), the exclusionary criteria were developed with safety and ethical considerations in mind.

Despite the limitations, there are several strengths of the present study. This study used a multivariate approach that simultaneously accounted for clinical variables of MA use problems (e.g., withdrawal, craving, and DSM-IV symptoms of abuse/dependence) to examine the relationship between MA use severity and measures of impulsivity and executive functioning. This approach is thought to better capture an existing relationship between MA use severity and impulsivity and neuropsychological functioning as it is able to account for multiple variables, associations, and error, concurrently.

The current study is unique as it examined neurocognition and impulsivity in the context of MA use related problems and not in comparison to a healthy control group. Because neurocognitive and impulsivity differences between MA users and control individuals have been

established in the literature, the current study advances the field by examining the relationship between MA use and these constructs within a group of individuals who regularly use MA. Additionally, the study was able to examine these relationships through the use of multiple variables for each construct, allowing for a more in-depth and complete evaluation of the associations between MA-use related problems and impulsivity and executive functioning.

Importantly, the study methodology addressed many criticisms of the existing literature that had previously examined MA use and neurocognitive functioning (Hart et al., 2012). One such criticism that was addressed in the current study was the evaluation of performance on neuropsychological tests based on normative scores rather than simply comparing MA users to non-substance users. Another critique that was addressed in the present study was the use of multiple tasks to measure each domain of executive functioning, as previous studies have been known to draw conclusions of a specific cognitive domain (e.g., memory, attention, etc.) from an individual's performance on a single task. As an additional strength, this study utilized a comprehensive neuropsychological battery to examine executive functioning rather than measuring neuropsychological functioning with only a few tests. These factors highlight the methodological strengths of the current study which allowed for greater confidence, not only in the measurement of executive functioning among MA users, but also in the results of the analyses of neuropsychological effects.

Lastly, a considerable strength of the study was the development of a MA Use Severity factor, comprised of measures of withdrawal, craving, and DSM-IV abuse/dependence symptoms. The goal is for the MA Use Severity factor to be tested in biologically based models, such as in neuroimaging or genetic studies. A similar approach has been successfully implemented by our group in studies of problem drinkers, both in the context of neuroimaging

(Courtney, Ghahremani, & Ray, 2013) and behavioral measures of impulsivity (Ashenhurst, Bujarski, Jentsch, & Ray, 2014). As the field awaits improvements in evidence-based treatments for stimulant use disorders, having instruments that facilitate the evaluation of MA use severity offer advantages that may improve the efficacy of current treatments. Further research is needed to investigate ways in which MA use severity may predict treatment outcomes with the hope that it can be utilized by clinicians in order to provide services that more effectively target patient needs. The successful development and validation of a MA use severity scale can be used to develop tailored treatment plans and may assist providers in identifying those at greatest risk of treatment dropout or relapse. Likewise, capturing MA use severity has broad implications for research, as it will facilitate the application of clinical neuroscience approaches to understanding MA use.

Conclusion

In conclusion, the current study sought to identify the ways in which individual differences in MA use variables were related to neurocognitive functioning, namely domains of impulsivity and executive functioning. To do so, individuals who regularly used MA completed an impulsivity battery consisting of a self-report measure of impulsiveness (BIS) and behavioral measures of response inhibition (SST) and delay reward discounting (DDT). Following the impulsivity battery and additional eligibility screening, a sub-sample went on to complete a neuropsychological battery consisting of measures of executive functioning (i.e., attention, cognitive flexibility, and working memory). A MA Use Severity factor was developed and comprised of MA-use related problems, such as self-reported withdrawal symptoms of MA, craving for MA, and DSM-IV symptoms of MA abuse and dependence.

The present study is unique as it examined the relationship of MA use severity and impulsivity and executive functioning, in a large, well-characterized sample of MA users. These relationships were tested in a multivariate SEM framework allowing for the simultaneous examination of the association between the constructs. The analyses of impulsivity found that as MA use severity increased, self-reported impulsivity increased as captured by the BIS. However, no relationship was found between MA use severity and the behavioral measures of impulsivity (SST and DDT). The current findings extend previous research (e.g., Lee et al., 2009; Tziortzis et al., 2011; Winhusen et al., 2013) examining the relationship between MA use and the BIS by providing additional evidence for increased impulsivity among MA users. Additionally, the findings further support the multidimensionality of impulsivity and highlight the importance of evaluating impulsivity as such.

Analyses of the association between MA use severity and executive functioning found no significant relationship between the two. Importantly, the current study aimed to examine variability in executive functioning within MA users and to address some of the recent criticisms of the current literature, such as examine performance based on normative data, utilize multiple measures to capture a particular cognitive domain, and collect a comprehensive neuropsychological battery rather than a few, select tests. Although the findings of the current study did not reject the null, it offers important information relevant to the ongoing debate regarding the relationship between MA use and neuropsychological impairments. The lack of relationship between MA use severity and executive functioning provides additional evidence that individual differences in clinical variables of MA do not directly affect neuropsychological functioning. Interestingly, because of the conceptual overlap between constructs of impulsivity, namely response inhibition, and executive functioning, the findings from the impulsivity analysis

serve to support results from the neuropsychological battery. As inhibitory control has also been conceptualized as a component of executive functioning due to its use of higher-order processes (Diamond, 2013), the fact that there was not a significant relationship between MA use severity and response inhibition provides additional evidence that executive functioning truly may not be affected by MA use related problems, such as withdrawal and craving.

Additionally, the findings from the analyses of neuropsychological functioning suggest that although MA users and healthy control individuals may differ on their performance on neurocognitive tests, when compared to normative data, MA use disorder individuals may continue to perform within the normal range. Follow-up analyses revealed that gender and frequency of MA use may moderate the relationship between MA use severity and measures of executive functioning. Analyses found as MA use severity increased, performance on executive functioning increased for females while greater MA use severity was related to decreased performance on neuropsychological tasks in low frequency users (< 15 days of MA use in one month). Future studies with larger sample sizes are needed in order to further explore these associations within the multivariate framework. In sum, the findings examining the relationship between MA use severity and neuropsychological functioning expand on previous literature and provide more evidence for the MA use-neuropsychological impairment debate, specifically that (1) MA use related problems are not directly related to tasks of executive functioning and (2) MA users in the current study performed within the normal range on all but one task of executive functioning, thus highlighting that simply comparing performance between clinical and non-clinical populations on neuropsychological tests is not sufficient evidence of deficits in cognitive functioning.

To that end, the current study examined a large sample of individuals who use MA regularly and evaluated whether individual MA use differences were related to measures of impulsivity and executive functioning. The findings of the current study extend the existing literature and provide additional areas in need of investigation. Future research examining neurocognition in MA users should build on the strengths of the current study by interpreting impairments and deficits in the context of neurocognitive norms and by utilizing multiple neuropsychological tasks to capture a single cognitive domain. Additionally, longitudinal studies would provide greater insight to the relationship between MA use, impulsivity, and executive functioning as well as allow for more accurate collection of substance use patterns over time. Of interest to the candidate would be to examine executive functioning and impulsivity across multiple substance using groups, such as comparisons between individuals with a MA use disorder, alcohol use disorder, and nicotine use disorder. Because substance users have been shown to reliably differ from healthy control participants, a comparison across multiple substance using groups would be arguably more informative to the field and to treatment development for those suffering from co-substance use disorders. As treatment seekers may have different clinical presentations than non-treatment seekers, a future study of interest to the candidate would be to examine the relationship between MA use severity, impulsivity, and executive functioning in a sample of individuals who are interested in or enrolled in treatment. Additionally, future studies should expand on the current findings by examining the effects of MA use severity and impulsivity on treatment outcomes, by further investigating the role gender and frequency of MA use may play in the relationship between clinical MA use variables and neuropsychological functioning, and by utilizing the MA Use Severity factor in longitudinal and biologically based approaches, such as genetic and neuroimaging studies. To that end, studies

may effectively triangulate between biological mechanisms, behavioral phenotypes, and clinical presentations and outcomes.

Table 1

Study Appendix

In-Person Screen (N=203) (Aim 1)	**Neurocognitive Assessment (N =63)** (Aim 2)
Pre-Visit: 1. Informed Consent by Study RA 2. Breathalyzer 3. Urine drug test **(must be MA+)** **<u>Visit</u>** **Interviews:** 1. SCID 2. 30-day TLFB 3. MAWQ 4. Digit Span 5. Shipley (Vocab/Abstract) **Self-Report Measures:** 1. Demographics 2. Current Smoking Habits (SHQ) 3. FTND 4. BDI-II 5. BAI 6. Alcohol Consumption Questionnaire (ACQ) 7. Drug Use Questionnaire (DUQ) 8. FTQ—alcohol 9. FTQ—drugs 10. ADHD Self-Report (Childhood) 11. ADHD Self-Report (Current) 12. AUDIT 13. DOSPERT 14. MAUQ 15. IDAS 16. Routes of Administration 17. Stroop **Impulsivity Tasks:** 1. Stop-Signal Task (SST) 2. BART 3. BIS-11 4. Delay Discounting Task **<u>Post-Visit</u>** Schedule neurocognitive assessment (if eligible)	**Pre-Visit:** 1. Urine drug test **(must be MA-)** **<u>Visit</u>** 1. REY-O 2. DKEFS 3. WAIS (Digit Span/Coding) 4. WASI 5. TOPF 6. CVLT-II 7. DVT

Table 2

Summary of Measures

The neurocognitive tasks that are utilized in the dissertation project, along with the specific domain of executive functioning it measures, are listed below.

	Attention	Cognitive Flexibility	Working Memory
Delis-Kaplan Executive Function System (D-KEFS)			
• Trails Condition 1	X		
• Trails Condition 4		X	
• Verbal Fluency Test		X	
• Color-Word Interference		X	
• Tower Test	X		
Weschler Adult Intelligence Scale (WAIS-IV)			
• Digit Span (Forward)	X		
• Digit Span (Backward)			X
• Coding			X
REY-O Complex Figure Delay			X

Table 3

Means, standard deviations, and frequencies of demographic and methamphetamine (MA) use variables among completers of Aim 1.

Variable	N	Full Sample Mean (SD)/ Frequency (%)
Age	177	35.44 (8.8)
Sex (Male)	177	127 (71.5%)
Ethnicity	176	
Caucasian		54 (30.5%)
African American		39 (22.0%)
Asian		5 (2.8%)
Latino		57 (32.2%)
Native American		1 (0.6%)
Multiple Ethnicities		20 (11.3%)
Education (years)	176	12.64 (3.0)
Age of First Use	173	22.79 (7.9)
Years of MA Use	173	12.53 (8.6)
Met Criteria for Abuse Only	177	17 (9.6%)
Met Criteria for Dependence Only	177	35 (19.8%)
Met Criteria for Abuse & Dependence	177	115 (65.0%)
Met No Diagnosis	177	2 (1.1%)
Diagnostic Orphan	177	8 (4.5%)
Average Symptom Count	177	5.90 (2.4)
Symptom Count	177	
0		2 (1.1%)
1		4 (2.3%)
2		7 (4.0%)
3		23 (13.0%)
4		16 (9.0%)
5		25 (14.1%)
6		24 (13.6%)
7		27 (15.3%)
8		22 (12.4%)
9		16 (9.0%)
10		7 (4.0%)

11		4 (2.3%)
Days of MA Use in Past 30 Days	177	19.0 (8.8)
MA Use Questionnaire	177	17.36 (11.5)
MA Withdrawal Questionnaire	177	15.27 (11.5)
Beck Depression Inventory	177	13.50 (10.2)
Beck Anxiety Inventory	177	9.84 (10.2)
Primary Route of Administration	147	
Smoke		110 (74.8%)
Inject		10 (6.8%)
Snort		23 (15.6%)
Ingest		4 (2.7%)
Fagerstrom Test of Nicotine Dependence	111	5.54 (2.5)

Note: Collection of Primary Route of Administration began after the inpatient group had already enrolled participants. Only those who endorsed smoking cigarettes completed the Fagerstrom Test of Nicotine Dependence questionnaire.

Table 4

Means and standard deviations of outcome variables among completers of Aim 1.

Variable	N	Full Sample Mean (SD)
Barratt Impulsivity Scale Total	176	68.00 (12.7)
Stop Signal Task	177	
Stop Signal Delay Ladder 1 (SSD1)		283.81 (103.4)
Stop Signal Delay Ladder 2 (SSD2)		322.16 (101.9)
Mean Go Reaction Time (MGRT)		525.97 (91.5)
Delayed Discounting Task	177	
Small k		0.09 (0.1)
Medium k		0.08 (0.1)
Large k		0.05 (0.1)

Table 5

Correlation matrix for Aim 1 with methamphetamine use variables and impulsivity outcome variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Age	1														
2. Education (years)	-0.11	1													
3. Years of MA Use	0.58*	-0.17*	1												
4. Age of First Use	0.47*	0.08	-0.44*	1											
5. Frequency of MA Use	-0.06	0.02	0.11	-0.21*	1										
6. MAUQ	-0.06	-0.02	0.04	-0.12	0.11	1									
7. MAWQ	-0.06	-0.11	-0.02	-0.08	0.08	0.30*	1								
8. Average Symptom Count	0.09	-0.13	0.22*	-0.14	0.17*	0.31*	0.40*	1							
9. Barratt Impulsivity Scale	-0.03	-0.05	0.22*	-0.29*	0.09	0.29*	0.49*	0.45*	1						
10. Small k	0.26*	-0.18*	0.22*	0.089	0.039	0.09	0.09	0.12	-0.02	1					
11. Medium k	0.21*	-0.12	0.22*	0.02	0.04	0.04	0.10	0.07	-0.05	0.78*	1				
12. Large k	0.13	-0.04	0.12	0.04	0.12	0.08	0.12	0.09	-0.009	0.73*	0.75*	1			
13. Stop Signal Delay Ladder 1 (SSD1)	0.03	0.08	0.05	-0.06	0.01	0.07	0.10	-0.03	0.14	-0.05	-0.04	-0.08	1		
14. Stop Signal Delay Ladder 2 (SSD2)	0.05	0.09	0.003	0.03	-0.04	0.05	0.06	-0.04	0.05	-0.02	-0.001	-0.005	0.80*	1	
15. Mean Go Reaction Time (MGRT)	0.20*	0.001	0.09	0.09	-0.04	0.02	0.04	-0.01	0.02	0.03	0.05	0.08	0.57*	0.69*	1

*$p < .05$

Table 6

Means, standard deviations, and frequencies of demographic and methamphetamine (MA) use variables among completers of Aim 2.

Variable	N	Full Sample Mean (SD)/ Frequency (%)
Age	63	35.32 (8.7)
Sex (Male)	63	43 (68.3%)
Ethnicity	63	
Caucasian		18 (28.6%)
African American		11 (17.5%)
Asian		2 (3.2%)
Latino		22 (34.9%)
Native American		0
Multiple Ethnicities		10 (15.9%)
Education (years)	63	12.52 (3.4)
Age of First Use	61	23.28 (8.8)
Years of MA Use	61	11.80 (7.8)
Primary Route of Administration	61	
Smoke		52 (85.3%)
Inject		2 (3.3%)
Snort		6 (9.8%)
Ingest		1 (1.6%)
Met Criteria for Abuse Only	63	7 (11.1%)
Met Criteria for Dependence Only	63	14 (22.2%)
Met Criteria for Abuse & Dependence	63	42 (66.7%)
Average Symptom Count	63	6.22 (2.2)
Symptom Count	63	
2		1 (1.6%)
3		9 (14.3%)
4		6 (9.5%)

5		6 (9.5%)
6		13 (20.6%)
7		8 (12.7%)
8		10 (15.9%)
9		7(11.1%)
10		1 (1.6%)
11		2 (3.2%)
Days of MA Use in Past 30 Days	63	19.25 (8.7)
MA Use Questionnaire	63	20.75 (13.4)
MA Withdrawal Questionnaire	63	16.89 (12.0)
Beck Depression Inventory	63	13.65 (11.0)
Beck Anxiety Inventory	63	10.63 (11.2)
Fagerstrom Test of Nicotine Dependence	41	5.46 (2.7)

Note: Only those who endorsed smoking cigarettes completed the Fagerstrom Test of Nicotine Dependence questionnaire.

Table 7

Means (*z*-scores) and standard deviations of outcome variables among completers of Aim 2.

Variable	N	Full Sample Mean (SD)
Attention		
Trails: Visual Scanning	62	0.19 (0.8)
Digit Span Forward	62	-0.04 (1.0)
Tower Test	62	-0.14 (0.7)
Cognitive Flexibility		
Verbal Fluency	62	0.14 (1.0)
Color-Word Interference: Inhibition	62	0.03 (0.9)
Trails: Letter-Number Switching	62	-0.19 (1.0)
Working Memory		
REY-O	61	-2.09 (1.2)
Coding	61	-0.28 (0.8)
Digit Span Backward	62	-0.26 (0.9)

Table 8

Means and standard deviations of impulsivity outcome variables among completers of Aim 2.

Variable	N	Full Sample Mean (SD)
Barratt Impulsivity Scale	63	69.45 (13.6)
Stop Signal Task	63	
Stop Signal Delay Ladder 1 (SSD1)		276.24 (110.8)
Stop Signal Delay Ladder 2 (SSD2)		313.29 (111.1)
Mean Go Reaction Time (MGRT)		527.44 (110.7)
Delayed Discounting Task	63	
Small k		0.11 (0.1)
Medium k		0.08 (0.1)
Large k		0.06 (0.1)

Table 9

Correlation matrix for Aim 2 with methamphetamine use variables, neurocognitive outcome variables, and impulsivity variables for completers of Aim 2.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1. Age	1																							
2. Education (years)	-0.02	1																						
3. Years of MA Use	0.44*	-0.11	1																					
4. Age of First Use	0.60*	0.08	-0.5*	1																				
5. Frequency of MA Use	-0.18	-0.08	0.16	-0.3*	1																			
6. MAUQ	-0.08	-0.11	0.07	-0.15	0.05	1																		
7. MAWQ	-0.06	-0.13	0.05	-0.13	0.14	0.25*	1																	
8. Average Symptom Count	0.15	-0.17	0.27*	-0.10	0.12	0.21	0.25*	1																
9. Trails Visual Scanning	-0.09	0.02	-0.19	0.09	0.03	-0.01	-0.11	-0.10	1															
10. Digit Span Forward	-0.17	0.26*	-0.06	-0.13	0.02	-0.15	0.02	0.16	0.12	1														
11. Tower Total	-0.05	0.28*	0.02	-0.11	0.08	-0.05	0.08	0.05	0.19	0.14	1													
12. Trails: Number Letter	0.09	0.26*	-0.05	0.12	0.15	0.13	0.03	-0.08	0.39*	0.23	0.38*	1												
13. Verbal Fluency Category	-0.03	0.19	-0.03	0.00	0.01	0.09	0.17	0.03	-0.05	0.11	-0.06	0.33*	1											
14. Color-Word Interference Inhibition	0.12	0.05	0.13	0.00	0.05	0.23	0.09	0.09	0.14	0.11	0.24	0.47*	0.07	1										
15. Coding	-0.10	0.21	-0.10	-0.01	-0.04	0.12	0.16	-0.05	0.24	0.29*	0.26*	0.51*	0.33*	0.44*	1									
16. Rey-O	-0.23	0.03	-0.17	-0.09	0.07	-0.17	-0.05	-0.3*	0.02	-0.06	-0.06	-0.04	-0.08	0.05	0.08	1								
17. Digit Span Backward	-0.13	0.30*	-0.18	-0.03	-0.05	-0.02	-0.08	0.05	0.18	0.56*	0.18	0.38*	0.17	0.23	0.21	-0.02	1							
18. Barratt Impulsivity Scale	-0.05	-0.11	0.33*	-0.4*	0.04	0.26*	0.56*	0.34*	-0.13	0.19	0.09	-0.06	-0.08	0.15	0.13	-0.16	-0.07	1						
19. Small k	0.13	-0.14	0.16	0.01	-0.01	-0.02	-0.13	0.22	-0.05	0.04	-0.07	-0.06	-0.09	-0.01	-0.04	-0.17	-0.04	0.03	1					
20. Medium k	0.04	0.04	0.15	-0.08	0.08	-0.08	-0.15	0.08	0.05	0.03	-0.05	0.07	-0.06	0.15	-0.02	0.00	0.04	-0.07	0.69*	1				
21. Large k	0.02	-0.03	0.11	-0.08	0.24	0.02	0.00	0.16	0.07	0.09	0.04	0.11	-0.14	0.12	0.00	-0.02	0.07	0.06	0.77*	0.79*	1			
22. Stop Signal Delay 1 (SSD1)	0.06	-0.01	0.04	-0.02	0.02	0.12	0.20	-0.03	-0.12	0.13	-0.23	0.08	0.19	-0.03	0.15	0.004	0.25*	0.17	-0.07	-0.07	-0.02	1		
23. Stop Signal Delay 2 (SSD2)	0.07	0.10	-0.03	0.06	0.08	0.09	0.14	-0.02	-0.07	0.12	-.25*	-0.11	-0.03	-0.14	-0.06	-0.01	0.24	0.12	-0.06	-0.08	0.07	0.81*	1	
24. Mean Go Reaction Time	0.24*	0.00	0.01	0.19	0.16	-0.02	0.06	0.02	-0.01	0.03	-0.3*	-0.02	-0.11	-0.11	-0.16	-0.04	0.21	-0.03	0.02	0.09	0.21	0.53*	0.66*	1

*$p < .05$

Table 10

Individual items of the Barratt Impulsivity Scale –11 (BIS) that capture Cognitive Impulsivity and Behavioral Impulsivity factors of the BIS according to Reise and colleagues (2013).

BIS: Cognitive Impulsivity	BIS: Behavioral Impulsivity
Item 1: I plan tasks carefully. Item 7: I plan trips well ahead of time. Item 8: I am self-controlled. Item 9: I concentrate easily. Item 20: I am a steady thinker. Item 12: I am a careful thinker.	Item 19: I act on the spur of the moment. Item 17: I act on "impulse." Item 21: I change where I live. Item 16: I change jobs. Item 24: I change hobbies. Item 26: I have outside thoughts when I'm thinking. Item 6: I have "racing" thoughts.

Table 11

Factor loadings for MA use variables.

Variable	Factor 1 loadings	Factor 2 loadings
Yrs_Use	.04	**.82**
Onset	-.12	**-.82**
Frequency	.25	**.43**
MAUQ	**.70**	.09
MAWQ	**.79**	.01
Sx_Count	**.75**	.29

Factor loadings >.40 are in boldface.

Table 12

Factor loadings for neurocognitive variables.

Variable	Factor 1 loadings	Factor 2 loadings
Digit Span Forward	**.78**	.28
Verbal Fluency	**.55**	-.30
Digit Span Backward	**.82**	.38
Trails: Visual Scanning	.10	**.64**
Tower Test	.12	**.72**
Color-Word Interference	.28	**.55**

Factor loadings >.40 are in boldface.

Table 13

Individual differences and MA use severity variable comparisons between completers and non-completers of the neuropsychological battery.

Variable	Non-completers Mean (SD)/ Frequency (%) (n=56)	Completers Mean (SD)/ Frequency (%) (n=63)	Test of Differences	*p* value
Age	36.05 (8.5)	35.32 (8.7)	t (117) = 0.46	.64
Education (years)	13.29 (2.5)	12.52 (3.4)	t (117) = 1.43	.16
Sex (male)	34 (60.7%)	43 (68.3%)	χ^2 (1) = 0.74	.39
MA Use Severity factor	-.05 (.88)	.25 (.96)	t (115)= -1.79	.08
Average Symptom Count	6.32 (2.2)	6.22 (2.2)	t (117)= 0.25	.81
Days of MA Use in Past 30 Days	22.46 (8.0)	19.25 (8.7)	t (117)= 2.09	.04
MA Use Questionnaire	15.75 (9.8)	19.79 (9.9)	t (117)= -2.23	.03
MA Withdrawal Questionnaire	13.30 (9.8)	16.89 (12.0)	t (117)= -1.77	.08
Age of Onset	20.80 (6.4)	23.28 (8.8)	t (115)= -1.73	.09
Years of Use	15.25 (9.5)	11.80 (7.8)	t (115)= 2.15	.03
Beck Depression Inventory	14.63 (9.3)	13.65 (11.0)	t (117)= 0.52	.60
Beck Anxiety Inventory	7.95 (7.6)	10.63 (11.2)	t (117)= -1.52	.13

Figure Captions

Figure 1. The proposed structural equation model for Aim 1: The relationship between MA use severity and impulsivity.

Figure 2. The proposed structural equation model for Aim 2: The relationship between MA use severity and executive functioning.

Figure 3. The initial structural equation model for Aim 1: The relationship between MA use severity and impulsivity.

Figure 4. The second structural equation model for Aim 1with impulsivity split into multiple factors.

Figure 5. The third structural equation model for Aim 1 with MA Use Severity split into two separate factors capturing MA use and MA use related problems.

Figure 6. The final structural equation model for Aim 1 which examines the relationship between MA Use Severity and the impulsivity factors (BIS: Cognitive Impulsivity, BIS: Behavioral Impulsivity, Stop Signal Task, and Delay Reward Discounting).

Figure 7. The initial structural equation model for Aim 2: The relationship between MA use severity and executive functioning as captured by attention, working memory, and cognitive flexibility.

Figure 8. The second structural equation model for Aim 2 with the multiple domains of executive functioning collapsed into a singular factor. Additionally, the MA Use Severity factor includes only MA use related problem indicator variables.

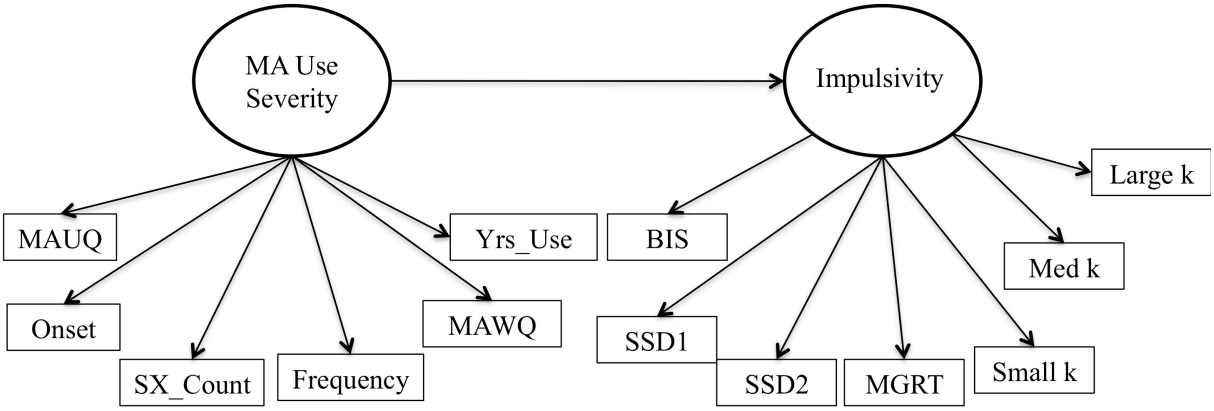
Figure 9. The third structural equation model for Aim 2 with executive functioning split into two empirically derived factors capturing memory/attention (Executive Functioning 1) and cognitive flexibility/attention (Executive Functioning 2).

Figure 10. The final structural equation model for Aim 1 which examines the relationship between MA Use Severity factor and the two empirically derived executive functioning factors.

Figure 11. Relationship of MA Use Severity factor score and Executive Functioning 1 factor score across gender. There was a statistically significant difference across genders ($z = -3.32$, $p < .01$).

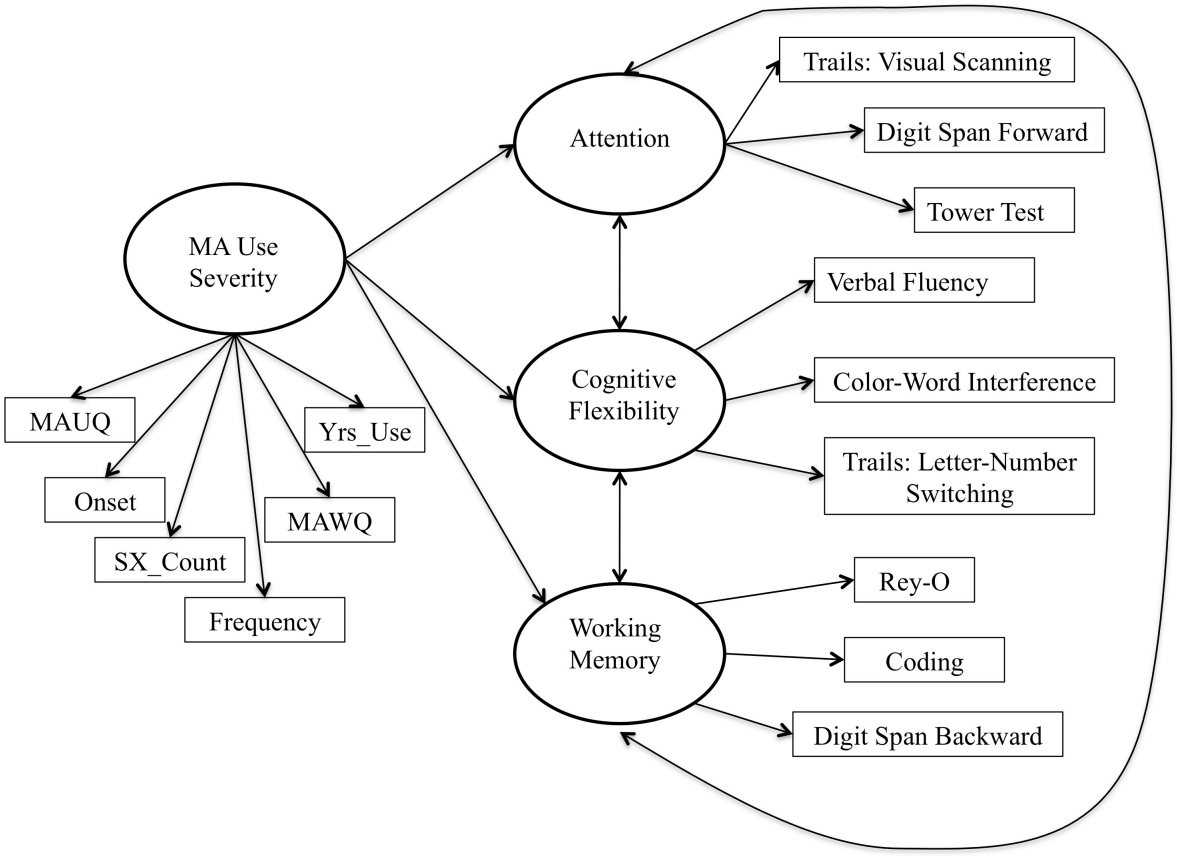
Figure 12. Relationship of MA Use Severity factor score and Executive Functioning 2 factor score across low frequency MA use (< 15 days of use per month) and high frequency MA use (≥ 15 days of use per month). There was a statistically significant difference between low and high frequency users ($z = -2.26$, $p < .05$).

Figure 1.



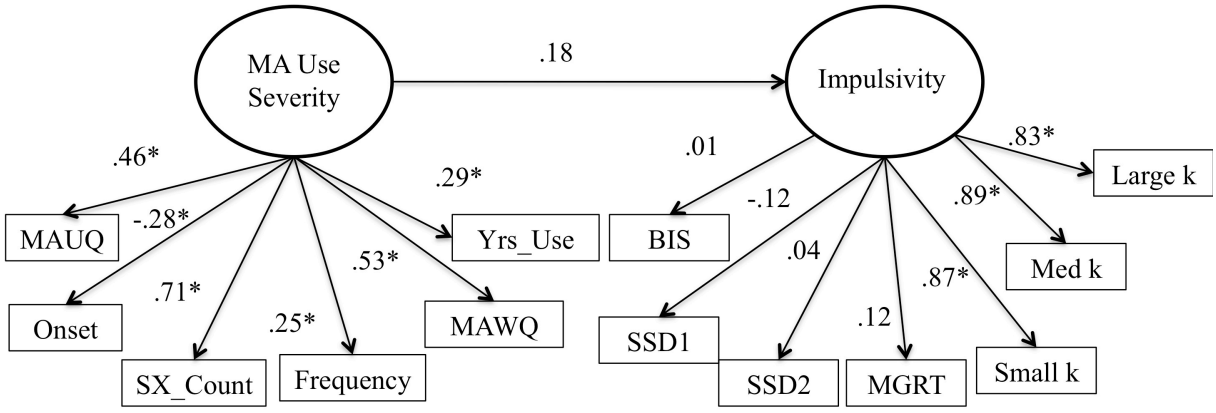
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); total years using MA (Yrs_Use); Barratt Impulsivity Scale (BIS); stop signal reaction time (SSRT); and delay reward discounting (DDT).

Figure 2.



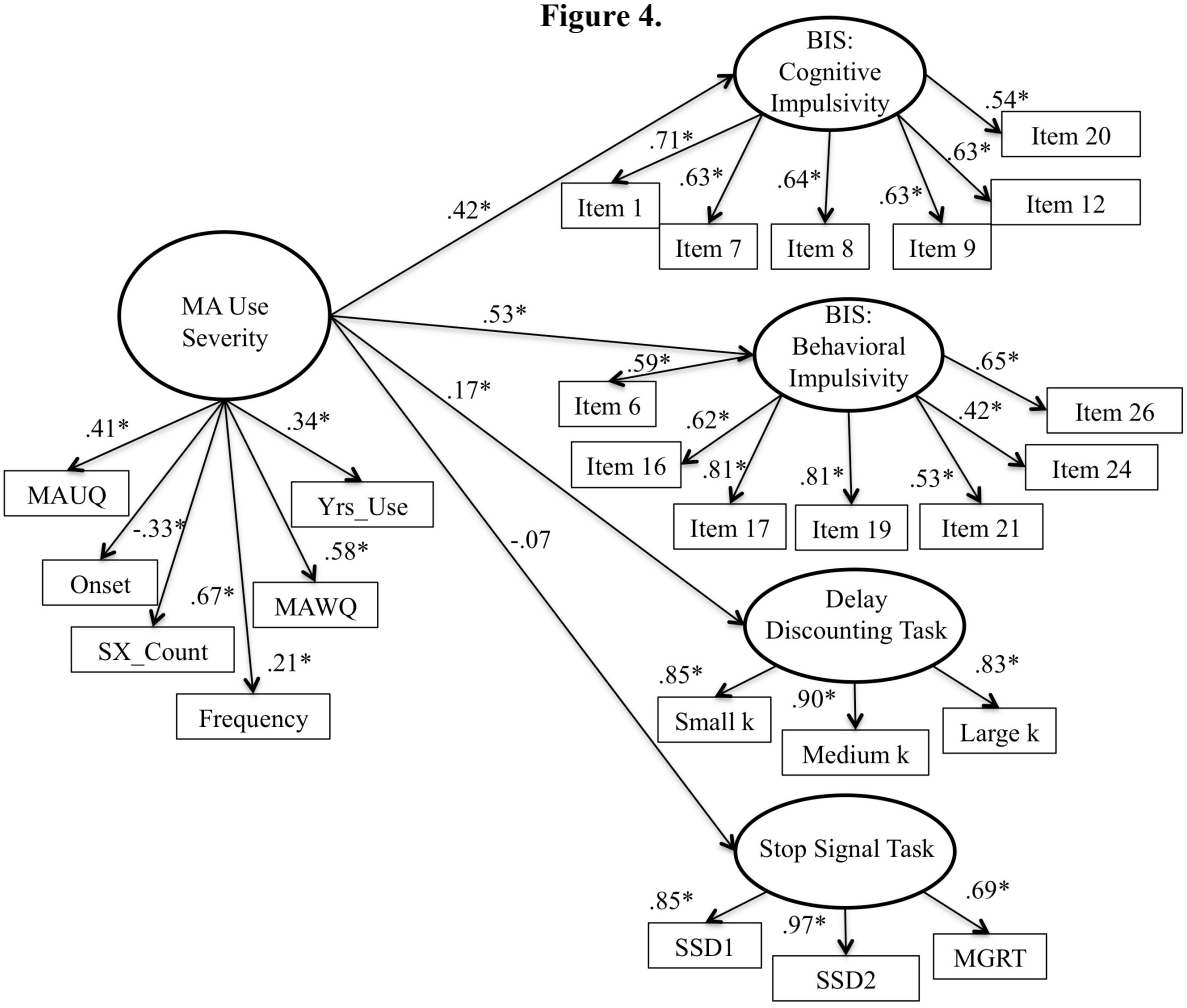
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); and total years using MA (Yrs_Use).

Figure 3.



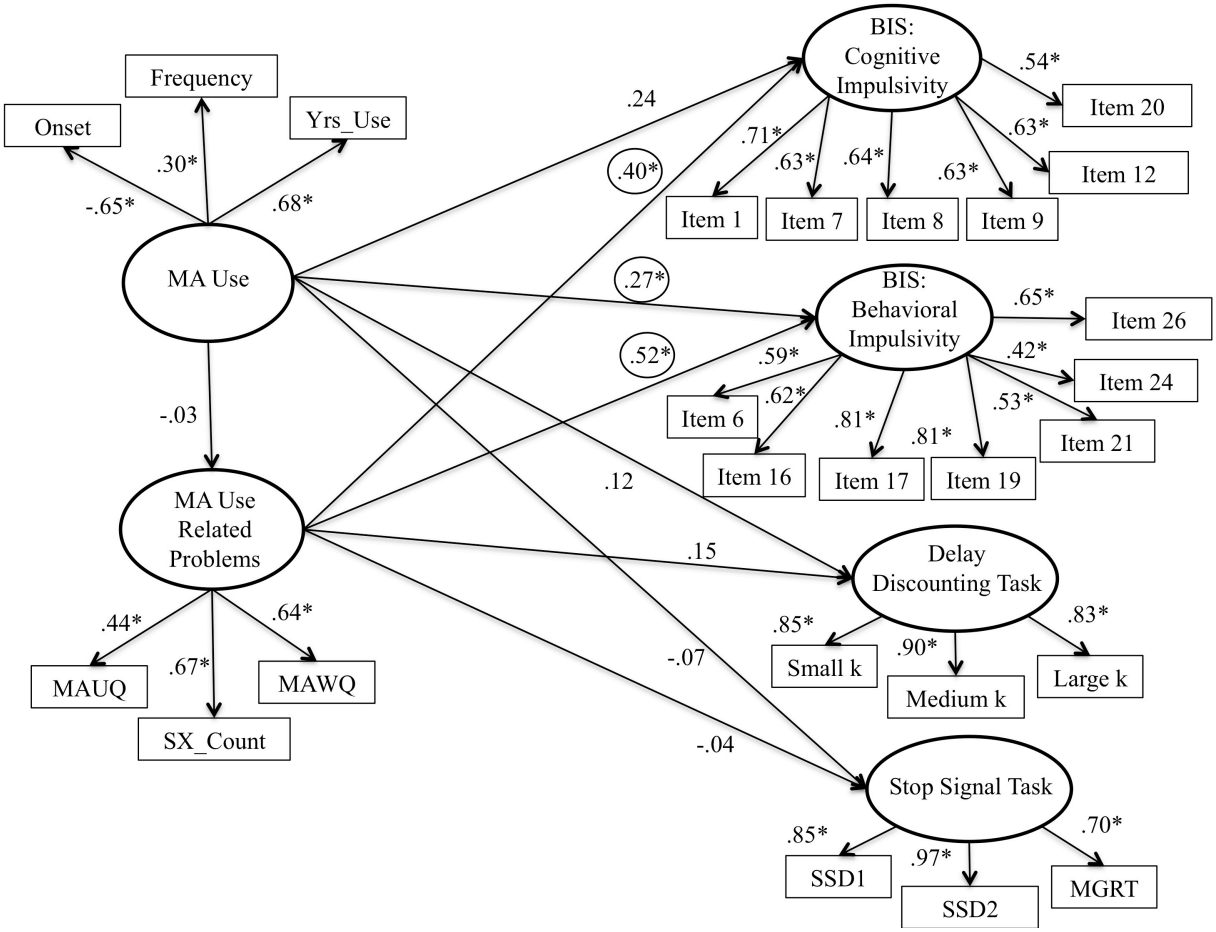
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); total years using MA (Yrs_Use); Barratt Impulsivity Scale (BIS); stop signal delay ladder 1 (SSD1); stop signal delay ladder 2 (SSD2); and mean go reaction time (MGRT).

Figure 4.



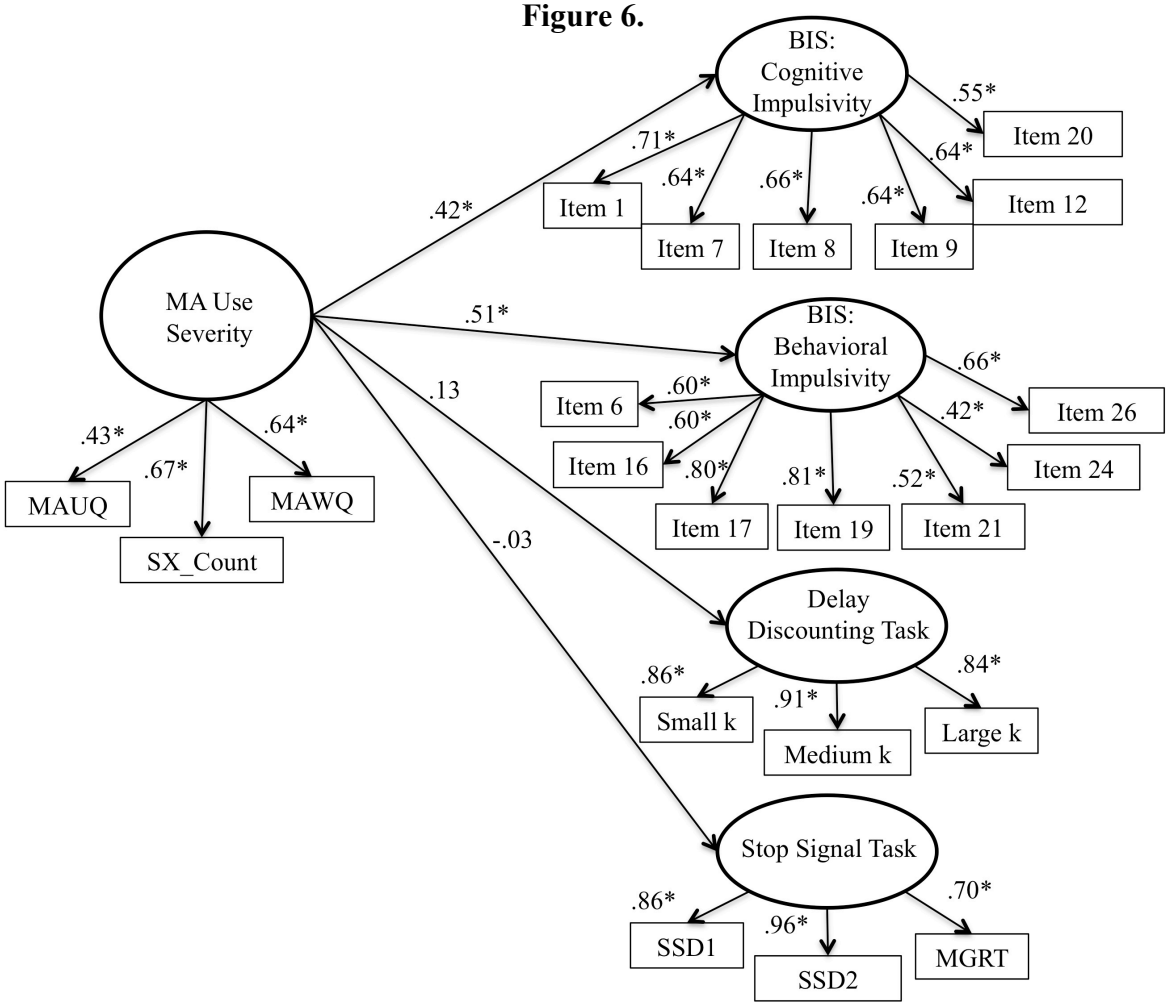
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); total years using MA (Yrs_Use); Barratt Impulsivity Scale (BIS); stop signal delay ladder 1 (SSD1); stop signal delay ladder 2 (SSD2); and mean go reaction time (MGRT).

Figure 5.



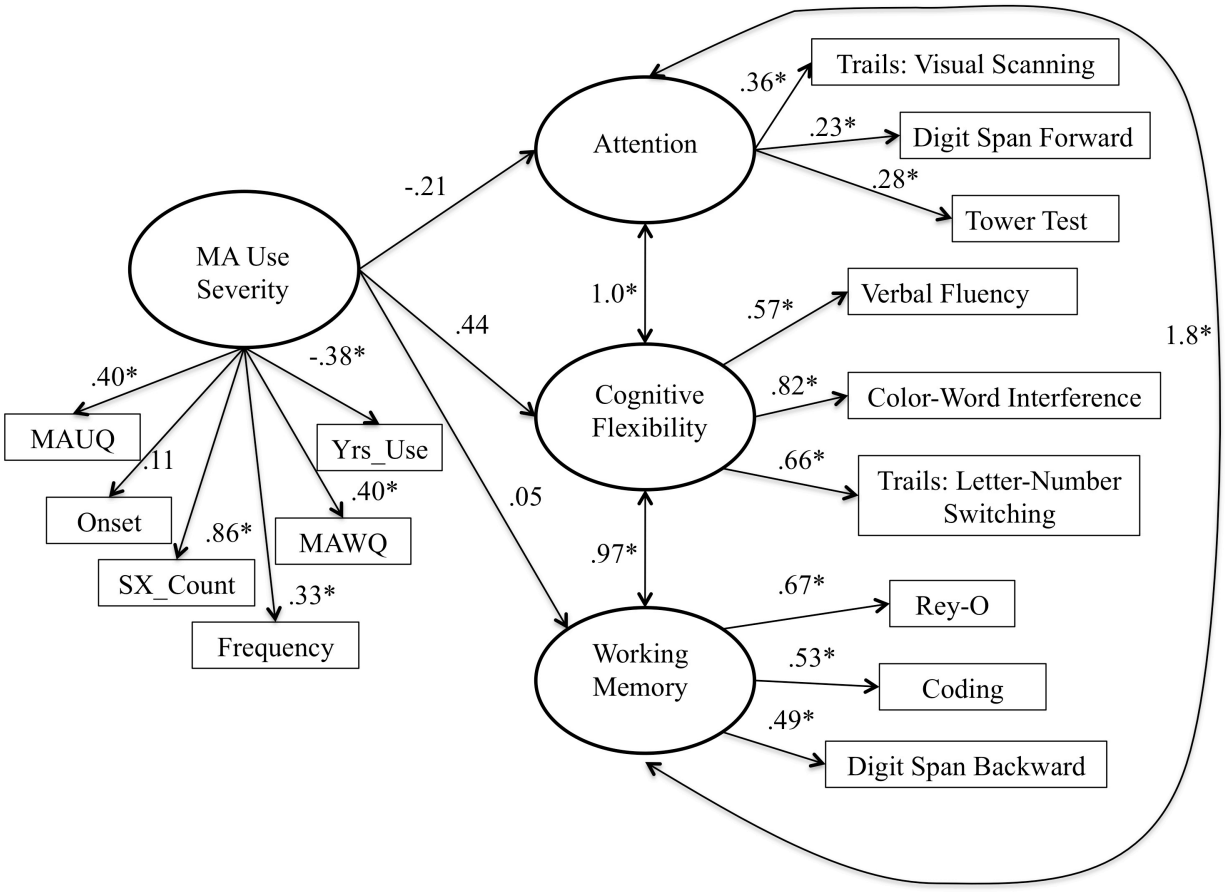
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); total years using MA (Yrs_Use); Barratt Impulsivity Scale (BIS); stop signal delay ladder 1 (SSD1); stop signal delay ladder 2 (SSD2); and mean go reaction time (MGRT).

Figure 6.



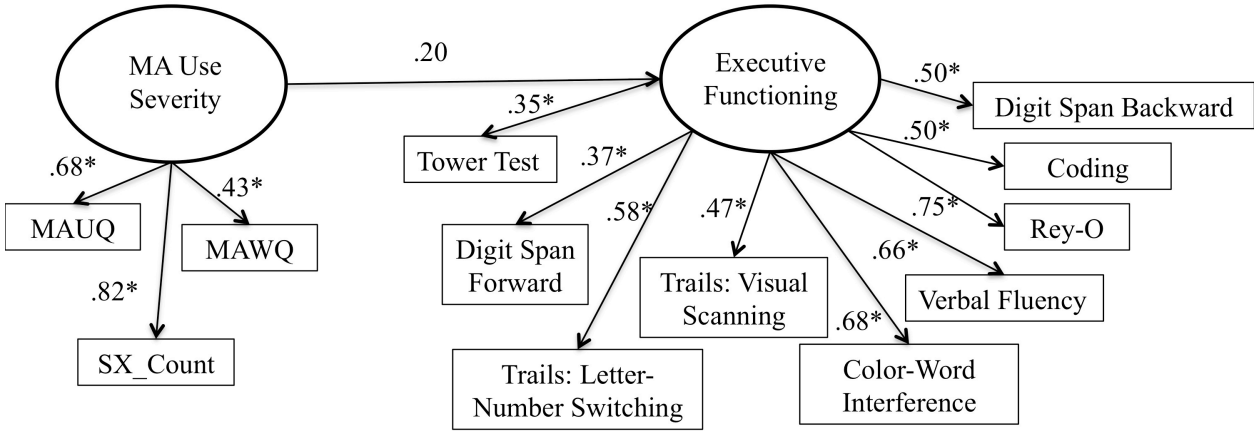
Note: MA Urge Questionnaire (MAUQ); number of diagnostic criteria met for MA use disorder (SX_Count); MA Withdrawal Questionnaire (MAWQ); Barratt Impulsivity Scale (BIS); stop signal delay ladder 1 (SSD1); stop signal delay ladder 2 (SSD2); and mean go reaction time (MGRT).

Figure 7.



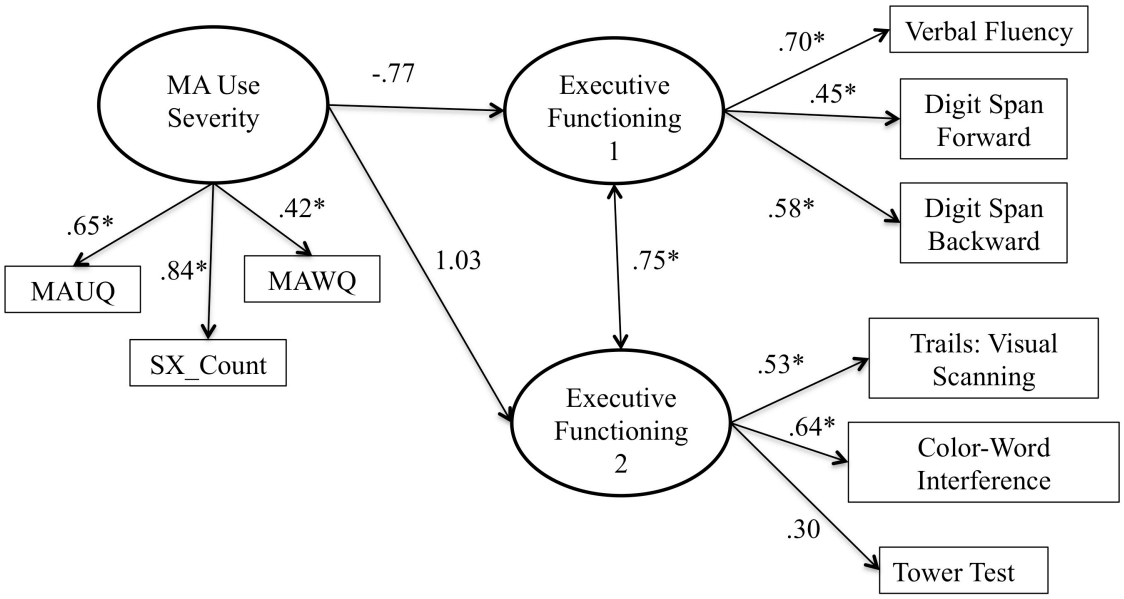
Note: MA Urge Questionnaire (MAUQ); age of onset of MA use (Onset); number of diagnostic criteria met for MA use disorder (SX_Count); number of days using MA out of the 30 days (Frequency); MA Withdrawal Questionnaire (MAWQ); and total years using MA (Yrs_Use).

Figure 8.



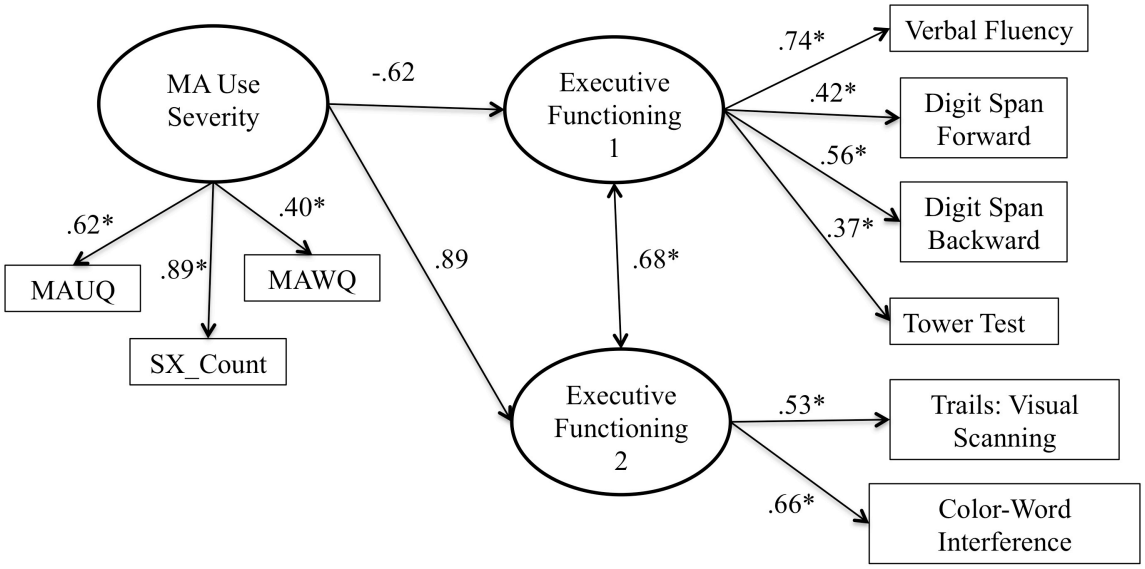
Note: MA Urge Questionnaire (MAUQ); number of diagnostic criteria met for MA use disorder (SX_Count); and MA Withdrawal Questionnaire (MAWQ).

Figure 9.



Note: MA Urge Questionnaire (MAUQ); number of diagnostic criteria met for MA use disorder (SX_Count); and MA Withdrawal Questionnaire (MAWQ).

Figure 10.



Note: MA Urge Questionnaire (MAUQ); number of diagnostic criteria met for MA use disorder (SX_Count); and MA Withdrawal Questionnaire (MAWQ).

Figure 11.

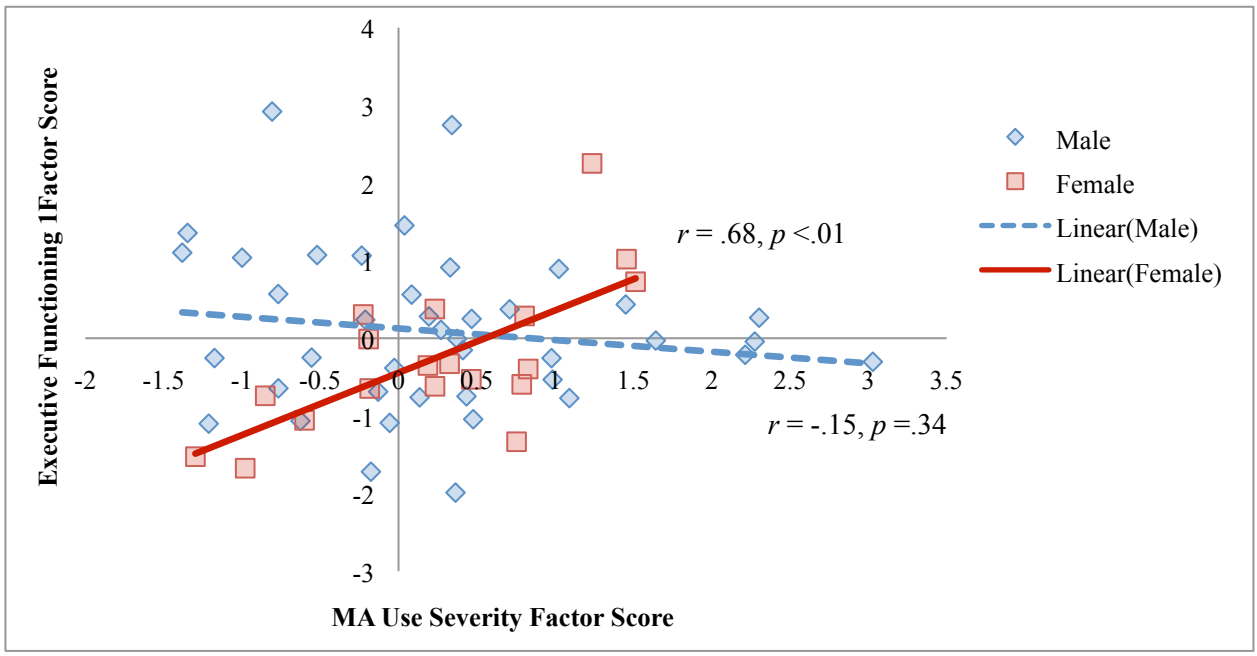
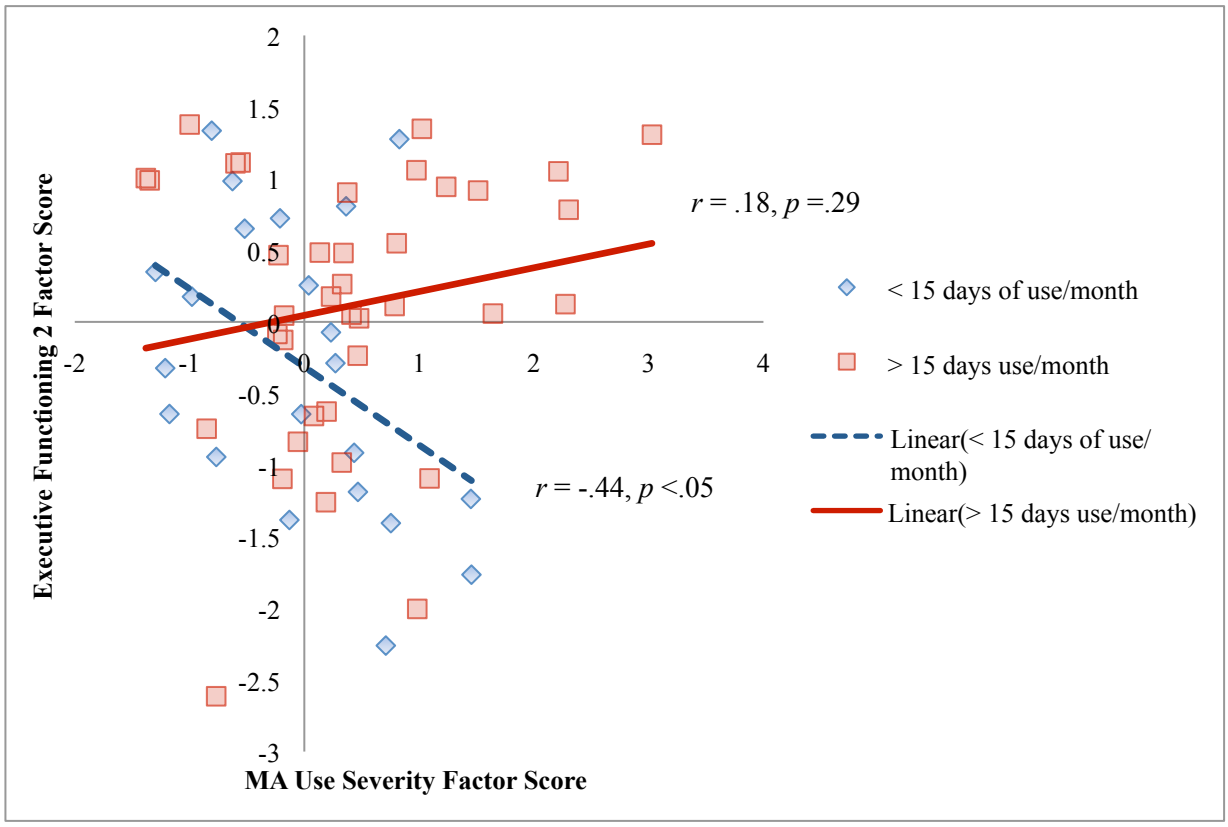

Executive Functioning 1Factor Score
MA Use Severity Factor Score
4
3
2
1
0
-1
-2
-3
-2
-1.5
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
r = .68, p <.01
r = -.15, p =.34
Male
Female
Linear(Male)
Linear(Female)

Figure 12.


Executive Functioning 2 Factor Score
MA Use Severity Factor Score
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-2.5
-3
-2
-1
0
1
2
3
4
r = .18, p =.29
r = -.44, p <.05
< 15 days of use/month
> 15 days use/month
Linear(< 15 days of use/ month)
Linear(> 15 days use/month)

References

Aharonovich, E., Hasin, D. S., Brooks, A. C., Liu, X., Bisaga, A., & Nunes, E. V. (2006). Cognitive deficits predict low treatment retention in cocaine dependent patients. *Drug Alcohol Depend, 81*(3), 313-322.

Aharonovich, E., Nunes, E., & Hasin, D. (2003). Cognitive impairment, retention and abstinence among cocaine abusers in cognitive-behavioral treatment. *Drug Alcohol Depend, 71*(2), 207-211.

Alvarez, J. A., & Emory, E. (2006). Executive function and the frontal lobes: a meta-analytic review. *Neuropsychol Rev, 16*(1), 17-42.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision)*.

Aron, A. R., Fletcher, P. C., Bullmore, E. T., Sahakian, B. J., & Robbins, T. W. (2003). Stop-signal inhibition disrupted by damage to right inferior frontal gyrus in humans. *Nat Neurosci, 6*(2), 115-116.

Ashenhurst, J. R., Bujarski, S., Jentsch, J. D., & Ray, L. A. (2014). Modeling behavioral reactivity to losses and rewards on the Balloon Analogue Risk Task (BART): moderation by alcohol problem severity. *Exp Clin Psychopharmacol, 22*(4), 298-306.

Aytaclar, S., Tarter, R. E., Kirisci, L., & Lu, S. (1999). Association between hyperactivity and executive cognitive functioning in childhood and substance use in early adolescence. *J Am Acad Child Adolesc Psychiatry, 38*(2), 172-178.

Baddeley, A. (1992). Working memory. *Science, 255*(5044), 556-559.

Baddeley, A., & Hitch, G. J. (1994). Developments in the concept of working memory. *Neuropsychology, 8*, 485-493.

Baicy, K., & London, E. D. (2007). Corticolimbic dysregulation and chronic methamphetamine abuse. *Addiction, 102 Suppl 1*, 5-15.

Bates, M. E., & Labouvie, E. W. (1997). Adolescent risk factors and the prediction of persistent alcohol and drug use into adulthood. *Alcohol Clin Exp Res, 21*(5), 944-950.

Bentler, P. M. (1990). Comparative fit indexes in structural models. *Psychol Bull, 107*(2), 238-246.

Bentler, P. M. (1995). EQS: Structural Equations Program Manual Encino, CA: Multivariate Software.

Bentler, P. M., & Weeks, D. G. (1980). Linear structural equations with latent variables. *Psychometrika, 45*, 289-308.

Browne, M. W., & Cudeck, R. (1993). Alternative ways of assessing model fit. In K. A. L. Bollen, J.S. (Ed.), *Testing Structural Models* (pp. 136-162). New York: Sage.

Byrne, B. M. (1989). *A Primer of LISREL: Basic Applications and Programming for Confirmatory Factor Analytic Models*. New York: Springer-Verlag.

Cherner, M., Suarez, P., Casey, C., Deiss, R., Letendre, S., Marcotte, T., . . . Heaton, R. K. (2010). Methamphetamine use parameters do not predict neuropsychological impairment in currently abstinent dependent adults. *Drug Alcohol Depend, 106*(2-3), 154-163.

Ciccarone, D. (2011). Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim Care, 38*(1), 41-58, v-vi.

Courtney, K. E., Arellano, R., Barkley-Levenson, E., Galvan, A., Poldrack, R. A., Mackillop, J., . . . Ray, L. A. (2012). The relationship between measures of impulsivity and alcohol misuse: an integrative structural equation modeling approach. *Alcohol Clin Exp Res, 36*(6), 923-931.

Courtney, K. E., Ghahremani, D. G., & Ray, L. A. (2013). Fronto-striatal functional connectivity during response inhibition in alcohol dependence. *Addict Biol, 18*(3), 593-604.

Cruickshank, C. C., & Dyer, K. R. (2009). A review of the clinical pharmacology of methamphetamine. *Addiction, 104*(7), 1085-1099.

Davidson, M. C., Amso, D., Anderson, L. C., & Diamond, A. (2006). Development of cognitive control and executive functions from 4 to 13 years: evidence from manipulations of memory, inhibition, and task switching. *Neuropsychologia, 44*(11), 2037-2078.

De Wit, H. (2009). Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addiction Biology, 14*(1), 22-31.

Dean, A. C., Groman, S. M., Morales, A. M., & London, E. D. (2012). An Evaluation of the Evidence that Methamphetamine Abuse Causes Cognitive Decline in Humans. *Neuropsychopharmacology*.

Dean, A. C., Sevak, R. J., Monterosso, J. R., Hellemann, G., Sugar, C. A., & London, E. D. (2011). Acute modafinil effects on attention and inhibitory control in methamphetamine-dependent humans. *J Stud Alcohol Drugs, 72*(6), 943-953.

Deckel, A. W., & Hesselbrock, V. (1996). Behavioral and cognitive measurements predict scores on the MAST: a 3-year prospective study. *Alcohol Clin Exp Res, 20*(7), 1173-1178.

Degenhardt, L., Bradley, M., Guarinieri, M., Panda, S., Phillips, B., Strathdee, S., . . . Wodak, A. (2007). *The global epidemiology of methamphetamine injection*. Sydney, Australia: University of New South Wales.

Diamond, A. (2013). Executive functions. *Annu Rev Psychol, 64*, 135-168.

Ersche, K. D., Jones, P. S., Williams, G. B., Turton, A. J., Robbins, T. W., & Bullmore, E. T. (2012). Abnormal brain structure implicated in stimulant drug addiction. *Science, 335*(6068), 601-604.

Ersche, K. D., & Sahakian, B. J. (2007). The neuropsychology of amphetamine and opiate dependence: implications for treatment. *Neuropsychol Rev, 17*(3), 317-336.

Everitt, B. J., & Robbins, T. W. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. *Nat Neurosci, 8*(11), 1481-1489.

Fergusson, D. M., Boden, J. M., & Horwood, L. J. (2008). The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. *Drug Alcohol Depend, 96*(1-2), 165-177.

Fernie, G., Cole, J. C., Goudie, A. J., & Field, M. (2010). Risk-taking but not response inhibition or delay discounting predict alcohol consumption in social drinkers. *Drug Alcohol Depend, 112*(1-2), 54-61.

Freye, E. (2010). Pharmacology of Methamphetamine *Pharmacology and Abuse of Cocaine, Amphetamines, Ecstasy and Related Designer Drugs: A comphrenesive review on their mode of action, treatment of abuse and intoxication* (pp. 119-124): Springer.

Galvan, A. (2010). Adolescent development of the reward system. *Front Hum Neurosci, 4*, 6.

Galvan, A., Hare, T. A., Parra, C. E., Penn, J., Voss, H., Glover, G., & Casey, B. J. (2006). Earlier development of the accumbens relative to orbitofrontal cortex might underlie risk-taking behavior in adolescents. *J Neurosci, 26*(25), 6885-6892.

Garon, N., Bryson, S. E., & Smith, I. M. (2008). Executive function in preschoolers: a review using an integrative framework. *Psychol Bull, 134*(1), 31-60.

Ghahremani, D. G., Tabibnia, G., Monterosso, J., Hellemann, G., Poldrack, R. A., & London, E. D. (2011). Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. *Neuropsychopharmacology, 36*(5), 950-959.

Goldstein, R. Z., & Volkow, N. D. (2002). Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry, 159*(10), 1642-1652.

Grant, I., Gonzalez, R., Carey, C. L., Natarajan, L., & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study. *J Int Neuropsychol Soc, 9*(5), 679-689.

Groman, S. M., Lee, B., Seu, E., James, A. S., Feiler, K., Mandelkern, M. A., . . . Jentsch, J. D. (2012). Dysregulation of D(2)-mediated dopamine transmission in monkeys after chronic escalating methamphetamine exposure. *J Neurosci, 32*(17), 5843-5852.

Harrison, E. L., Coppola, S., & McKee, S. A. (2009). Nicotine deprivation and trait impulsivity affect smokers' performance on cognitive tasks of inhibition and attention. *Exp Clin Psychopharmacol, 17*(2), 91-98.

Hart, C. L., Marvin, C. B., Silver, R., & Smith, E. E. (2012). Is cognitive functioning impaired in methamphetamine users? A critical review. *Neuropsychopharmacology, 37*(3), 586-608.

Harvey, D. C., Lacan, G., & Melegan, W. P. (2000). Regional heterogeneity of dopaminergic deficits in vervet monkey striatum and substantia nigra after methamphetamine exposure. *Exp Brain Res, 133*(3), 349-358.

Heatherton, T. F., Kozlowski, L. T., Frecker, R. C., & Fagerstrom, K. O. (1991). The Fagerstrom Test for Nicotine Dependence: a revision of the Fagerstrom Tolerance Questionnaire. *Br J Addict, 86*(9), 1119-1127.

Henry, B. L., Minassian, A., & Perry, W. (2010). Effect of methamphetamine dependence on everyday functional ability. *Addict Behav, 35*(6), 593-598.

Hillhouse, M. P., Marinelli-Casey, P., Gonzales, R., Ang, A., & Rawson, R. A. (2007). Predicting in-treatment performance and post-treatment outcomes in methamphetamine users. *Addiction, 102 Suppl 1*, 84-95.

Hoffman, W. F., Moore, M., Templin, R., McFarland, B., Hitzemann, R. J., & Mitchell, S. H. (2006). Neuropsychological function and delay discounting in methamphetamine-dependent individuals. *Psychopharmacology (Berl), 188*(2), 162-170.

Hu, L., & Bentler, P. M. (1995). Evaluating model fit In R. H. Hoyle (Ed.), *Structural Equation Modeling: Concepts, Issues, and Applications* (pp. 76-99). New York: Sage.

Hyman, S. E. (2005). Addiction: a disease of learning and memory. *Am J Psychiatry, 162*(8), 1414-1422.

Iudicello, J. E., Woods, S. P., Vigil, O., Scott, J. C., Cherner, M., Heaton, R. K., . . . Grant, I. (2010). Longer term improvement in neurocognitive functioning and affective distress among methamphetamine users who achieve stable abstinence. *J Clin Exp Neuropsychol, 32*(7), 704-718.

Izquierdo, A., Belcher, A. M., Scott, L., Cazares, V. A., Chen, J., O'Dell, S. J., . . . Marshall, J. F. (2010). Reversal-specific learning impairments after a binge regimen of methamphetamine in rats: possible involvement of striatal dopamine. *Neuropsychopharmacology, 35*(2), 505-514.

Jentsch, J. D., Ashenhurst, J. R., Cervantes, M. C., Groman, S. M., James, A. S., & Pennington, Z. T. (2014). Dissecting impulsivity and its relationships to drug addictions. *Ann N Y Acad Sci*.

Jentsch, J. D., & Taylor, J. R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl), 146*(4), 373-390.

Jovanovski, D., Erb, S., & Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *J Clin Exp Neuropsychol, 27*(2), 189-204.

Jurado, M. B., & Rosselli, M. (2007). The elusive nature of executive functions: a review of our current understanding. *Neuropsychol Rev, 17*(3), 213-233.

Kalechstein, A. D., Newton, T. F., & Green, M. (2003). Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *J Neuropsychiatry Clin Neurosci, 15*(2), 215-220.

Kalivas, P. W., & Volkow, N. D. (2005). The neural basis of addiction: a pathology of motivation and choice. *Am J Psychiatry, 162*(8), 1403-1413.

Katz, E. C., King, S. D., Schwartz, R. P., Weintraub, E., Barksdale, W., Robinson, R., & Brown, B. S. (2005). Cognitive ability as a factor in engagement in drug abuse treatment. *Am J Drug Alcohol Abuse, 31*(3), 359-369.

Kilpatrick, D. G., Acierno, R., Saunders, B., Resnick, H. S., Best, C. L., & Schnurr, P. P. (2000). Risk factors for adolescent substance abuse and dependence: data from a national sample. *J Consult Clin Psychol, 68*(1), 19-30.

King, G., Alicata, D., Cloak, C., & Chang, L. (2010). Neuropsychological deficits in adolescent methamphetamine abusers. *Psychopharmacology (Berl), 212*(2), 243-249.

Kirby, K. N., Petry, N. M., & Bickel, W. K. (1999). Heroin addicts have higher discount rates for delayed rewards than non-drug-using controls. *J Exp Psychol Gen, 128*(1), 78-87.

Koob, G. F. (1992). Neural mechanisms of drug reinforcement. *Ann N Y Acad Sci, 654*, 171-191.

Koob, G. F. (2003). Alcoholism: allostasis and beyond. *Alcohol Clin Exp Res, 27*(2), 232-243.

Kreek, M. J., Nielsen, D. A., Butelman, E. R., & LaForge, K. S. (2005). Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. *Nat Neurosci, 8*(11), 1450-1457.

Lawrence, A. J., Luty, J., Bogdan, N. A., Sahakian, B. J., & Clark, L. (2009). Impulsivity and response inhibition in alcohol dependence and problem gambling. *Psychopharmacology (Berl), 207*(1), 163-172.

Lee, B., London, E. D., Poldrack, R. A., Farahi, J., Nacca, A., Monterosso, J. R., . . . Mandelkern, M. A. (2009). Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci, 29*(47), 14734-14740.

London, E. D., Berman, S. M., Voytek, B., Simon, S. L., Mandelkern, M. A., Monterosso, J., . . . Ling, W. (2005). Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. *Biol Psychiatry, 58*(10), 770-778.

MacKillop, J., Amlung, M. T., Few, L. R., Ray, L. A., Sweet, L. H., & Munafo, M. R. (2011). Delayed reward discounting and addictive behavior: a meta-analysis. *Psychopharmacology (Berl), 216*(3), 305-321.

Mahmood, O. M., Goldenberg, D., Thayer, R., Migliorini, R., Simmons, A. N., & Tapert, S. F. (2013). Adolescents' fMRI activation to a response inhibition task predicts future substance use. *Addict Behav, 38*(1), 1435-1441.

Mark, K. A., Soghomonian, J. J., & Yamamoto, B. K. (2004). High-dose methamphetamine acutely activates the striatonigral pathway to increase striatal glutamate and mediate long-term dopamine toxicity. *J Neurosci, 24*(50), 11449-11456.

McCann, U. D., Kuwabara, H., Kumar, A., Palermo, M., Abbey, R., Brasic, J., . . . Ricaurte, G. A. (2008). Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. *Synapse, 62*(2), 91-100.

McCann, U. D., Wong, D. F., Yokoi, F., Villemagne, V., Dannals, R. F., & Ricaurte, G. A. (1998). Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: evidence from positron emission tomography studies with [11C]WIN-35,428. *J Neurosci, 18*(20), 8417-8422.

McKetin, R., & Mattick, R. P. (1998). Attention and memory in illicit amphetamine users: comparison with non-drug-using controls. *Drug Alcohol Depend, 50*(2), 181-184.

Monterosso, J. R., Aron, A. R., Cordova, X., Xu, J., & London, E. D. (2005). Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend, 79*(2), 273-277.

Monti, P. M., Tidey, J., Czachowski, C. L., Grant, K. A., Rohsenow, D. J., Sayette, M., . . . Pierre, P. (2004). Building bridges: the transdisciplinary study of craving from the animal laboratory to the lamppost. *Alcohol Clin Exp Res, 28*(2), 279-287.

Nation, M., & Heflinger, C. A. (2006). Risk factors for serious alcohol and drug use: the role of psychosocial variables in predicting the frequency of substance use among adolescents. *Am J Drug Alcohol Abuse, 32*(3), 415-433.

National Institute on Drug Abuse. (Revised 2013). *Methamphetamine Abuse and Addiction*. NIH Publication Number 13-4210.

Nestor, L. J., Ghahremani, D. G., Monterosso, J., & London, E. D. (2011). Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. *Psychiatry Res, 194*(3), 287-295.

Nicosia, N., Pacula, R. L., Kilmer, B., Lundberg, R., & Chiesa, J. (2009). *The Economic Cost of Methamphetamine Use in the United States, 2005*. Santa Monica: RAND Corporation.

Paulson, P. E., Camp, D. M., & Robinson, T. E. (1991). Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. *Psychopharmacology (Berl), 103*(4), 480-492.

Rawson, R. A., & Condon, T. P. (2007). Why do we need an Addiction supplement focused on methamphetamine? *Addiction, 102 Suppl 1*, 1-4.

Ray, L. A. (2012). Clinical neuroscience of addiction: Applications to psychological science and practice. *Clin Psychol Sci Prac 19*, 154-166.

Ray, L. A., Bujarski, S., Courtney, K. E., Moallem, N. R., Lunny, K., Roche, D., . . . Miotto, K. (2015). The Effects of Naltrexone on Subjective Response to Methamphetamine in a Clinical Sample: a Double-Blind, Placebo-Controlled Laboratory Study. *Neuropsychopharmacology*.

Reise, S. P., Moore, T. M., Sabb, F. W., Brown, A. K., & London, E. D. (2013). The Barratt Impulsiveness Scale-11: reassessment of its structure in a community sample. *Psychol Assess, 25*(2), 631-642.

Richards, J. B., Sabol, K. E., & de Wit, H. (1999). Effects of methamphetamine on the adjusting amount procedure, a model of impulsive behavior in rats. *Psychopharmacology (Berl), 146*(4), 432-439.

Rippeth, J. D., Heaton, R. K., Carey, C. L., Marcotte, T. D., Moore, D. J., Gonzalez, R., . . . Grant, I. (2004). Methamphetamine dependence increases risk of neuropsychological impairment in HIV infected persons. *J Int Neuropsychol Soc, 10*(1), 1-14.

Robinson, T. E., & Becker, J. B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res, 396*(2), 157-198.

Robinson, T. E., & Berridge, K. C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res Brain Res Rev, 18*(3), 247-291.

Robinson, T. E., & Berridge, K. C. (2001). Incentive-sensitization and addiction. *Addiction, 96*(1), 103-114.

Robinson, T. E., & Berridge, K. C. (2008). Review. The incentive sensitization theory of addiction: some current issues. *Philos Trans R Soc Lond B Biol Sci, 363*(1507), 3137-3146.

Robinson, T. E., Browman, K. E., Crombag, H. S., & Badiani, A. (1998). Modulation of the induction or expression of psychostimulant sensitization by the circumstances surrounding drug administration. *Neurosci Biobehav Rev, 22*(2), 347-354.

Salo, R., Nordahl, T. E., Galloway, G. P., Moore, C. D., Waters, C., & Leamon, M. H. (2009). Drug abstinence and cognitive control in methamphetamine-dependent individuals. *J Subst Abuse Treat, 37*(3), 292-297.

Salo, R., Nordahl, T. E., Moore, C., Waters, C., Natsuaki, Y., Galloway, G. P., . . . Sullivan, E. V. (2005). A dissociation in attentional control: evidence from methamphetamine dependence. *Biol Psychiatry, 57*(3), 310-313.

Salo, R., Nordahl, T. E., Possin, K., Leamon, M., Gibson, D. R., Galloway, G. P., . . . Sullivan, E. V. (2002). Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Res, 111*(1), 65-74.

Satorra, A., & Bentler, P. (2001). A scaled difference chi-square test statistic for moment structure analysis *Psychometrika, 66*, 507-514.

Schultz, W. (2010). Dopamine signals for reward value and risk: basic and recent data. *Behav Brain Funct, 6*, 24.

Schultz, W., Dayan, P., & Montague, P. R. (1997). A neural substrate of prediction and reward. *Science, 275*(5306), 1593-1599.

Scott, J. C., Woods, S. P., Matt, G. E., Meyer, R. A., Heaton, R. K., Atkinson, J. H., & Grant, I. (2007). Neurocognitive effects of methamphetamine: a critical review and meta-analysis. *Neuropsychol Rev, 17*(3), 275-297.

Seiden, L. S., & Sabol, K. E. (1996). Methamphetamine and methylenedioxymethamphetamine neurotoxicity: possible mechanisms of cell destruction. *NIDA Res Monogr, 163*, 251-276.

Seiden, L. S., Sabol, K. E., & Ricaurte, G. A. (1993). Amphetamine: effects on catecholamine systems and behavior. *Annu Rev Pharmacol Toxicol, 33*, 639-677.

Semple, S. J., Zians, J., Grant, I., & Patterson, T. L. (2005). Impulsivity and methamphetamine use. *J Subst Abuse Treat, 29*(2), 85-93.

Shoptaw, S., Peck, J., Reback, C. J., & Rotheram-Fuller, E. (2003). Psychiatric and substance dependence comorbidities, sexually transmitted diseases, and risk behaviors among methamphetamine-dependent gay and bisexual men seeking outpatient drug abuse treatment. *J Psychoactive Drugs, 35 Suppl 1*, 161-168.

Simon, S. L., Dacey, J., Glynn, S., Rawson, R., & Ling, W. (2004). The effect of relapse on cognition in abstinent methamphetamine abusers. *J Subst Abuse Treat, 27*(1), 59-66.

Simon, S. L., Domier, C., Carnell, J., Brethen, P., Rawson, R., & Ling, W. (2000). Cognitive impairment in individuals currently using methamphetamine. *Am J Addict, 9*(3), 222-231.

Simon, S. L., Domier, C. P., Sim, T., Richardson, K., Rawson, R. A., & Ling, W. (2002). Cognitive performance of current methamphetamine and cocaine abusers. *J Addict Dis, 21*(1), 61-74.

Sobell, L. C., Brown, J., Leo, G. I., & Sobell, M. B. (1996). The reliability of the Alcohol Timeline Followback when administered by telephone and by computer. *Drug Alcohol Depend, 42*(1), 49-54.

Sobell, L. C., & Sobell, M. B. (1980). *Convergent validity: An approach to increasing confidence in treatment outcome conclusions with alcohol and drug abusers, in evaluating alcohol and drug abuse treatment effectiveness: Recent advances.* Elmsford, NY: Pergamon Press.

Sofuoglu, M. (2010). Cognitive enhancement as a pharmacotherapy target for stimulant addiction. *Addiction, 105*(1), 38-48.

Sofuoglu, M., DeVito, E. E., Waters, A. J., & Carroll, K. M. (2013). Cognitive enhancement as a treatment for drug addictions. *Neuropharmacology, 64*, 452-463.

Squeglia, L. M., Jacobus, J., & Tapert, S. F. (2009). The influence of substance use on adolescent brain development. *Clin EEG Neurosci, 40*(1), 31-38.

Srisurapanont, M., Jarusuraisin, N., & Jittiwutikan, J. (1999a). Amphetamine withdrawal: I. Reliability, validity and factor structure of a measure. *Aust N Z J Psychiatry, 33*(1), 89-93.

Srisurapanont, M., Jarusuraisin, N., & Jittiwutikan, J. (1999b). Amphetamine withdrawal: II. A placebo-controlled, randomised, double-blind study of amineptine treatment. *Aust N Z J Psychiatry, 33*(1), 94-98.

Steiger, J. H. (1990). Structural model evaluation and modification: an interval estimation approach. *Multivariate Behav Res, 25*, 173-180.

Streeter, C. C., Terhune, D. B., Whitfield, T. H., Gruber, S., Sarid-Segal, O., Silveri, M. M., . . . Yurgelun-Todd, D. A. (2008). Performance on the Stroop predicts treatment compliance in cocaine-dependent individuals. *Neuropsychopharmacology, 33*(4), 827-836.

Substance Abuse and Mental Health Services Administration. (2013). *Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings*. Rockville, MD.

Substance Abuse and Mental Health Services Administration. (2014). *Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings*. Rockville, MD.

Tanaka, J. S. (1993). Multifaceted conceptions of fit in structural equation models. In K. A. L. Bollen, J.S. (Ed.), *Testing Structural Equation Models*. Newbury Park, CA: Sage.

Tapert, S. F., Brown, S. A., Myers, M. G., & Granholm, E. (1999). The role of neurocognitive abilities in coping with adolescent relapse to alcohol and drug use. *J Stud Alcohol, 60*(4), 500-508.

Tapert, S. F., Granholm, E., Leedy, N. G., & Brown, S. A. (2002). Substance use and withdrawal: neuropsychological functioning over 8 years in youth. *J Int Neuropsychol Soc, 8*(7), 873-883.

Tapert, S. F., Ozyurt, S. S., Myers, M. G., & Brown, S. A. (2004). Neurocognitive ability in adults coping with alcohol and drug relapse temptations. *Am J Drug Alcohol Abuse, 30*(2), 445-460.

Tarter, R. E., Kirisci, L., Mezzich, A., Cornelius, J. R., Pajer, K., Vanyukov, M., . . . Clark, D. (2003). Neurobehavioral disinhibition in childhood predicts early age at onset of substance use disorder. *Am J Psychiatry, 160*(6), 1078-1085.

Teichner, G., Horner, M. D., Roitzsch, J. C., Herron, J., & Thevos, A. (2002). Substance abuse treatment outcomes for cognitively impaired and intact outpatients. *Addict Behav, 27*(5), 751-763.

Tziortzis, D., Mahoney, J. J., 3rd, Kalechstein, A. D., Newton, T. F., & De La Garza, R., 2nd. (2011). The relationship between impulsivity and craving in cocaine- and methamphetamine-dependent volunteers. *Pharmacol Biochem Behav, 98*(2), 196-202.

Valadez, A., & Schenk, S. (1994). Persistence of the ability of amphetamine preexposure to facilitate acquisition of cocaine self-administration. *Pharmacol Biochem Behav, 47*(1), 203-205.

Vocci, F. J. (2008). Cognitive remediation in the treatment of stimulant abuse disorders: a research agenda. *Exp Clin Psychopharmacol, 16*(6), 484-497.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Ding, Y. S., Sedler, M., . . . Pappas, N. (2001). Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry, 158*(12), 2015-2021.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Franceschi, D., Sedler, M., . . . Logan, J. (2001). Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J Neurosci, 21*(23), 9414-9418.

Volkow, N. D., Chang, L., Wang, G. J., Fowler, J. S., Leonido-Yee, M., Franceschi, D., . . . Miller, E. N. (2001). Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry, 158*(3), 377-382.

Volkow, N. D., Fowler, J. S., Wang, G. J., Baler, R., & Telang, F. (2009). Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology, 56 Suppl 1*, 3-8.

Volkow, N. D., Wang, G. J., Fowler, J. S., & Tomasi, D. (2012). Addiction circuitry in the human brain. *Annu Rev Pharmacol Toxicol, 52*, 321-336.

Walter, A. W., Bachman, S. S., Reznik, D. A., Cabral, H., Umez-Eronini, A., Nath, A., . . . Young, N. S. (2012). Methamphetamine use and dental problems among adults enrolled in a program to increase access to oral health services for people living with HIV/AIDS. *Public Health Rep, 127 Suppl 2*, 25-35.

Weiss, F., Martin-Fardon, R., Ciccocioppo, R., Kerr, T. M., Smith, D. L., & Ben-Shahar, O. (2001). Enduring resistance to extinction of cocaine-seeking behavior induced by drug-related cues. *Neuropsychopharmacology, 25*(3), 361-372.

Wilens, T. E., Martelon, M., Fried, R., Petty, C., Bateman, C., & Biederman, J. (2011). Do executive function deficits predict later substance use disorders among adolescents and young adults? *J Am Acad Child Adolesc Psychiatry, 50*(2), 141-149.

Winhusen, T., Lewis, D., Adinoff, B., Brigham, G., Kropp, F., Donovan, D. M., . . . Somoza, E. (2013). Impulsivity is associated with treatment non-completion in cocaine- and

methamphetamine-dependent patients but differs in nature as a function of stimulant-dependence diagnosis. *J Subst Abuse Treat, 44*(5), 541-547.

Winward, J. L., Hanson, K. L., Tapert, S. F., & Brown, S. A. (2014). Heavy alcohol use, marijuana use, and concomitant use by adolescents are associated with unique and shared cognitive decrements. *J Int Neuropsychol Soc, 20*(8), 784-795.

World Health Organization. (2004). *Neuroscience of psychoactive substance use and dependence*. Geneva, Switzerland.