ABSTRACT

The Effects of Prior Exposure to Methylphenidate on Later Methamphetamine Self-Administration

Clifton E. Haacker

Director: Erika Abel Ph.D.

Methylphenidate is the most common stimulant drug of choice for the treatment of Attention Deficit Hyperactivity Disorder. With a growing ADHD population, there is concern of overdiagnosis that may lead to the inappropriate use of stimulant medication. This study was designed to examine the impacts of MPH use in individuals who do not have ADHD. It is hypothesized that prior exposure to stimulant medication may have on later substance use, particularly illicit stimulants Research implicates that prior exposure to stimulant medication may play a role in later psychostimulant use and is effected by dose. This study demonstrates, both through experimentation and a review of the literature, how prior stimulant exposure relates to Methamphetamine self-administration. Further research is need to fully assess the impact that Methylphenidate use has in the general population regarding methamphetamine use. This work also proposes comparative studies for ADHD populations and possible age-related effects of Methylphenidate use.

APPROVED BY DIRECTOR OF HONORS THESIS:

_____

Dr. Erika Abel, Department of Biochemistry

APPROVED BY THE HONORS PROGRAM:

_____

Dr. Elizabeth Corey, Director

DATE:_____

THE EFFECTS OF PRIOR EXPOSURE TO METHYLPHENIDATE ON LATER METHAMPHETAMINE SELF- ADMINISTRATION

A Thesis Submitted to the Faculty of

Baylor University

In Partial Fulfillment of the Requirements for the

Honors Program

By

Clifton E. Haacker

Waco, Texas

May 2020

TABLE OF CONTENTS

Table of Charts and Figures. ii

Acknowledgements. iii

Chapter 1: Relationship between Methylphenidate and Methamphetamine. . . 1

Chapter 2: Effects of Stimulant Exposure on the Acquisition of Methamphetamine Self-Administration. 32

Chapter 3: Results and Discussion. 41

Chapter 4: Discussion of Risk Factors and Future Research. 51

Bibliography. 62

LIST OF TABLES AND FIGURES

Table 1: Rat Postnatal Days as Compared to Human Age. 36

Figure 1: Methamphetamine Response curve for Saline-treated rats. . . 42

Figure 2: Methamphetamine Response Curve for Methylphenidate-treated rats. . 43

Figure 3: Overall Response Comparison of Methamphetamine Administration. . 44

Figure 4: Overall Response Comparison of Methamphetamine Administration. . 45

ACKNOWLEDGEMENTS

The completion of this Honors thesis would not have been possible without the assistance of faculty and staff in the lab of Dr. Nicholas Goeders. His research at the Louisiana State University Health Science Center helped me to get into this field of neuropharmacological research. I would also like to thank Dr. Courtney Keller, a post doctorate in the lab, for helping to set up this experiment and for data collection and analysis. This project would not have been possible without the initial idea and set up arranged by her. I would also like to thank the committee members, Dr. Brad Keele and Dr. Alexander Engebretson, who contributed their time, both to my personal education and to reviewing my thesis and serving on my defense panel. Their constructive criticism and challenge to think critically was of great value.

I would like to extend a special thanks to Dr. Erika Abel, my advisor and mentor throughout this process. The completion of this thesis would have been impossible without her commitment, guidance, and encouragement. Dr. Abel made this experience enriching and satisfying and devoted many hours to its successful completion. I could not have done it without her assistance, and I truly appreciate her investment in my education.

CHAPTER ONE

Relationship Between Methylphenidate and Methamphetamine

Introduction

Methylphenidate (MP, MPH, Ritalin) is the primary psychostimulant drug used in treatment of Attention Deficit Hyperactivity Disorder (ADHD). It is effective in reducing symptoms in up to 70% of cases (Greenhill et al., 2002). Therapeutic doses of MPH can effectively improve cognitive function while reducing hyperactivity in both ADHD and non-ADHD populations (Cheng et al., 2014). With increases in ADHD prevalence, there has also come an increase in misdiagnosis (Thomas et al., 2015). Increase in misdiagnosis may be due to several factors, (i.e. difference in criteria, country, time, etc.), but the focus is on the prescription of stimulants if an individual is misdiagnosed. Human studies show that the use of MPH in non-ADHD populations has serious implications. It can produce agitation, restlessness, and hallucinations (Klein-Schwartz., 2002; Bruggisser et al., 2011; Morton & Stockton., 2000). Misuse of the drug may become a problem. The abuse of this drug may have reinforcing effects (Volkow et al., 2002).The use and misuse of this stimulant drug may then be relevant to additional comorbidities in all populations. Rat models show that healthy individuals respond to the reinforcing effects of MPH at higher rates than ADHD populations (Jaboinski et al., 2015). Prior exposure to MPH, in addition to increased incentivization of reward by MPH, may cause an individual to be prone to later psychostimulant use. This is in accordance with the incentivization effect produced by MPH (Brenhouse et al., 2009). These data suggest further investigation of the relationship between prior exposure of MPH and subsequent stimulant use.

MPH is a schedule II medication, with a black box warning for potential abuse. It shares a similar mechanism with amphetamines, which also have abuse potential. This is due to their effects on catecholamine transmission in the prefrontal cortex. Despite the pharmacological similarities between the amphetamines and MPH there are several important differences between these drugs. The drugs differ slightly in their neurochemical mechanisms of action (Ritz and Kuhar, 1989) and in their effects on the release and transmission of catecholamines. Differences have also been reported in the subjective responses to these drugs (Smith and Davis, 1977), but these may be dose dependent. This highlights the possibility that while amphetamines and MPH may differ in their reinforcing effects and in their abuse potential (Chait, 1994), there is a correlation between the two.

With such high prevalence of use and variability in effects, it is imperative to understand the mechanisms of how MPH works and associated brain regions. This is particularly relevant to non-ADHD individuals who do not have the cognitive deficits of ADHD and, by definition, misuse the drug. Its action as a stimulant medication, and abuse as such, may have implications in the use of other stimulant substances. The mechanism by which a therapeutic dose of MPH acutely improves cognitive functioning is known. The effects of how larger doses of MPH produce side effects is unclear. It is important to understand the abuse potential and long-term toxicity of MPH, as well as its association with use of other stimulant drugs. The increase in MPH usage, increase in ADHD among younger populations, (Gahr and Plener., 2016) and the lack of knowledge surrounding long-term effects of psychostimulants on neuronal development are all concerns. The investigation of how MPH works in ADHD populations may give insight on how it works in general populations. To understand the mechanisms of MPH in the treatment of ADHD,

it is important to understand ADHD. An understanding of how it improves cognitive functioning in deficit individuals may help rationalize why MPH is abused in the general population.

ADHD and concerns regarding Methylphenidate treatment

Attention-deficit hyperactivity disorder (ADHD) is one of the most prevalent cognitive and behavioral disorders treated among youth today (Spencer, Biederman, & Mick., 2007). With an overall prevalence around 11% (The Center for Disease Control and Prevention., 2019) the need for research of treatment for the disorder has become increasingly necessary. The increase in stimulant drug use may pose problems in treatment and in later development. (Morton et al., 2000). ADHD is a major clinical and public health concern due to the cognitive impairment it can induce in childhood, adolescence and persistence into adulthood. ADHD has the potential to apply a high burden of stress on the individual and their families and friends. These interpersonal effects may have a broader impact on the lives of people with ADHD. An examination of the psychological and sociological impacts of ADHD over a lifetime reveals other, comorbid, diagnoses. Multiple studies have shown that individuals diagnosed with ADHD are at an increased risk of developing additional psychopathologies in childhood, adolescence, and adulthood, including antisocial, mood, anxiety, and substance use disorders (Biederman et al., 1995). Misuse of MPH may be enhanced by these comorbid disorders. (Kollins et al., 2008).

Diagnostic Criteria

ADHD is characterized by its early-onset inattention, hyperactivity, and impulsivity. The *Diagnostic and Statistical Manual of Mental Disorders V* (DSM 5)

presents ADHD symptomology into three subcategories: an inattentive subtype, a hyperactive-impulsive subtype, and a combined subtype. To qualify for the diagnosis of the inattentive subtype of ADHD , the individual must have six or more symptoms of inattention for children up to age 16, or five or more for adolescents 17 and older. The symptoms of inattention must be present for at least 6 months and must be considered inappropriate for the individual's developmental level. To qualify, presentations include being easily distracted, being forgetful in daily activities, and not listening, even when being spoken to directly. The hyperactive-impulsive subtype has the same requirements and presents with frequent fidgeting, excessive talking, and interrupting or intruding on other's personal space. In addition, other conditions must be met for all types, such as being present before the age of 12, being present in more than one setting, and must be debilitating without interference from other disorders. The disorder is often first observed in early childhood. The peak age for the appearance of ADHD symptoms is between three and four years of age (Palfrey, Levine, Walker, & Sullivan, 1985; Biederman et al., 1998). Many overactive children may show signs or symptoms of ADHD without having the disorder and will not go on to develop ADHD. Those that do go on to develop ADHD show a distinctive progression that may help with making the diagnosis.

Prevalence of ADHD

Prevalence estimates of childhood ADHD are between 2-10% (Young et al., 2014; Polanczyk et al., 2007), with a decline of prevalence in adulthood. Prevalence drops to 2-5% into adulthood (Barkley et al., 2010). This can vary by gender and subtype, but overall, there is a decrease in ADHD symptomology with increasing age. There is sufficient

evidence that the prevalence of the disorder is of public concern, but prevalence estimates may vary due to several factors. Estimates may vary based on the method of acquisition, subtype inclusion, age, and gender. The research methodology to estimate prevalence of ADHD varies by inclusion criteria, included impairments, pervasiveness in a certain area, the informants reliability, and type of assessment used (Rowlan et al., 2013).Gender and age affect the estimates of prevalence and are closely linked with the subtype breakdown. ADHD is generally more prevalent amongst males, and manifestations vary by gender. Males tend to exhibit hyperactivity and impulsivity more frequently, while females tend to exhibit the inattentive subtype. These differences in subtype yield different impairments. (Miller et al., 2010). The inattentive subtype tends to have fewer emotional and behavioral problems compared to the other subtypes. Inattention (inattentive or combined) tends to suggest a more significant academic impairment. The combined subtype is the most at-risk for co-occurring psychiatric and substance abuse and is the most impaired overall. (Molina et al., 2003). All subtypes present with adverse educational and subsequent career outcomes, as well as issues related to self-esteem, which may lead to increased crime rates and personality disorders (Spencer, Biederman, & Mick., 2007).

ADHD Symptomology over Patient Lifespan

In order to be diagnosed with ADHD, an individual must manifest symptoms before the age of twelve (DSM-V: American Psychiatric Association, 2013). The peak age for the symptoms of ADHD to appear is between three and four years of age (Palfrey, Levine, Walker, & Sullivan, 1985; Biederman et al., 1998). According to developmental models, preschoolers diagnosed with ADHD tend to be characterized predominantly by hyperactive

symptoms, whereas older affected children show inattentive symptoms, in addition to hyperactivity and impulsivity (Barkley, Koplowitz, Anderson, & McMurray, 1997). During adolescence and adulthood, hyperactivity symptoms decline, while attention deficits tend to persist with age (Biederman, Mick & Faraone, 2000). The prefrontal cortex (PFC) plays a significant role in this transition and in the persistence of symptoms; it is one of the last parts of the brain to develop during maturation and is responsible for higher cognitive functioning. The dysregulation of the frontal lobe is an important area of interest in ADHD treatment. Brain imaging studies show a shift in the focus and location of brain abnormalities from the midbrain in childhood to the prefrontal cortex (PFC) in adulthood, and this area is the primary target for drug actions (Arnsten et al., 2006; Schulz et al., 2005).

To be diagnosed with ADHD, adults must have a childhood-onset of the disorder and show both persistent and current symptoms of ADHD that are not the results of any other confounding comorbidities (Faraone et al., 2005). Adults often present with similar symptomology: inattention, distractibility, organizational difficulty; these symptoms are reminiscent of those seen in childhood and culminate in life histories of academic and occupational difficulties. There is a relative decline of ADHD symptoms from childhood to early adulthood. It has been shown that there is a symptomatic decline for inattention and hyperactivity/ impulsivity at a modest rate. In terms of duration, it has also been shown that the disorder can persist and continue into adulthood in about 40% of the affected population. This means that these individuals have a higher comorbidity rate of developing a mood disorder, antisocial personality disorder, and/or substance abuse problems (Faraone

et al., 1997). The importance of these personality coaggregates suggests a biological underpinning that can influence psychosocial factors and impact an individual's life.

Specifically, the symptoms of inattention tend to decline at a more modest rate as compared to the hyperactive-impulsive types that are much more abrupt (Hart et al., 1995). Inattentive symptoms tend to remain relatively stable throughout the teenage years and are the ones most likely to carry over into adulthood. This points to a distinct age-related shift in the symptom expression of ADHD that may have major implications in treatment and subsequent comorbid diagnosis. Those who have symptoms that persist into adulthood can be partially predicted by parental psychopathology, psychiatric comorbidity, and impulsive symptomology (Biederman, Mick & Faraone., 1998). This is confirmed by the fact that ADHD adults have, on average, more psychopathologies. Along with ADHD, lower socioeconomic status, fewer years of education, and lower employment that are all risk factors for psychopathology (Prince, Morrison, & Wilens., 2015).

ADHD and its associated psychopathologies may have implications on the development of a substance use disorder. Many of these factors are qualitative predictors of later substance use (Courtmney & Ray.,2014). Among patients with substance use disorders, those with ADHD had strong predictors of maladjustment, immaturity, fewer social assets, lower occupational achievement, and high rates of separation and divorce (Wilens, Biederman, & Mick., 1998). These comorbid factors have high overlap with the diagnosis of ADHD. In examining how a child with ADHD may become an adult who uses illicit substances, it is important to understand the neurobiology of the disorder itself. The deficits in individuals with ADHD help to show the effects of MPH. With examination of the circuitry and mechanisms associated with MPH, its long-lasting effects become more

apparent. The effects of MPH over time may explain the use of illicit substances in adulthood.

Neurobiology of ADHD

The underlying neural circuits of ADHD contribute to the dysfunctional nature of the disorder. Most prominently, data suggests a weak frontal cortical inhibitory control over limbic functions. These frontoparietal intracortical circuits are important for attenuating attention and orienting responses. Also, in the prefrontal cortex (PFC), there is a dorsal frontostriatal circuit that is composed of the dorsolateral PFC, dorsal striatum, and thalamus that executes its effects on inhibitory control. The last pathway that has been determined in the PFC is the mesocorticolimbic pathway, containing the orbitofrontal cortex, ventral striatum (with nucleus accumbens), and the anterior hippocampus, which helps regulate anticipation of reward and motivation. The common factor between these circuits is that they exert their effects through the innervation of dopaminergic or noradrenergic effects (Faraone & Biederman., 1998).

In terms of the exact catecholaminergic dysregulation underlying ADHD, less is known. It appears that both dopamine release by nigrostriatal and mesolimbic dopaminergic neurons and dysregulation of noradrenergic pathways of the locus coeruleus play a role in the hyperactivity and inattention of the disorder. This understanding can provide insight into the possible mechanisms of drug treatment and the actions of MPH in both the ADHD and general populations. Understanding this deficit may provide insight into the mechanism of action for MPH in producing cognitive enhancements. MPH is a drug with a high potential for increasing cognitive effects and should be looked at

objectively to determine its effects independent of ADHD. MPH produces many effects among non-ADHD individuals. Understanding the effects of MPH in individuals without the deficits of ADHD may be useful for assessing its abuse potential and later effects.

Methylphenidate Mechanism

MPH is in the same stimulant class as the amphetamines, including methamphetamine, since it is similar to isomeric forms of amphetamine. MPH peak level of efficacy and activity is reached 8–20 min after administration and is similar to amphetamine in that regard. MPH can easily pass the blood-brain barrier, exerting most of its effects through concentrates of catecholamines in the brain. MPH works through a rapid uptake into the brain but has a much lower rate of clearance from the brain than other stimulants (Swanson et al., 2002). Its longer effect does have a role in its misuse as it allows for a more controlled stimulant experience. It also explains the why the pattern of abuse may differ from other amphetamines.

The dopamine transporter (DAT) and norepinephrine transporter (NET) mediate the reuptake of catecholamines into the presynaptic terminals. They are blocked by MPH, preventing the inward transport of DA and NE, thus elevating the concentration of dopamine and norepinephrine at the synapse and in the extracellular space (Berridge et al., 2006). MPH also affects the vesicular monoamine transporters (VMAT) that load neurotransmitters into vesicles for release. MPH effectively redistributes VMAT and its associated vesicle in the nerve terminal from the synaptosomal membrane to the cytoplasm, increasing transmission. Specifically, MPH works by blocking DA transporters in the striatum and has stimulatory effects on D_1 receptors in the PFC, reducing hyperactivity.

The prefrontal cortex (PFC) helps to mediate cognitive end executive functioning and is the main target of MPH (Arnsten., 2009). Delayed maturation of the PFC (Shaw et al., 2007), dysfunction of the frontostriatal circuitry (Arnsten., 2006), and hypoactivation of the frontal cortex (Cortese et al., 2012) have been implicated in ADHD. There may also be effects on D_2 type receptors, but these are not well documented. While the distribution of MPH in the brain is heterogeneous, binding is much higher in the basal ganglia, the brain region with the highest density of DAT (Volkow et al., 2002). The therapeutic effect of MPD in the treatment of ADHD is its ability to bind to the DAT in the presynaptic cell membrane and block the re-uptake of DA. This causes an increase in extracellular DA levels, an effect that has been linked to its reinforcing properties. In rats, MPD administration in low doses (2.0–5.0 mg/kg) stimulates locomotor activity and in high doses (10.0 mg/kg and higher) stimulates stereotypical behavior (Achat-Mendes et al., 2003).

It has also been shown that the drug works on NE through action at postsynaptic α_{2A} adrenoceptors in the PFC, promoting working memory, response inhibition, and lessened distractibility. There is also evidence that low doses of MPH have effects on NE in the hippocampus (HP), while still affecting NE in the PFC. The evidence for this comes from the fact that NE play a role in working memory, which is linked to the long-term memory associated with the hippocampus (Berridge et al., 2006). This theory of functioning is confirmed in the event of very high levels of DA and NE release, in which the PFC does not exert proper functioning. The mechanisms of which are most likely due to DA, D_1 ,and D_4 receptors and NE α1 and β1 receptors. The glutamatergic system is involved in synaptic plasticity and cognitive processes (Cheng et al., 2014), and may be

part of the neuronal mechanism of MPH. A study by Cheng et al., found that in adolescent rats, administration of low-dose MPH potentiates NMDAR trafficking and function through the norepinephrine system, thus enhancing PFC-mediated cognition. High doses of MPH suppress PFC glutamatergic transmission and induces hyperlocomotion.

Dose-Response to Methylphenidate

Studies have shown that cognitive improvement is achieved when MPH is administered at relatively low doses, and there is no clinically relevant cognitive improvement at higher dosages. Increases behavioral effects (i.e. those seen with amphetamine) are seen with higher doses of MPH (Swanson et al., 2011; Yang et al., 2006). The dose response to MPH, often measured by catecholamine presence, shows an inverted U-shape curve (Yang et al., 2006). With low doses of MPH not producing any relevant effects and large doses producing adverse side-effects. Intermediate levels of MPH are the most clinically relevant, giving the optimal cognitive enhancement for an individual. Immediate-release MPH is usually given to children in 5-30 mg doses up to twice a day and can go up to 60 mg a day (Kidd., 2000). More specifically, oral doses are typically given between 18-54 mg, once daily (Anderson & Keating., 2007). Correct dosage can vary by individual depending on age, weight, and gender. Patients usually begin with a relatively low dose which is titrated until symptoms subside. MPH is commonly administered orally and is completely dispensed throughout the bloodstream in 1 to 3 hours, which corresponds with the most notable behavioral changes (Swanson et al., 1998). The half-life of MPH is roughly 2 to 3 hours, with a range up to 5, unless a long release acting form is used.

MPH exerts its effects in the ventral tegmental area (VTA), locus coeruleus (LC), and in the PFC in a dose-dependent manner. By using in vivo micro-dialysis testing, MPH has been shown to act in a dose-dependent manner on DA levels in the PFC, with doses of clinical efficacy having the greatest effect (Urban & Gao., 2015). Behavioral results, like locomotor calming and cognitive enhancement, are a result of the combination of locus coeruleus modulation and increased catecholamine release and uptake in the PFC. Specifically, the catecholamines work through a combination of adrenergic α2 and dopaminergic D_1 receptors (Arnsten & Dudley., 2005). These specific pathways and receptors may be the targets responsible for drug effects and overuse of them may play a role in the sensitization seen with chronic MPH use.

Animal studies have raised concern over stimulant treatment due to findings regarding sensitization of drug effects. The sensitization hypothesis, a neuroadaptation model, maintains that exposure to stimulants results in alterations in the DA system, which increases sensitivity to the reinforcing effects of the previously experienced substance. Behavioral sensitization has been demonstrated in a number of mammalian species, including nonhuman primates, and has been found to be long-lasting (Robinson & Becker, 1986). Consistent with this model, some studies have suggested that there may be a causal link between stimulant treatment in adolescence and later substance abuse. Both in regard to MPH itself and other psychostimulants (Kollins et al.,2001; Vitiello et al., 2001). The potential role of previous stimulants in the pathogenesis of substance use disorder is a major public health concern, since stimulant use is widespread and stimulants are increasingly prescribed to young children (Zito, 2000). Some animal studies have also reported developmental effects of stimulant sensitization. Specifically, with earlier MPH

treatment in adolescence there is a decrease in psychostimulant use later. Opposed to later MPH treatment in adolescence, where later stimulant use is more prevalent. This shows that while sensitization may occur in older individuals, there may be a protective effect at younger ages (Andersen, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon, 2001; Brandon, Marinelli, Baker, & White, 2001). This also suggests that age of exposure may modulate long-term drug effects on the brain. However, no study has examined the exact association between age at first exposure to stimulants and later substance use disorder.

Age-Related Effects of Methylphenidate

MPH may produce specific age-related effects during certain stages of development. In studies conducted with preschoolers, there have been improved outcomes on Gordon's visual CPT, a test of continuous performance on a task, and on a visual and auditory vigilance tests with the use of MPH. School-age ADHD children treated with MPH showed enhanced maintenance of attention, accuracy, working memory, and ability to block out additional stimuli (Rapport et al., 1987). It has been demonstrated that attention intensity is best accelerated by higher MPH doses (Denney & Rapport, 2001), whereas executive functions are best influenced by moderate doses (Tannock, Ickowicz, & Schachar 1995; Konrad, Günther, Hanisch, & Herpertz-Dahlmann 2004). The difference here is that among preschoolers, the majority of subjects showed deficits in the supervisory attention system, which in mediated by the PFC and striatal structure. This would lead to higher doses needed earlier in childhood for the most appropriate effects. Grade-schoolers were more impaired in the selectivity and intensity domains of attention (Hanisch, Konrad, Günther, & Herpertz-Dahlmann, 2004). Leading towards more moderate doses with

increase in age. This points to a marked transition period around the time of maturation from childhood to adolescent, possibly mediated by the neurobiological changes associated with maturation. The sustained exposure of MPH in juvenile rat brains showed a cross-sensitization of dopamine-related responses in the PFC and nucleus accumbens. This may create a predicted protective factor in younger individuals who use more MPH in treatment.

The late prefrontal cortical development is of particular relevance in the treatment of ADHD and may highlight the differential effects between the juvenile and adult brain. In a study by Humphreys et al., (2013) MPH during adolescence promotes desensitization and may predispose an individual to later stimulant use. These important neural changes take place within the dopaminergic circuitry of the PFC during development. The changes may also persist into adulthood and could have cognitive effects in the adult brain.

This idea of age-related effects can be further emphasized by looking at adult studies, in which there is marked hypoactivity in the PFC (Ernst et al., 1998). This may suggest a discrepancy between PFC functioning outcomes in adults versus adolescents. Administration of equivalent doses of MPH to adults and adolescents reveals a potential for long-lasting PFC changes in MPH-treated children (Urban et al., 2012). Specifically, this long-term treatment may up-regulate the DA transporter in certain parts of the brain that reflects the mechanisms of some psychostimulants. This creates a sensitization effects in those who have a longer history of use with MPH. This adaptation may have neuroplastic consequences with a further decrease in DA signaling when the individual with ADHD is not medicated, and a loss of efficacy for MPH (Wang et al., 2013). Contributing to this was the finding by Kuzenski et al., (2002) detailing how MPH prevented cross-sensitization through increased hippocampal norepinephrine, but not nucleus accumbens dopamine

release. This is particular to the adolescent brain. It points towards a potential abuse of the drug and additional psychostimulant use.

Furthermore, there are age-dependent effects of MPH on development of prefrontal neurons. Since MPH works by blocking DA and NE transporters, thereby increasing the concentrations of both. It is possible that there are long term effects through compensation of decreased catecholamine transmission via up-regulation of receptors. High doses of MPH have significant suppressant effects on the excitability of juvenile PFC neurons. With long-term misuse of MPH , there may be a decreased response to MPH in adults, pointed towards age-related effects (Berridge et al., 2006). Long-term abuse of MPH at a young age may then affect the ability to activate the same stimulant mechanisms later in life. This has implications for illicit substance use. It has also been suggested that there are fewer receptor terminals in the PFC of adults who have ADHD. The DA increases in the ventral striatum in particular are associated with long-term symptom improvement in adults with ADHD (Devilbiss & Berridge., 2008). In terms of the long-term use of MPH, it is important to look at the short-term effects that it has in the prefrontal cortex and subcortical structure. This would help to determine possible effects that increased catecholamines may have on respective areas necessary for cognitive functioning and sensitization (Yang et al., 2007). Overall, it can be said that chronic use of MPH elicits plasticity in the PFC that is dependent upon age and needs further investigation.

Abuse Potential of Methylphenidate

Currently, there are two methods of thinking when it comes to the abuse potential of MPH. The first suggests that the earlier someone is exposed to a drug that has the

potential for abuse, such as MPH, the greater the risk that there will be recurring signs of drug abuse and dependence later in adulthood. This especially common in academic settings, shown in studies of college students(Teter et al., 2003: DuPoint et al., 2008: Outram et al., 2010), that look at the abuse of MPH in relation to other stimulant use. In contrast, the second model proposes the opposite: that stimulant treatment of adolescents with ADHD medication may actually reduce the prevalence of substance use later on due to the lack of novelty in higher dose stimulants that one may use. Since the population in question does not have the cognitive deficits of ADHD, the former argument is the most applicable.

Some research suggests that MPH has a significant abuse potential ,such as amphetamine and cocaine. Abuse happens at a much lower rate and is more dose-dependent. These effects have more implications in non-ADHD individuals because the drug is not compensating for ADHD-associated deficits. MPH was found to have more reinforcing effects in the general population than in an ADHD population (Jaboinski et al., 2015). MPH works very similarly to these other stimulants in the neurotransmitter systems it affects. The main effects of MPH are on extracellular dopamine, norepinephrine, and serotonin and contribute to its abuse potential.

Dopamine is the main catecholamine affected by MPH and is the most relevant for stimulant saliency, making it the main target for drug abuse. This makes it a prime suspect for the potential overlap in mechanisms of MPH and psychostimulants. The general mechanism of MPH is its ability to bind to the DA transporter (DAT) in the presynaptic membrane, inhibiting DA uptake. The blockage of DAT is the initial trigger that MPH increases synaptic and extracellular DA (Volkow et al., 2002).It binds with a potency

similar to that of amphetamines (Arnold et al., 2000). As a result, it appears to have its effect in the caudate putamen (CP), increasing extracellular DA and causing an excitatory response. The caudate putamen is innervated by dopaminergic neurons from the Substania Nigra, whereas the ventral portion, the nucleus accumbens (NAc), is innervated by dopaminergic neurons from the ventral tegmental area (VTA). Both are sites of DA production and are part of the DA reward pathways that produce the reinforcing effects of drugs.

In terms of saliency, DA cells fire at increased rates to rewarding stimuli. This points towards the role of DA in relevancy and attenuation. This may contribute to the therapeutic use of MPH, which relies on increasing DA transmission. In a study by Volkow et al., (2008) it was shown that MPH produces a significant increase of DA in the dorsal striatum, supporting the role of MPH in signal enhancement for appetitive stimuli. The increase in DA increases the incentive salience of the conditioned stimulus. This, in turn, increases the motivational state of an individual for that particular reward, without enhancing its hedonic properties. In a follow up study in humans, Volkow et al.,(2004) showed the context-dependency of the ability of MPH to increase extracellular DA. This has significant clinical relevance if someone decides to use Ritalin in a context-dependent manner. This may create an abuse of the drug or may lead to other context-specific behaviors that may be relevant to stimulant use.

The time course for MPH activity differs with route of administration. Intravenous MPH peaks in the brain at around 8-15 minutes after administration and gives the highest potential for abuse. (Parran and Jasinski., 1991). When given orally, this peak is shifted to around 60-90 minutes after administration (Volkow et al., 2002). The slow uptake of MPH

would predict a low abuse potential for the oral administration of the drug, since the rate of entrance into the brain is correlated with its reinforcing effects. Taking more than recommended doses can substantially increase the abuse potential or oral administration of MPH (Morton & Stockton., 2000). This is of particular concern in the general population and may contribute to excessive drug use, whose effects cause sensitization to other stimulants

Behavioral Sensitization

Behavioral and locomotor sensitization refers to a phenomenon whereby the repeated administration of stimulants produces a progressive augmentation of responses. It persists for a long time and is thought to be one of the early manifestations of neuronal plasticity associated with chronic administration of a drug of abuse. It may play a central role in the development of addictive behavior, especially in the high rate of relapse that occurs after a period of abstinence (Robinson et al., 1993). MA has already shown to produce behavioral sensitization (Pierce and Kalivas., 1997), and has connections with MPH sensitization effects (Meririnne et al., 2001).

Behavioral experiments in animal models have shown that repeated exposure to psychostimulants produce behavioral sensitization (Yang et al., 2007). This is induced by intermittent administration of low doses of psychostimulants, such as with MPH treatment, while higher doses produce tolerance. Behavioral sensitization is manifested by neuronal plasticity with repeated administration of psychostimulants and may play a role in addictive behavior (Robinson and Berridge., 1993).Similarly, chronic MPH elicited plasticity in the PFC, showing neurophysiological sensitization to MPH (Yang et al., 2007).

Behavioral sensitization provides an animal model for the induction of persistent changes in the neural circuitry of motivation and reward. This is a result of chronic exposure to psychostimulants. Several scientific reviews have also suggested the importance of behavioral sensitization as a model for drug craving (Pierce and Kalivas ., 1997; Robinson & Berridge., 2000) thus, behavioral sensitization can serve as a model to study the induction of persistent changes in the neuronal circuitry of motivation and reward following chronic exposure to psychostimulants. (Kalivas et al., 1998; Robinson et al., 1993).

Repeated MPH administration elicits behavioral sensitization. Behavioral sensitization exhibits two distinct temporal profiles: induction/initiation and expression. There is evidence suggesting that the induction and the expression of behavioral sensitization to psychostimulants involve different anatomical and physiological mechanisms. The induction of behavioral sensitization is defined as the transient sequence of cellular and molecular events precipitated by psychostimulants that leads to the enduring changes in neuronal function responsible for behavioral augmentation. The dopaminergic (DA) neurons within the ventral tegmental area (VTA) are believed to mediate the induction of behavioral sensitization to psychostimulants (Kalivas et al., 1993; Pierce et al., 1997). MPH increases dopamine, and this increase in DA is the underlying mechanism of behavioral sensitization and psychosis induced by psychostimulants, as well as of craving/drug addiction. The expression of behavioral sensitization is defined as the neural alteration arising from the initiating process that mediates the augmented behavioral response for a prolonged period of time. There is some evidence indicating that behavioral sensitization is mediated by the nucleus accumbens (NAc) (Pierce et la., 1995). The

neuronal network that contributes to the long-term expression of behavioral sensitization to psychostimulants is distributed among several interconnected mesolimbic nuclei, the 'motive circuit' (Kalivas et al., 1993; Pierce et al., 1997). This sensitization may have effects on the theory of prior exposure leading to increased psychostimulant use.

ADHD Treatment as a Risk Factor for Methamphetamine Use

Repeated exposure to psychostimulants like cocaine and amphetamine has been shown to elicit adverse effects in behavior such as sensitization, dependence, and abuse (Segal et al., 1981; Robinson & Becker, 1986; Kalivas et al., 1998). More importantly, behavioral cross-sensitization, a phenomenon involving behavioral augmentation that occurs when pretreatment with one stimulant leads to greater sensitivity to another (Aizenstein et al., 1990), has been found to occur between amphetamine and cocaine (Bonate et al., 1997). Studies have also demonstrated that repeated exposure to nicotine, caffeine, and amphetamine (i.e. low-dose stimulants) enhances the likelihood that the subject will later acquire cocaine self-administration (i.e. high-dose stimulants) (Horger et al., 1992; Schenk et al., 1994; Schenk and Davidson, 1998). Stimulant drug pre-exposure, therefore, may influence a subject's subsequent vulnerability to substance abuse as demonstrated by the presence of cross-sensitization between stimulants.

MPH is a derivative of. and structurally related to amphetamine. The neuropharmacologic profile of MPH is similar to that of other stimulants (Hoffman and Lefkowitz,1996). Methylphenidate has an abuse potential similar to that of D-amphetamine and cocaine (Kollins et al., 2001) Furthermore, methylphenidate and cocaine show similar pharmacokinetic and pharmacodynamic profiles in the human brain (Volkow et al., 1995)

and have very similar actions at the dopamine transporter (Volkow et al., 1999). Dopamine neurotransmission is central to this model of ADHD and SUD, and replicated evidence in studies of both have shown a blunted striatal DA release and disrupted neural circuitry between the anterior cingulate cortex and striatum with the PFC (Frodl., 2010). The model of this association suggests a dysregulation in ventrolateral frontal, cingulate cortices, and basal ganglia regions in both ADHD and SUD. Because of its structural and pharmacological similarity to drugs such as cocaine and D-amphetamine, there is reason to suspect that methylphenidate may have significant abuse potential in all populations.

There is sensitization that occurs in response to exposure of the MPH at a young age (Yang et al., 2003; Valvassori et al., 2007). Intermittent stimulant use may lead to an enduring behavioral response pattern of re-administration if the effects are rapid enough, as is the case with other stimulants (Radfar et a., 2014). Repeated exposure to psychostimulants such as cocaine, amphetamine, and MPH has been found to elicit locomotor sensitization (Robinson and Berridge, 1993; Kalivas, 1995; Gaytan et al., 1997a; Kuczenski and Segal,2001; Yang et al., 2001). Locomotor sensitization results from a variety of neuroadaptations associated with processes underlying addiction (Robinson and Berridge, 1993; White and Kalivas, 1998); therefore, sensitization is believed to be a crucial component in the development of drug dependence, i.e., sensitization and cross-sensitization between different drugs are considered as markers/indicators of drug dependence (Robinson and Becker, 1986). It has been reported that prolonged exposure to a psychostimulant could enhance a person's susceptibility to substance abuse(Robinson and Berridge,1993; Schenk and Davidson, 1998; Brandon et al., 2001; Schenk and Izenwasser, 2002).

Although MPD, cocaine, and amphetamine enhance dopamine levels by different mechanisms, it is possible that these psychostimulants exert their effects via a common site of drug-transmitter interaction that leads to their stimulating effects(Aizenstein et al., 1990). All of these drugs increase locomotor activity. The observations that MPD elicits sensitization and cross-sensitizes with cocaine and amphetamine provide additional evidence that MPH has the characteristics of a drug of abuse like methamphetamine. Pretreatment with MPH then enhances the subject's responsiveness to methamphetamine ,supporting some existing evidence that repeated pretreatment with MPH can influence subsequent exposures to other drugs (Yang et al., 2003).

Definition of Addiction

Drug addiction is a chronic relapsing disorder expressed by craving, protracted abstinence, and sensitization of the neuronal system. Addiction is most commonly seen as a pattern of drug-taking and drug-seeking behavior. It forms from an initial impulsive stage in which the individual is driven by positive reinforcement to take the drug for the rewarding effects. Over time, through intermittent remission and relapse, the individual is driven into a compulsive cycle of drug taking. This is done to relieve withdrawal symptoms and escape from the pain of not having their substance in this negative feedback loop (Koob & Volkow, 2016; American Psychiatric Association, 2013).

Reward Systems

The reward circuitry consists of an 'in-series' circuit that consists of the ventral tegmental area, nucleus accumbens and ventral pallidum via the medial forebrain. This system is responsible for the rewarding properties of the drug, attentiveness to stimuli,

expectancy of reward, disconfirmation of reward expectancy, and incentive motivation. The hedonic dysregulation of the reward pathway is a major factor in addiction (Volkow et al., 2011). The dopaminergic regulation in the reward circuitry is the crucial addictive-drug-sensitive component. All addictive drugs enhance dopaminergic reward synaptic function in the nucleus accumbens. . The drug enhances the rewarding properties of the system by increasing extracellular DA in the NAcc, by either enhancing VTA firing or acting locally to release DA from dopaminergic nerve terminals and then blocking its reuptake. These drug-induced elevation in DA are similar to an increase in firing of the dopaminergic neurons and cause an activation of the low-affinity D_1 neurons (Koob, 2005). Addictive drugs can produce tolerance to the euphoric effects of the system. This means that there is an allostatic shift in the hedonic state of the individual to where it now takes drug use to induce a normal functioning state, as the baseline for homeostasis has shifted (Sterling & Eyer, 1988). This develops with chronic use. This is when addicts no longer use drugs to get high, but to maintain normalcy.

The brain circuits mediating the pleasurable effects of addictive drugs are different from those mediating physical dependence, and from those mediating craving and relapse. (Robinson & Berridge, 1993) . There are important genetic variations in vulnerability to drug addiction, yet environmental factors such as stress and social defeat also alter brain-reward mechanisms in such a manner as to impart vulnerability to addiction. Drug addiction progresses from occasional recreational use to impulsive use to habitual compulsive use. This correlates with a progression from reward-driven to habit-driven drug-seeking behavior. This behavioral progression correlates with a neuroanatomical progression from ventral striatal (nucleus accumbens) to dorsal striatal control over drug-

seeking behavior. Drug-triggered relapse involves the nucleus accumbens and the neurotransmitter dopamine. Stress-triggered relapse involves the central nucleus of the amygdala, the bed nucleus of the stria terminalis, the neurotransmitter corticotrophin-releasing factor, and the lateral tegmental noradrenergic nuclei of the brain stem and the neurotransmitter norepinephrine. Cue-triggered relapse involves the basolateral nucleus of the amygdala, the hippocampus and the neurotransmitter glutamate. (Koob & LeMoal, 2008; Koob 2009, 2015). The antireward system refers to this mechanism of a between-system change, that involves corticotropin-releasing factor increase in response to excessive activation of the reward system under stress. The combination of both a deficit in the reward system and recruitment of the brain stress systems provides a powerful motivational state mediated in part by the antireward system (Koob & Le Moal 2005).

Theories of Addiction

There are three general theories of how addiction develops over the course of drug use. The gateway theory poses that drug use usually begins in adolescence and progresses from legal substances, such as alcohol and tobacco, to marijuana or potentially harder drugs (Swendsen & LeMoal, 2011). The second theorized progression consists of a cycle of pathological drug use that consists of three stages: preoccupation-anticipation, binge-intoxication, and withdrawal-negative affect. This causes a sort of spiraling distress that will eventually lead to addiction (Koob and LeMoal,1997). The repeated use of a drug can lead to physical dependence, giving rise to unpleasant withdrawal, or abstinence syndrome. This is in contrast to the initial positive effects of the drug in the impulsive stage through the mesolimbic reward pathway. This hypothesized shift to the compulsive stage enacts

this aversive symptom and contribute to the continued relapse behavioral, through the recruitment of the antireward system (Koob & LeMoal, 2005).

The last theory of addiction is the opponent-process model (Solomon & Corbit, 1974). The recruitment of the reward system as already been discussed, but it is this antireward system associated with later drug use happens after dependence has been established. In this stage, drug-use is motivated by negative reinforcement. Use of the drug helps to alleviate aversive withdrawal symptoms through the antireward system. This system is comprised of the extended amygdala and is activated during stress and drug withdrawal. Activation of this system results in increased release of norepinephrine (NE), cortical releasing factor (CRF), and dynorphin, and endogenous opioids. These factors help to address stress and pain. The model supports the idea that there is an allostatic reduction in the baseline hedonic state, or mood, that persists after long-term abstinence (Koob & LeMoal., 2005). With this abstinence comes the final step in the compulsive stage: the preoccupation-anticipation stage of addiction, characterized by intrusive thoughts, craving, and impulsivity, which accounts for the strong rate of relapse in addicts. The loss of control over drug use is then associated with the transition of behavioral control from the ventral striatum to the dorsal striatum, which is important for response habit learning. This can also be paired with reduced executive function that becomes impaired with chronic drug use. This is mainly seen in the dysregulation of the PFC and of the descending glutamatergic projections from the PFC. Other cortical areas to the striatum and other subcortical structures. (Koob & LeMoal., 2008)

Psychosocial variables may either increase addiction risk or have a protective effect. One risk factor is having a co-occurring anxiety, mood, or personality disorder, and

may increase drug use (Linford-Hughes et al., 2002). There also may be a shared etiology among these disorders that could account for the high rate of comorbidity. Personality variables predispose individuals to things such as impulsivity, antisocial disorder, high stress reactivity, sensation seeking, and extraversion. These may increase the likelihood of drug exposure and subsequent addiction (Verhaul & van den Bink, 2000). Drug use may produce effects that promote social facilitation, remove the user from their normal social role and responsibilities, promote solidarity, or lead to association with a specific drug subculture (Swendsen et al.,2009). All of these factors combine into a biopsychosocial model of addiction.

Methamphetamine Use and Risk Factors

Methamphetamine (MA, meth) is the most commonly consumed, and regularly abused substance in the stimulant class. It uses a lot of the pathways and mechanisms as MPH (Kuczenski &Segal., 1997). MA has a much higher abuse potential. This overlap makes it of concern as to how MPH may affect MA use. MA is a stimulant that is highly addictive , physically and psychologically, with craving lasting for years after cessation of use (Meredith et al., 2005). Its use and prevalence has been growing in since it was first introduced, and has become the second most commonly used class of illicit drugs worldwide (United Nations Office on Drugs and Crime, 2012) MA can lead to social, legal, and psychological problems (Barati et al., 2014). It has adverse health effects, such as memory loss, violent behavior, malnutrition, and is associated with a host of sexual consequences (Courtney & Ray., 2014). There are several significant factors that seem to be highly related, comorbid with, and increase the risk of MA abuse.

Methamphetamine Mechanism

MA can be taken orally (pill, capsule, or powder), intranasally (snorting powder), by intravenous injection, or by smoking. It is especially potent with rapid onset of drug action when smoked or injected. The rapid onset has a positive correlation with the addictiveness of the substance. Chronic use of MA in any form can lead to serious psychiatric, cardiovascular, metabolic, and neuromuscular changes (Allain et al., 2019).

The neuropharmacological identity of MA places it in the stimulant class, affecting primarily the central nervous system. MA works on the catecholamine system and their pathways, much in the same way as MPH. In terms of the synaptic mechanism of MA there is a strong release of catecholamines that is independent of nerve cell firing that leads to behavioral activation. MA stimulates the release, and partially blocks the reuptake, of newly synthesized catecholamines in the CNS (Cho and Melega, 2002). Due to its structural similarity, MA substitutes for the dopamine transporter (DAT), noradrenaline transporter (NET), serotonin transporter (SERT) and vesicular monoamine transporter-2 (VMAT-2) and reverses their endogenous function. This redistributes monoamines from storage vesicles into the cytosol. This process results in the release of dopamine, noradrenaline, and serotonin into the synapse. This then stimulates postsynaptic monoamine receptors (Courtney & Ray., 2014; Cruickshank & Dyer, 2009). MA also attenuates the metabolism of monoamines by inhibiting monoamine Oxidase (MAO), that degrades monoamines. (Sulzer et al., 2005). This further enables the buildup of excess monoamines in the synapse.

The monoamines released due to the presence of MA act on the major dopaminergic, noradrenergic, and serotonergic pathways of the brain. In the case of dopamine, MA activates the mesolimbic and mesocortical circuit, which have been related to the euphoric effects observed immediately after the ingestion of the drug (Homer et al., 2008). The medial basal forebrain, the hippocampus, and the prefrontal cortex (PFC) represent noradrenergic regions, with various functions related to arousal, memory consolidation, and cognitive processing, respectively (Berridge and Waterhouse, 2003). Affected serotonergic neurons are dispersed throughout the brain, regulating diverse functions such as respiration, pain perception, sexual drive, reward, and higher-order cognitive processing (Hornung, 2003). Interactions between the monoamine pathways, baseline dopamine functioning, and peripherally mediated effects of MA add to the complexity of MA's effect on the monoamine systems (Cruickshank and Dyer, 2009).

The potentiation of dopaminergic neurotransmission within the mesocorticolimbic circuit is thought to underlie the reinforcing properties of drugs of abuse, although evidence is accumulating on a converging role of the endogenous opioid systems in the establishment of reinforcement (Boutrel, 2008). Three families of endogenous opioid peptides have been identified (dynorphins, endorphins and enkephalins), each associated with a distinct polypeptide precursor (prodynorphin, proopiomelanocortin, and proenkephalin). These precursors produce a number of active ligands including β-endorphin, met- and leuenkephalin, dynorphins, and neo-endorphins (Kieffer and Gaveriaux-Ruff, 2002). Each ligand expresses a different affinity for each opioid receptor. Anatomically speaking, endogenous opioid receptors are widely distributed throughout the CNS, with differential distributions per opioid receptor type. Importantly, opioid receptors

and peptides are highly expressed in brain areas involved in reward and motivation, such as the ventral tegmental area (VTA) and nucleus accumbens (NAcc) (Mansour et al., 1995a). Administration of classical exogenous opioids facilitates dopamine release in the mesolimbic reward system by activating μ- and δ-opioid receptors in the NAcc (Hirose et al., 2005; Murakawa et al., 2004), and by decreasing GABA-inhibition via μ- and κ-opioid receptors, which are mainly located on GABA interneurons in the VTA (Bonci and Williams, 1997; Shoji et al., 1999). Many non-opioid drugs of abuse are also known to interact with the endogenous opioid system (Trigo et al., 2010). Further, preclinical data suggest that the endogenous opioid system is involved in the induction and expression of MA induced behavioral (locomotor) sensitization (Chiu et al., 2006), analogous to compulsive drug seeking behavior in humans (i.e., drug craving) (Itzhak and Ali, 2002), through its modulatory actions of the mesolimbic dopamine system (Ford et al., 2006). MA has pervasive effects not only on the dopaminergic system, but also on noradrenergic, serotonergic, and opioidergic neurotransmitter systems throughout the brain. It is through the culmination of these complex neurochemical modulations that significant behavioral and cognitive changes result.

Dose-response to Methamphetamine

Low doses of MA use result in increased wakefulness, respiration, hyperthermia, euphoria, physical activity, and decreased appetite. However, dosage amounts for producing neurotoxic effects in humans are not certain, since most of the information on MA neurotoxicity has been obtained from animal studies. Central nervous system effects

and symptoms include irritability, insomnia, confusion, tremor, convulsions, anxiety, paranoia, and aggressiveness. This toxicity can be caused either by stress on the vasculature or a direct toxic effect on neurons (Cruickshank and Dyer, 2009).

Sensations of the drug include euphoria and feelings of energy, power, and control (Irwin, 1995). MA may also temporarily alleviate anxiety and depression; however, dependence and withdrawal symptoms eliminate the euphoric effects and may even lead to psychosis and long-term mental illness (Sato, 1992; Wada & Fukui 1991). These stimulant and euphoric effects are reinforcing, and even more so due to its slow metabolism, with a half-life of about ten to eleven hours (Lukas, 1997). The dynamics of chronic use, tolerance, dependence, and sensitization are not yet fully understood for MA, but it apparent that age of first use, specific social and psychological factors play a role in its development of use.

In studies of adult, chronic MA users, neuroimaging has shown that prefrontotemporal areas and frontostriatal pathways, marked by smaller cortical thickness reduced white matter connectivity. The functionality of these brain regions is associated with inhibitory control and preference for delayed gratification, and have significant overlap with the regions where active maturation continues in adolescence. This could point toward stimulant-related changes in these brain regions during the adolescent period. This is a major implication in the potential for developing a substance use disorder later, and suggests that adolescents who start taking stimulants are at a greater risk of developing an MA addiction depending on if they have prior use of stimulants (Lyoo et la., 2015). Combining all of this evidence, looking at how MPH is related to MA use would prove beneficial in understanding the relationship of the two stimulants.

Psychostimulant Treatment and Substance Use Disorder

MPH may be a strong predictor of later substance abuse among the general population. This generalization is made from the results found in ADHD populations. Overlap in the mechanisms of actions for addictive behaviors and stimulant medication efficacy has been supported using animal models with an increased response to psychostimulant drugs of abuse following MPH treatment (Valvassoru et al., 2007). This is complicated by route of administration, dosage, length of usage, and presence of ADHD symptomology. Both MPH and MA have the ability to increase dopamine concentration in the nucleus accumbens. This helps to account for their reinforcing effects and their potential abuse. This could lead to dependence of either drug. Human epidemiological studies have shown that, in general, the earlier an individual is exposed to addictive substances, the greater the risk of drug use later (Volkow et al., 2008). An analytic review of ADHD medication by Faraone et al., in 2003 showed that there may be a protective factor on medication use in adolescence and even into adulthood, but to a lesser extent. However, with more research, the data has yielded mixed results. Some report protective association (Biederman et al., 1999; Loney et al., 2002; Mannuzza et al., 2008), others suggest certain predispositions (Lambert et al.,1998, 2005, 2006) and some point towards no association (Biederman et al., 2008; Molina et al., 2007; Barkley et al., 2003). This also proves to be the case in the general population. This makes it a prime area of study when determining the relationship between MPH use and later substance abuse without the confounding variable of ADHD.

It has been shown that adults who suffer from substance use disorders are more likely to have children that suffer from some form of psychopathology, including ADHD (Clark et al., 1997). This shared etiology among relatives make ADHD a commonly shared trait that is associated with elevated substance use. This is due, in part, to shared underlying causes, but may also be due to some of the effects that MPH treatment has on ADHD. The psychostimulant use for ADHD has been controversial with respect to the risk of its misuse and abuse, and to the extent to which stimulant treatment may be associated with subsequent substance use. The psychostimulants themselves, as discussed, have abuse potential, and it has been shown that MPH and amphetamine produce similar reinforcing effects alongside other drugs of abuse (Kollins et al., 2003). Furthermore, the risk of substance use disorder among those with ADHD is high (Biederman et al., 1995) and in this case, substance use tends to start earlier and follow a more aggressive course (Schubiner et al., 2000; Wilens, Biederman, Mick, Faraone, & Spencer., 1997). This leads to concerns about the relationship between Ritalin and illicit stimulant use, and whether or not the use, and possible abuse of MPH, is related to meth.

CHAPTER TWO

Effects of Stimulant Exposure on the Acquisition of Methamphetamine Self-Administration

The number of children diagnosed with ADHD has grown exponentially over the past several years (The Center for Disease Control and Prevention [CDC]., 2019). Misdiagnosis and general over-diagnosis in the population means that many who show signs of ADHD may not actually have the disorder (Davidovitch et al., 2017). Changing definitions of ADHD may affect prevalence as well as heightened awareness and recognition of symptoms. Guidelines for diagnosing ADHD are not applied the same, contributing to misdiagnosis. In a study of 50 pediatric practices, only half of clinicians said they followed diagnostic guidelines to determine symptom criteria from at least two sources and across two settings, yet nearly all (93%) reported immediately prescribing medications for treatment (Giuliano & Geyer., 2017). Psychostimulants that may be appropriately prescribed can be misused. This pattern of greater rates of prescribing of psychoactive medications being associated with greater rates of misuse (Dunlop & Newman., 2016), and accounts for the misuse of MPH by those without a diagnosis of ADHD.

This poses a problem for prescription treatment and misuse of stimulant medication in individuals who do have ADHD. The long-term consequences of giving children without ADHD stimulants is not fully understood. There may be a relation between prior stimulant use and later psychostimulant use. This study evaluated the effects of prior exposure to stimulant medications on MA-related behaviors. If exposure to stimulants increases meth-

administration, the effects could be drastic. For example, individuals could have loss of job productivity, health problems, and they may even engage in illegal behaviors (Wermuth .,2000). Further, there is no FDA-approved treatment for MA use disorder that could be administered to help individuals that use MA. If these studies establish a relationship between prescription stimulants and MA use disorder, it suggests that prescribing stimulants to treat ADHD should be done with extreme caution.

Of particular concern is that exposure to stimulants as children and adolescents may increase the risk that they will abuse other drugs when they are older, as effects persist into adulthood (Volkow & Swanson., 2008). While studies have shown that ADHD is prevalent among MA users (Barati et al., 2014; Yang et al., 2007), the role that previous stimulant medication may have played in meth administration is largely dependent on MA dosage (Shanks et al., 2015). Therefore, the overall goal of this study was to determine the impact of exposure to MPH on future MA use at varying doses. This experiment may elucidate long-term consequences of stimulants prescribed to treat ADHD. It will also assess the exact dosage response (i.e. lever presses for self-administration) of MA to those with prior exposure to MPH as compared to control. This will give a measure of pre-treated rats with MPH response to the saliency of MA administration at various doses.

Methods & Materials

Animals and Treatments

Animals were housed separately, since all of these animals had catheters with external connective mounts on their backs. Group housed rats would, more often than not, chew each other's mounts over the length of the experiment. Animals were kept on a

reversed light/dark cycle; white lights off at 6am and on at 6pm. The rats acclimate to the change in about one week, which is the minimum time before they are used in an experiment. This allows the critical parts of the experiments to be conducted during the animals' active cycle since they are nocturnal animals, and it also corresponds to the experimenter's workday. Corticosterone levels, which are important to psychostimulant self-administration (SA) , fluctuate widely in a replicable fashion depending upon the time of day. This makes them more regulated for testing. Red lights are required during the dark cycle so that the experimenters can see while the animals cannot. There was no enrichment in the home cage. There is a growing amount of data in the area of drug reinforcement research that uses enrichment as a potential treatment for addiction (Imperio et al., 2018). Therefore, enrichment could not compromise our studies.

Pre-Treatment

We tested 8 males for each treatment, as substance use is more common in males, This included a 25% attrition rate due to catheter failure and other technical problems. Therefore, each group included 10 rats, such that 30 rats were needed for the entire study (3 treatment groups X 10 rats/group = 30 rats). This experiment tested the most commonly prescribed drug for treating ADHD, MPH. This drug is most often taken orally. Experimentally naïve male and female Wistar rats ~35 days old at the start of the experiments were used. The animals were housed individually on a reversed 12-hour light, 12-hour dark cycle Once the rats acclimated to the Animal Resources facility (about one week), the procedures began. Adolescent Wistar rats were first exposed to two weeks of MPH or vehicle (saline control) treatment by use of mealworms (larval Darkling beetles).

Our experiment mimics ADHD medication administration at a young age by administering the drugs to rats starting at approximately 42 postnatal days, which is during the peri-adolescent period for rats. MPH treatment was completed by injecting frozen mealworms on a mg/kg basis, in accordance with the specific weight of the individual rat and then orally taken (i.e., consumed) to simulate regular oral drug intake. Darkling beetles were used to administer drug orally. The beetles were procured and kept in the larva stage (mealworms) by being maintained in a climate-controlled atmosphere. To best replicate the human condition, MPH and vehicle were administered in mealworms. MPH could be administered with a sucrose or water suspension, but the rats must then be deprived to induce motivation to drink, an inherent confounding variable. While an oral gavage method could be used to administer the drugs, it is stressful to the animal and could confound the results. Previous studies have shown that mice prefer frozen mealworms over a wafer cookie and that rodents will consume mealworms injected with d-amphetamine, and so, should similarly work for MPH . Rats were given MPH, or vehicle for two weeks (Monday-Friday). Rats were not given the drugs on Saturday and Sunday to better model how humans typically take the drug (Martins et al., 2004).

MPH and vehicle were injected into frozen mealworms and the mealworms were fed to the rats. Mealworms vary in individual capacity to hold liquid, and therefore were only filled to certain amounts based on physical size of the mealworm. Due to this, rats were fed several mealworms in a combination of sizing, in order to summate to the correct dosage for each individual rat. MPH was administered in a dose of 2 mg/kg, twice daily. This dose was selected as it results in plasma concentrations of the drug that are similar to

the concentration that is obtained with clinically relevant doses in humans (Valvassori et al., 2007).

Table 1: Rat postnatal days as compared to human age (years) (Sengupta et al., 2013)

Correlating human year with rat days with different phases of life		
Entire life span	13.2 rat days	=1 human year
Weaning period	42.4 rat days	
Pre-pubertal period	3.3 rat days	
Adolescent period	10.5 rat days	
Adulthood	11.8 rat days	
Aged phase	17.1 rat days	
Average	16.4 rat days	
Rat age versus human age: Social maturity phase		
Rat age (years)		**Human age (years)**
6 months (0.5)		18
12 months (1.0)		30
18 months (1.5)		45
24 months (2.0)		60
30 months (2.5)		75
36 months (3.0)		90
42 months (3.5)		105
45 months (3.75)		113
48 months (4.0)		120

Surgical Procedures

General Procedures

All surgeries were conducted in the animal surgical suite located in the animal care facility at Louisiana State University Health Science Center using accepted aseptic surgical techniques (Haile & Kosten., 2001; Kosten et al.,1997). Instruments and catheters were sterilized before the procedure using an autoclave. Instruments were cleaned and sterilized using a bead sterilizer between procedures when multiple surgeries where performed. Animals were anesthetized, had the hair removed from the incision site, had the site cleaned

with Betadine and were draped with sterile gauze. The person performing the surgery wore fresh outer wear, a mask and sterile gloves. Anesthesia for all rats and each procedure below consisted of Isoflurane (5% for induction; 1-2% for maintenance) by mask. The Isoflurane was scavenged and applied to the depth that the animal no longer responds to a toe pinch. Brevital, methohexital sodium, (1.5 mg, iv) were also be used during surgery as a supplement once the catheter was in place. The animals were injected with sterile penicillin G procaine suspension (75,000 units, i.m.) and with an appropriate analgesic agent (carprofen, 5-10 mg/kg, s.c. or ketoprofen, 2-5 mg/kg, s.c.) immediately before surgery. Topical antibiotic ointment was applied to all incisions. The rats were allowed a minimum of five to seven days to recover following surgery. They were also weighed and handled daily (Monday-Friday) and their general condition assessed. This included checking incisions for infection until healed and evaluating the animal's behavior, appearance and activity levels.

Implantation of Jugular Catheter

Animals were implanted with a chronic indwelling jugular catheter under anesthesia at approximately 56 days of age. The catheter (0.012 in i.d. x 0.025 in o.d., silicone tubing) was inserted into the right posterior facial vein and pushed down into the jugular vein until it terminated outside the right atrium. The catheter is anchored to the vein and continued subcutaneously to the back where it exits on the back through a 22-gauge guide cannula assembly that is used for attachment of a leash. During all SA procedures a stainless-steel spring leash was attached to the guide cannula assembly and to a leak-proof fluid swivel suspended above the cage. Tubing connected the swivel to a 20-

ml syringe in a motor-driven pump located outside the chamber. The swivel and leash assembly were counter-balanced to permit relatively unrestrained movement of the animal. The swivel and leash assembly remained connected during the experimental sessions. The patency of the catheters was tested at least once each week. If blood could be obtained via the catheter, then it was judged to be patent. If not, then the rat was injected via the catheter with Brevital (1.5 mg, iv). An immediate light anesthesia indicates that the catheter is functional.

Animals were allowed a recovery period of 5 to 7 days after surgery before beginning the SA procedure. Assessment of the rats' pain and distress levels was monitored daily and pain medication administered accordingly. Rats were evaluated for rapid or labored respiration, lack of grooming, increased aggression, porphyrin discharge, abnormal appearance or posture, immobility, or decreased food or water consumption. Factors that would indicate inadequate health for continuation in the experiment. All animals were handled and weighed Monday – Friday (days that the experiments were conducted) by the researchers and their general behavior, appearance and activity levels monitored. Any changes in food or water consumption, coat appearance, lethargy, or reaction to handling were monitored closely (twice per day, at the beginning and end of the experimental procedure). Any recommended treatment or termination was done in accordance with th National Research Council's Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (2003), and with the approval of an Institutional Animal Care and Use Committee. Food was provided in the afternoon according to schedule. The rats were removed from the experiment if they did not consume food or water. The humane endpoint criteria for the rats in the experiment were as follows:

If the rat does not eat or drink during recovery from surgery or during the experiment and 15% of lost body weight is not recovered within one day, a veterinarian will be notified to check the health status of the rat. Proper food or medical treatment were employed, or it was be removed from the study and euthanized.

Self-Administration Operant Chambers

Animal SA experiments are typically performed in standard operant conditioning chambers adapted for the catheters used to deliver a drug intravenously. The chamber houses two levers: one whose depression results in the delivery of a drug, the other whose depression does nothing. Activity on these levers can be used to measure drug administration (via activity at the drug-inducing lever) as well as changes in nonspecific behavior that reflect short- and long-term effects of the drug (via activity at the non-inducing lever). The sterile intravenous catheter used to deliver the drug into the bloodstream of the subject is typically composed of a flexible plastic, silastic tubing and nylon mesh placed subcutaneously. It is attached to a mechanical pump that can be calibrated to deliver a specific amount of drug upon depression of one of the levers in the chamber.

Self-Administration Procedure

MA is most commonly first used in early adolescence (Brecht et al., 2004). SA was conducted in young, adolescent rats (~63 postnatal days) as this is the age that most humans begin using MA. SA of putatively addictive drugs is considered one of the most valid experimental models to investigate drug-seeking and drug-taking behavior (Gardner.,

2000; Edwards & Koob 2013; O'Connor et al., 2011). The higher the frequency with which a test animal emits the operant behavior, the more rewarding (and addictive), the test substance is considered. SA of addictive drugs has been studied most commonly in rats. Following initiation and stabilization of MA-maintained operant responding, effects on SA behavior can be tested. In this protocol, a fixed ratio schedule was used so that rats received one injection of the variable dose each time that they pressed the lever. This was kept consistent throughout the experiment. The operant software is programmed to record number of responses (i.e., response rates) and earned reinforcers (i.e., stimuli) for the solution presented (methamphetamine). Data was recorded at each dosage amount and response rates made into graphs. Once the number of responses and reinforcers of the MA had been determined for the individual dose periods, analysis of the data allowed evaluation of the reinforcing efficacy (i.e., strength) of the solutions in connection with the pre-treatment.

Experiments were conducted in standard plastic and stainless steel, sound-attenuating chambers. Rats self-administered MA during daily 2-hour sessions. If not in session, rats were kept in their regular housing. Initially, rats where tested with a very low dose of MA (0.015 mg/kg/infusion). They were tested for SA with this dose for one week. The dose of MA was doubled each week so that each rat was tested with 0.015, 0.03, 0.06, 0.12, and 0.24 mg/kg/infusion MA for one week at each dose. After titration of MA, the rats were given one week of saline injection to help restore them back to baseline for further treatment.

CHAPTER THREE

Results and Discussion

Results

This study evaluated the effects of prior exposure to the stimulant medication, MPH, on MA-related behaviors. To emulate more closely the dosing regimens and plasma drug concentrations that occur most frequently in humans (Gerasimov et al. 2000), we pretreated adolescent rats with a low dose of MPH (2 mg/kg/day) for 14 days. A total of n=16 animals were implanted with jugular vein catheters. Of these, two were removed due to catheter-related issues. Thus, a total of 14 animals met acquisition criteria by the end of the study. Stable patterns of responding were obtained within 30 SA sessions (once daily for six weeks) following prior exposure to either methylphenidate or saline. Adolescent rats pre-treated with methylphenidate or saline control were allowed to self-administered methamphetamine (mg/kg) five days a week for six weeks. Using the low-dose MP treatment protocol, we determined whether adult rats would acquire SA of methamphetamine at various doses. SA training commenced 2 weeks following the last MP injection and 1 week following surgery for implantation of IV catheters. Following five days (one week) of methamphetamine administration, the dosage of methamphetamine was doubled (0.015, 0.03, 0.06, 0.12, 0.24) each week in both in groups. Figure 1 shows the trends of the saline-treated cohort. Saline pretreatment had a regular course on SA of methamphetamine. This is in representative of the usual drug-taking behavior seen in rats without any other variables. Figure 2 shows the same course, but with the MPH-treatment cohort. MPH pretreatment enhanced SA of methamphetamine at higher doses. MPH

pretreatment enhanced intake of methamphetamine measured by significantly more self-infusions (Figure 4) for the 0.12 and 0.24 doses. Both the saline and MPH-pretreated groups showed acquisition of methamphetamine SA measured by their number of lever presses.

Methamphetamine Response Curve for Saline-Treated Rats

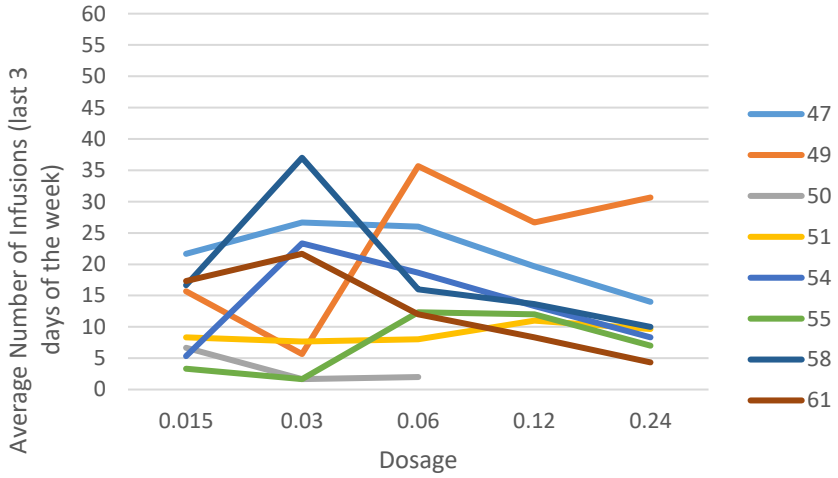

Figure 1:The average number of infusions shown is based on the mean taken from the last three days of the week at each specific dose. If there is break in line graph for a particular rat, it indicates that they were removed from the study due to some complication.

Methamphetamine Response Curve for Methylphenidate-Treated Rats

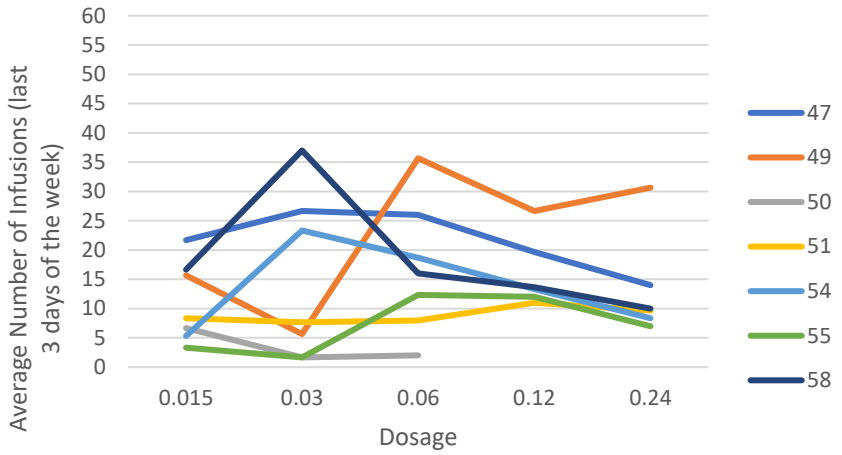

Figure 2:The average number of infusions per day shown is based on the mean taken from the last three days of the week at each specific dose. If there is break in line graph for a particular rat, it indicates that they were removed from the study due to some complication.

The charts for individual rats give a more in-depth look at how the response to MA was affected by the pre-treatment. It is important to remember that rats must be trained to self-administer and need an acclimation period in general and for subsequent dose changes. This helps to account for some of the variability seen and is why the average was taken from only the last three days of the week. If there is break in line graph for a particular rat, it indicates that they were removed from the study due to some complication.

Saline rats followed the general trend of the MA dose-response curve. There is some deviation with individual rats, but compared to the overall, the trend in standard. The peak for most was around the 0.03 mg dose, with some variability due to human error in measurement while filling and switching syringes. Individual differences in trends can also be accounted for by behavioral differences in rats and time of acclimation.

Comparatively, the MPH-treated rats showed much more individual variability. The peak doses for most rats was between the 0.03 mg and 0.06 mg doses of MA. The overall trend for MPH rats points more towards a peak SA at the 0.06 mg dose. Another interpretation of this data is the MPH pre-treated rats don't have as high of a peak in MA intake at low doses. This shows a protective effects at lower doses of MA with prior MPH exposure. This may account for the shift in peak response by the MPH-treated rats. It is also noticeable that the MPH-treated rats generally do not have the same shard decline in the 0.12mg to 0.24 mg range. Instead, lines tend to stay relatively even, with a few individual rats even taking more MA than the average peak dose.

Overall Response Comparison of Methamphetamine Administration

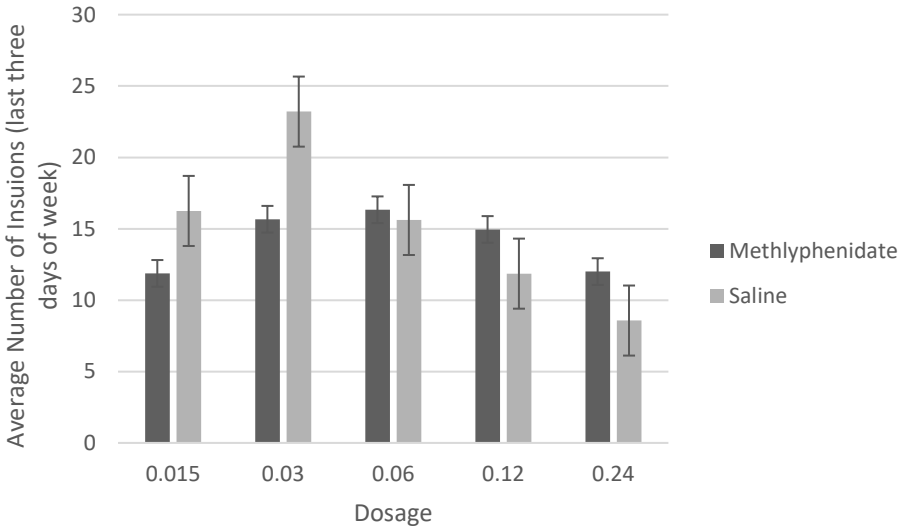

Figure 3: Overall Responses. This figure shows the average number of infusions at each dose.

Overall Response Comparison of Methamphetamine Administration

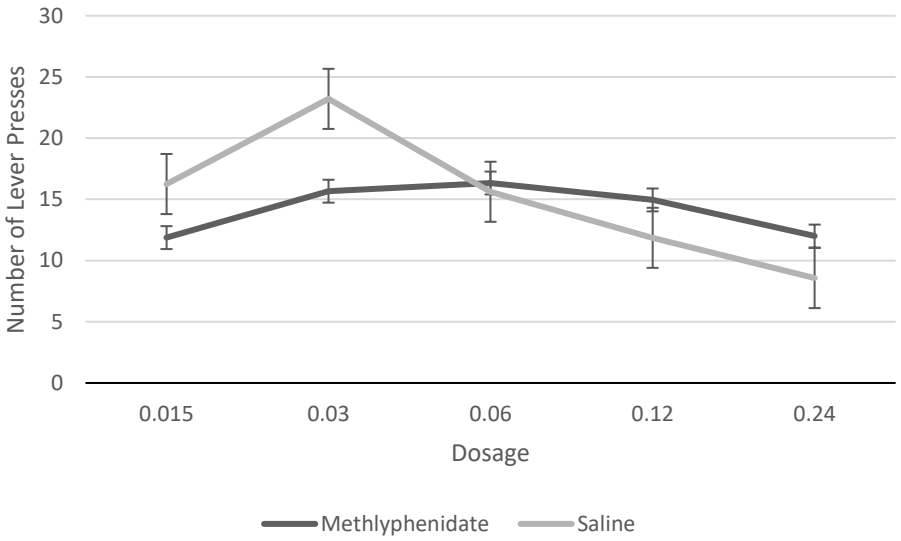

Figure 4: Overall Response Curve. This figure shows drug intake as a trend line over the different doses

Looking at general trends, there can be seen distinct difference in the MA dose-response curves. At the 0.015 dose, there can already be seen a difference between the MPH group and the saline group. The saline pre-treatment group then shows a marked increase in self-administered lever presses at the 0.03 mg dose, which is considered to be the peak of the dose for a normal MA dose-response curve (McMillan et al., 2004). This shows that saline-treated rats followed the normal progression of MA SA. Comparatively, at this dosage, the MPH-treated rats show some marked increase in response, but not to the peak of the normal response; sustained attenuation to MA. At the 0.06 mg dosage the saline-treated rats started to decline in number of averaged lever presses during that week. The MPH-treated rats reached their peak. This is significant in that the peak dosage has shifted towards the right, but also is not at the same number of presses as the saline-treated

rats during their peak. The trend then reverses with the higher doses of MA. At the 0.12 mg dosage, it is now the MPH-treated rats that have, on average, slightly higher acquisition of the drug. The saline-treated rats continue the dose-response as predicted. The last dose of 0.24 mg showed that the MPH-treated rats shows sustained MA acquisition at higher doses compared to the saline-treated rats.

Discussion

This is the first study to evaluate the dose response of MA SA in rats with prior MPH treatment. Previous studies have looked at the effects of oral MPH treatment alone. There have also been studies to look at relationship between MPH and other stimulants, such as amphetamine and cocaine. The relationship between MPH and MA can be conjectured upon based on these studies, but none have looked at how MPH directly effects dose response in MA self-administration. The finding of this sub-sectional study supports the idea that: (1) prior MPH treatment has a protective effect on low dose MA administration (2) prior MPH treatment maintains above average MA administration at higher doses of MA

MPH possesses many of the same neuropharmacological effects as illicit stimulants (Volkow et al., 1995, 1999). Repeated exposure to psychostimulants such as cocaine, amphetamine, and MA has been found to have sensitization effects (Robinson and Berridge, 1993; Kalivas, 1995; Gaytan et al., 1997a; Kuczenski and Segal,2001; Yang et al., 2001). Locomotor sensitization results from a variety of neuroadaptations associated with processes underlying addiction (Robinson and Berridge, 1993; White and Kalivas, 1998); therefore ,sensitization may be a critical component in the development of drug

dependence. Sensitization and cross-sensitization between different drugs are considered as markers and indicators of drug dependence (Robinson and Becker, 1986). It has been reported that prolonged exposure to a psychostimulant could enhance a person's susceptibility to substance abuse (Robinson and Berridge,1993; Schenk and Davidson, 1998; Brandon et al., 2001; Schenk and Izenwasser, 2002).

The peak shift by the MPH poses that there may be some sensitization occurring. This may account for the dosage shift, but also the acquisition shift that occurs with the relative peak doses. There is also consideration for the titration of the MA doses. If the doses had been broken down into more steady phase shifts, response curve may have shown greater variability among doses. This may have produced different attenuation to MA and could of shifted the peak for the MPH-treated rats even further to the right. The last consideration here would be if the experiment was continued to even higher doses of MA. The hypothesis being that the MPH-treated rats would have sustained higher maintenance of MA administration throughout higher doses. These effects should be taken into consideration when interpreting these results and when in proposition of further studies.

Animal studies show that pre-exposure to psychomotor stimulants enhances subsequent SA of stimulant drugs (Horger et al. 1990, 1991, 1992; Pierre and Vezina 1997; Vezina et al. 1999; Lorrain et al. 2000). Consistent with pre-exposure to low-dose exposure to amphetamine (Pierre and Vezina 1997) we found a differential effect of low-dose MPH preexposure on the reinforcing effects of methamphetamine. Low-dose pre-exposure to MPH maintained the reinforcing effects of MA at higher doses of the drug. The impact of the psychostimulants on reward processes is of particular interest, because some authors have attributed behavioral aberrations in ADHD to an elevated reward threshold (Solanto.,

1998). Our findings can be considered consistent with other results showing that MPH increases reinforcement efficacy of low reinforcers (Heyman 1992), in our case, different doses of methamphetamine. One of the long-lasting alterations following repeated psychostimulant administration that may contribute to increased extracellular DA levels is reduction in DAT synthesis in the prefrontal cortex and NAc (Kuhar & Pilotte., 1996). Consistent with these findings, therapeutic treatment with MPH decreases DAT binding in ADHD patients who had previously presented with increased DAT binding compared to controls (Krause et al. 2000). Treatment with MPH lowers increased striatal DAT availability, suggesting a potential mechanism for MPH's therapeutic effect. This implies that one of the alterations shown to occur following repeated MA might also occur following repeated low-dose exposure to MP; thereby, creating neuroadaptations associated with both therapeutic effects and drug vulnerability, complicating interpretations of clinical studies and perhaps accounting in part for inconsistencies in clinical studies on the relationship between ADHD and drug dependence.

Limitations of the current study was that MPH was only tested at clinically relevant dosages, not accounting for the abuse potential of the drug. Larger dosage of MPH in the pre-treatment phase would need to be administered to assess this. It could pose problems in terms of determining the dosage required to produce an abuse model. The abuse mechanism may have a significant impact on MA acquisition. This study also did not include a relevant model of ADHD. This is in accordance with the review of literature that shows that misuse of Ritalin is more prevalent among the general population. However, ADHD models should also be assessed in contrast to these results to provide significance.

Clinically, the main limitation is that these are not human trials. It is hard to measure the exact neurobiological changes that happen during the transition to adolescence, as they are usually a progressive change over time. It is not known when exactly they will take places as they tend to vary by individuals, with differences in onset and duration. For future research into this area, it would be difficult to collect a sample at an exact age to compare the preadolescent and adolescent phase in terms of maturation changes in rats. There will be some variability in terms of the correspondence to human application because of this. Another limitation of this study is that it does not account for the change in relevant dose that may be clinically relevant in humans. As humans age, dosages of MPH may change to compensate for age of the child, the time spent on the drug, height, weight, and individual differences, all of which may be hard to factor in for an animal study. The universal, clinically relevant dose is also not always the standard as MPH does have abuse potential. This should also be tested in separate studies.

Future studies are necessary to investigate these phenomena, but this data suggest that prior exposure to MPH does not increase low doses of MA taking in adult male rats. It does shows that there is sustained administration at higher doses of MA. This mixed finding is consistent with a lot of literature that has found similar data and may propose several mechanisms that match these results. Of particular interest would be looking at the dose response of MPH on MA administration with ADHD individuals. This would help to determine if it is MPH itself, or the combination of ADHD and MPH affects that produce the MA response. It would also be relevant to look at age-related effects in both populations to determine how stimulant treat is affected by maturation.

In summary, this study suggests that prior exposure to MPH leads to maintenance of MA administration at higher doses. Without the prior exposure to MPH, meth administration follows the proposed drug-response curve. That is, there is higher acquisition to the drug and at greater rates, at lower doses of meth administration. The implication here is that the previous treatment with MPH has a protective effect on low-dose MA use. The neuropharmacological explanation of these results points towards a habituation of the receptors and pathways used by MA with previous MPH exposure. The neurobiological pathways that were being activated had already experienced this type of stimulation, and so acquisition of addictive behavior was less likely. At the higher doses of MA, sensitization seemed to occur. The higher doses of MA elicited a sustained response from the MPH-treated rats. This points to a sensitization mechanism, where larger doses of stimulants are needed to elicit the same type of response that low-dose MA could not. The prior exposure to MPH could account for this lack of response in the low-dose MA response.

CHAPTER FOUR

Discussion of Risk Factors and Future Research

ADHD as a Risk Factor for Methamphetamine Use

It has been shown that individuals who suffer from substance use disorders (SUD) are more likely to have children that suffer from some form of psychopathology, including ADHD (Clark et al., 1997). This shared etiology among relatives make ADHD a common trait that is associated with elevated SUD. Among the ADHD population, there is an elevated instance of substance use, particularly psychostimulants. Prevalence rates for ADHD are as high as 10.4% among one-time meth users, and up to 20.8% among chronic users (Mihan, 2018).This makes ADHD a risk factor for MA use due to its genetic component and associated comorbidities.

Family, genetic, twin, and adoption studies provide consistent evidence suggestive of genetic contribution to ADHD and SUD (Biederman et al., 1997; Qian et al., 2003). A number of studies imply that individuals with the combined and inattentive subtypes of ADHD are significantly more likely to meet criteria for ADHD as adults compared with those with the hyperactive/impulsive subtype of ADHD, and the former groups have higher risk for SUD (Clure et al., 1999). A number of studies indicated the psychiatric comorbidity between SUD and anxiety disorders, mood disorders, eating disorders as well as disruptive behavior disorders (King et al., 1999; Weinberg, Rahdert, Colliver, & Glantz, 1998). Much of the factors that contribute to this elevated use, comes from the deficits of ADHD itself Associated morbidities may just increase the risk. This makes ADHD a wholistic risk factor for SUD.

Children with ADHD are believed to be at greater risk for drug use/abuse (Barkley, Fischer, Smallish, & Fletcher, 2004). ADHD may also worsen prognosis of SUD and antisocial behaviors into adulthood (Barkley et al., 2004; King, Brooner, Kidorf, Stoller, & Mirsky, 1999; Riggs, 1998; Riggs, Hall, Mikulich-Gilbertson, Lohman, & Kayser, 2004). ADHD appears to be a risk factor for late adolescent to young adult onset SUD (Wilens, 2004; Wilens, Biederman, Mick, Faraone, & Spencer, 1997). The age of initial substance use did not differ between ADHD and non-ADHD participants, but age of regular substance use tended to be younger for ADHD participants and diagnosis of substance dependency (Thompson et al., 1996). Adolescents with ADHD had a significantly shorter transition time from abuse to dependence (Biederman et al., 1997). ADHD appears to be a risk factor for late adolescent to young adult SUD (Wilens et al., 1997).

Prospective longitudinal studies have shown that a diagnosis of ADHD in childhood or adolescence leads to an increased risk for substance use in general. Often occurring at later stages of adolescence (Biederman, Monuteaux et al., 2006; Manuzza et al., 1991), at about a rate of 6.2 (21%) times higher than the general population (Katusic et al., 2005). Even without other confounding variables, it is clear that ADHD serves as an independent risk factor (Kousha et al., 2012).

Commonly comorbid with ADHD and another strong predictor of SUD, is conduct disorder (CD). Compared with the normal population, the risk of SUDs is twice as high among people with ADHD and four times as high among people with ADHD with comorbid conduct disorder (CD) (Ercan, Coskunol, Varan, & Toksoz, 2003). This association increases the risk of substance use among ADHD individuals with the

comorbidity (Schubiner et al., 2000). CD is the most consistent predictive factor associated with ADHD for development of a SUD. Flory and colleges (2003) showed that the double diagnosis of ADHD and CD contribute to a virulent form of substance use, specifically with harder drugs. There are several psychological and social factors that play a role into this. Characteristics used to define this combination may include the impaired executive functioning in these individuals, a lack of behavioral control, and increased impulsivity.

ADHD children frequently show high levels of social aggression and conduct problems (Barkley, 1998; Hinshaw, 1987). In adolescent, it is sometimes the case that those children with ADHD will have comorbid aggression and show a potential for the development of conduct disorder, manifested in delinquent activities and later antisocial personality disorder. (Barkley 1990; Klein & Mannnuzza, 1991). Along with these risks comes a greater propensity of being arrested at some point in life, substance exposure, and substance use (Biederman, 1997), particularly among the subset of ADHD children that show prepubescent signs of having conduct disorder by their adolescent years (Molina, Smith, & Pelham, 1999). This proposes that ADHD children are at risk for adult arrests, antisocial disorders, and general cognitive impairment, all risk factors for SUD. While this may vary by individual, the severity of the ADHD and cooccurring conduct disorder in adolescence may show certain contributions to various antisocial and drug use activities in adulthood (White et al., 2001). Usually, if engaged in one type of behavior, individuals will also engage in similar, or related behaviors, and this holds true here as well. ADHD alone can then be seen as a risk factors for the development of SUDs in children with ADHD beyond that conferred by the comorbidity with conduct disorders. It is also the case that these comorbidities increase the chances of developing SUDs in children with ADHD.

Within ADHD, it is that persistent ADHD, conduct and mood disorder comorbidity predict later SUD in individuals with ADHD

Age of Treatment of ADHD as a Risk Factor for Methamphetamine Use

The age at which an ADHD individual begins treatment may be as risk factor because of the developmental effects over the lifespan. Adolescent individuals with ADHD may show signs of sporadic behavior with employment, start hanging out with crowds that support drug behavior, and commit impulsive-type crimes. In general, the more deviant the developmental environment, the more likely the adolescent will perform poorly in school, use illicit substances, and participate in crime (Chaiken & Chaiken, 1990). The question then becomes at what age of an at-risk individual is it best to intervene in order to prevent further development of substance use as there may be age-related effects of MPH throughout life.

The juvenile and adolescent brain is a rapidly developing network due to the high plasticity of the brain. This makes it susceptible to actions of chronic drug treatment. With stimulant medication considered to be the primary treatment method for children with ADHD, it is possible that there may be a causal relationship between the two since they work on the same molecular mechanisms (Kuczenski & Segal., 1997). Because stimulant medications mimic the increase in dopamine in the mesolimbic pathway, the same as drugs of abuse, there may be concern for cross-sensitization. This increase is responsible for the drug's reinforcing, addictive properties. Both MPH and MA are abused in some settings and this misuse can produce dependence (Volkow & Swanson, 2008). Misuse of the drug

may also lead to the need for a higher dosage than can be clinically achieved, and so MA becomes an option (Konstenius et al., 2014; Levin et al., 2015; Cook et al., 2017).

The sensitization hypothesis, a neuroadaptation model, maintains that exposure to stimulants results in dopamine system alterations. Such alterations increase sensitivity to the reinforcing effects of the previously experienced substance. Behavioral sensitization has been demonstrated in numerous mammalian species and has been found to be long lasting (Robinson & Becker, 1986). Some studies have suggested that there may be a causal link between stimulant treatment in adolescence and later substance use disorder (Kollins et al.,2001; Vitiello et al., 2001) . Of relevance to this controversy, some animal studies have reported developmental effects on stimulant sensitization. Specifically, psychostimulants use in rats is decreased with MPH treatment in childhood years as opposed to adolescent-age MPH treatment, in which it is increased. This shows that while sensitization may occur in older individuals, there may be a protective effect at younger ages (Andersen, Arvanitogiannisv Pliakas, LeBlanc, & Carlezon, 2001; Brandon, Marinelli, Baker, & White, 2001). This also suggests that age of exposure may modulate long-term drug effects on the brain for ADHD individuals. Our study examined this relationship in adolescent rats without ADHD and showed similar results with the proposed mechanism for adolescent age rats. There was a sensitization effect in the rats because they had surpassed the childhood protective effect of MPH exposure. This proposes that there may be similar sensitization effects by MPH in all populations, with regards to the age-related factor.

Drug use generally starts and progresses more rapidly during adolescence. For example, the time between initial use to the onset of dependence for most drugs of abuse

is shorter in adolescents when compared to adults (Clark et al., 1998).Once dependence develops, adolescents are more likely to engage in harmful and potentially lethal drug binges (Baumeister & Tossmann, 2005; Estroff et al., 1989; McCambridge & Strang, 2005). Even if abstinence does occur, adolescents are more resistant to treatment interventions and are at an increased risk for relapse as compared to adults (Brown and D'Amico, 2001; Catalano et al., 1990; Chung et al.,2006; Dennis et al., 2004; Perepletchikova et al., 2008; Wintersand Lee, 2008). These drug abuse patterns are enduring, as epidemiological evidence indicates, and adolescence marks the period when individuals are most susceptible to developing lifelong drug addiction. This proposes that ADHD children are at risk for comorbid disorders and increased substance use and are less likely to seek treatment. While this varies by individual, the severity of the ADHD and cooccurring conduct disorders in adolescence may contribute to various antisocial and drug use activities in adulthood (White et al., 2001). Usually, individuals who engage in one type of behavior will also engage in similar behaviors, and this holds true in this scenario

In terms of age-relation, the major shift comes around adolescence with an increase in risk-taking behavior and less parental supervision, whether it be for medication treatment or experimentation with illicit drugs. Adolescence is a critical period of brain development that can be interrupted by environmental factors that derail the typical brain development and increase the risk of irreversible damage to the brain, many of which are heritable and show increased expression in families. The development of conduct disorder and subsequent antisocial personality disorder may play a role in substance use due to developmental issues. It may also be certain comorbidities with neurodevelopmental disorders, such ADHD pose a risk of an enhanced risk for substance abuse.

The timing of stimulant exposure is a major component in the development of a use disorder, and the timing and intiation of treatment may also play a role in later meth use. Studies in rats have shown that preadolescent treatment with MPH resulted in a decrease in the rewarding effects of illicit stimulants during adulthood (Anderson, Arvanitogiannis, Pliakas, LeBlanc, & Carlezon., 2002; Mague, Anderson, and Carlezon., 2005). In contrast, a study in which animals were exposed to stimulant drugs during adolescence or adulthood showed increase in drug abuse (Brandon, Marinelli, & White., 2003). Clinical data suggest that these finding also apply to humans, giving a definitive status to the age-related effects of ADHD treatment on later substance use.

MPH may produce specific age-related effects during certain stages of development in ADHD individuals (Urban, Waterhouse, & Gao., 2012; Hanish et al., 2004; Schrantee et al., 2016). Within the ADHD population, there may be age-related effects of MPH throughout life. It has been shown that low doses do not produce lasting neurophysiological changes, but that higher doses and abuse of MPH may cause long-term effects (Urban, Waterhouse, & Gao, 2012). In studies conducted with preschoolers, there have been improved outcomes on Gordon's visual CPT, a test of continuous performance on a task, and on a visual and auditory vigilance test with the use of MPH. School-age ADHD children treated with MPH showed enhanced maintenance of attention, accuracy, working memory, and increased inhibition of blocking out additional stimuli. It has been demonstrated that attention intensity is best accelerated by higher MPH doses (Denney & Rapport, 2001), whereas executive functions are best influenced by moderate doses (Tannock, Ickowicz, & Schachar 1995; Konrad, Günther, Hanisch, & Herpertz-Dahlmann 2004). Among preschoolers, the majority of subjects showed deficits in the supervisory

attention system, which in mediated by the PFC and striatal structure. Grade-schoolers were more impaired in the selectivity and intensity domains of attention (Hanisch, Konrad, Günther, & Herpertz-Dahlmann, 2004). This points to a marked transition period around the time of maturation from childhood to adolescent , possibly mediated by the neurobiological changes associated with development. The effects surrounding this developmental change in relation to substance use have not been fully studied.

There are age-related effects present in adulthood that are dependent on the age of first MPH treatment. Looking at adult studies, there is marked hypoactivity in the PFC in adults who begin MPH treatment later in life (Ernst et al., 1998). This may suggest a discrepancy between PFC functioning outcomes in adults versus adolescents following administration of equivalent doses of MPH. This reveals a potential for long-lasting PFC changes in MPH-treated children (Urban et al., 2012). Specifically, this long-term treatment may up-regulate the DA transporter in certain parts of the brain that reflects the mechanisms of psychostimulants, such as methamphetamine. This adaptation may have neuroplastic consequences with a further decrease in DA signaling when the individual with ADHD is not medicated, and a loss of efficacy for MPH (Wang et al., 2013). The effects of adolescent MPH exposure are particularly relevant to the PFC, as they increase catecholamine neurotransmission at low doses.(Berridge et al., 2006). The long-term effects of this increase may lead to habituation of receptors and pathways. This overlap in mechanism and reduced plasticity in cognitive functioning with extended exposure to MPH may contribute to later substance use.

Future research should also focus on the role of neurohormones and neurotransmitters that are active during puberty and their relationship to MPH treatment

during this time. It could also be that certain cortical or subcortical structures have developmental problems or deficits during this time with MPH accompaniment. In understanding the age-related effects of MPH treatment, other factors that could play a role in the development of substance use disorders could become clearer.

The idea that specific brain areas play a crucial role in the development of our personality, such as the propensity to begin using drugs, there are certain areas that are of particular interest for study. The PFC plays a functional role in our cognitive development, and since it has been shown that it is involved in the therapeutic actions of MPH at low doses, may be functionally affected by treatment. Mechanistically, DA afferents in the PFC show a certain sensitivity to environmental and pharmacological influences in subcortical DA systems (Berridge et al., 2006). Raising the questions of the degree as to which low-dose stimulant medication influence both DA and NE transmission in the PFC. There has been evidence that low doses enhance cognitive function through increases in DA and NE within the PFC relative to subcortical regions. However, this shows a sensitivity to only low doses and may not account for increases in dosage that occurs with increases in age and sensitization with treatment. Moreover, there is shown to be minimal impact of low-doses stimulants on the circuitry that underlies the abuse potential of these drugs. This could possibly show a protective action of these drugs, but still not accounting for factors previously mentioned.

Looking at specific receptor actions in relation to age, it has been postulated there may be fewer catecholamine terminals in the PFC of adults with ADHD (Ernst et al., 1998). In a study by Arnsten and Dudley (2005), there was shown that clinically moderate doses improved delayed alteration performance, while higher doses producing perseveration

errors. These errors may be, in part, due to over excitation of DA D_1 or NE α_1 receptors in the PFC and also stress exposure, that causes high levels of catecholamine release in the PFC that may be functionally related to these receptors. It then becomes important to understand how MPH improves cognitive functioning through these receptors and their interactions. This may also be important since it has been shown that higher clinical doses and abuse doses may cause long-term changes in PFC by depressing the activity of pyramidal neurons in the PFC at receptor sites (Urban et al., 2012). The developmental age and MPH relevant dose play a critical role in determining the drug effects on these PFC neurons and may result in a significant reduction in both excitability of receptors, synaptic transmission, and certain second messenger systems in preadolescence. The expression of these DA receptors is then shown to change with development, with D_2 (inhibitory) higher during juvenile period and D_1 (excitatory) levels higher in adulthood, making the optimal dose range dependent on age and a need for further investigation.

In applying these finding to potential drug use, there may be a significance in terms of place preference and sensitization to the rewarding properties (Meririnne, Kankaanpää, & Seppälä, 2001). This may have significant influence in some of the sociological and psychological factors that are associated with ADHD, such has the high impulsivity and comorbidity with antisocial personality disorder. These factors may play a large role in accordance with underlying neurobiological factors to make someone susceptible to drug use later on. It is difficult to quantify these factors and so further research and psychological tests need to be developed in order to accurately quantify and qualify how these factors are associated with the underlying age-related transitions in the neurobiological factors. This makes further experiments even more important in determining the exact relationship

between MPH and psychostimulant use, so that it can either be further studied or put aside for these other factors that may play a bigger role in the development of substance use disorders.

BIBLIOGRAPHY

Achat-Mendes, C. (2003). Methylphenidate and MDMA adolescent exposure in mice: Long- lasting consequences on cocaine-induced reward and psychomotor stimulation in adulthood. *Neuropharmacology*, *45*(1), 106–115

American Psychiatric Association. (2013). Diagnostic and statistical manual of mental disorders (5th ed.).

Allain, F., & Samaha, A. N. (2019). Revisiting long-access versus short-access cocaine self-administration in rats: intermittent intake promotes addiction symptoms independent of session length. *Addiction biology*, *24*(4), 641-651.

Andersen, S. L., Arvanitogiannis, A., Pliakas, A. M., LeBlanc, C., & Carlezon Jr, W. A. (2002). Altered responsiveness to cocaine in rats exposed to methylphenidate during development. *Nature neuroscience*, *5*(1), 13.

Anderson, V. R., & Keating, G. M. (2007). Spotlight on Methylphenidate Controlled-Delivery Capsules (Equasym™ XL, Metadate CD™) in the Treatment of Children and Adolescents with Attention-Deficit Hyperactivity Disorder. *CNS drugs*, *21*(2), 173-175.

Appelbaum, K. L. (2009). Attention Deficit Hyperactivity Disorder in Prison: A Treatment Protocol. *The Journal of the American Academy of Psychiatry and the Law*, *37*(1), 5.

Arnsten, A. F., & Dudley, A. G. (2005). Methylphenidate improves prefrontal cortical cognitive function through α2 adrenoceptor and dopamine D1 receptor actions: Relevance to therapeutic effects in Attention Deficit Hyperactivity Disorder. *Behavioral and Brain Functions*, *1*(1), 2.

Askenasy, E. P., Taber, K. H., Yang, P. B., & Dafny, N. (2007). Methylphenidate (Ritalin): behavioral studies in the rat. *International Journal of Neuroscience*, *117*(6), 757-794.

Babinski, L. M., Hartsough, C. S., & Lambert, N. M. (1999). Childhood conduct problems, hyperactivity-impulsivity, and inattention as predictors of adult criminal activity. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *40*(3), 347-355.

Banaschewski, T., Becker, K., Scherag, S., Franke, B., & Coghill, D. (2010). Molecular genetics of attention-deficit/hyperactivity disorder: An overview. *European Child & Adolescent Psychiatry*, *19*(3), 237–257.

Barati, M., Ahmadpanah, M., & Soltanian, A. R. (n.d.). *Prevalence and Factors Associated with Methamphetamine Use among Adult Substance Abusers*. 6.

Barbaresi, W. J., Colligan, R. C., Weaver, A. L., Voigt, R. G., Killian, J. M., & Katusic, S. K. (2013). Mortality, ADHD, and Psychosocial Adversity in Adults With Childhood ADHD: A Prospective Study. *PEDIATRICS*, *131*(4), 637–644.

Baumeister, S. E., & Tossmann, P. (2005). Association between early onset of cigarette, alcohol and cannabis use and later drug use patterns: an analysis of a survey in European metropolises. *European Addiction Research*, *11*(2), 92-98.

Barkley, R. A., Fischer, M., Smallish, L., & Fletcher, K. (2003). Does the Treatment of Attention-Deficit/Hyperactivity Disorder With Stimulants Contribute to Drug Use/Abuse? A 13-Year Prospective Study. *PEDIATRICS*, *111*(1), 97–109.

Barkley, R. A., & Murphy, K. R. (2010). Impairment in Occupational Functioning and Adult ADHD: The Predictive Utility of Executive Function (EF) Ratings Versus EF Tests. *Archives of Clinical Neuropsychology*, *25*(3), 157–173.

Barkley, Russell A., Fischer, M., Smallish, L., & Fletcher, K. (2004). Young adult follow-up of hyperactive children: Antisocial activities and drug use. *Journal of Child Psychology and Psychiatry*, *45*(2), 195–211.

Bartl, J., Link, P., Schlosser, C., Gerlach, M., Schmitt, A., Walitza, S., Riederer, P., & Grünblatt, E. (2010). Effects of methylphenidate: The cellular point of view. *ADHD Attention Deficit and Hyperactivity Disorders*, *2*(4), 225–232.

Batra, V., Guerin, G. F., Goeders, N. E., & Wilden, J. A. (2016). A General Method for Evaluating Deep Brain Stimulation Effects on Intravenous Methamphetamine Self-Administration. *Journal of Visualized Experiments*, *107*.

Becker, J. B., Perry, A. N., & Westenbroek, C. (2012). Sex differences in the neural mechanisms mediating addiction: A new synthesis and hypothesis. *Biology of Sex Differences*, *3*(1), 14.

Berridge, C. W., & Arnsten, A. F. (2013). Psychostimulants and motivated behavior: arousal and cognition. *Neuroscience & Biobehavioral Reviews*, *37*(9), 1976-1984
.

Berridge, C. W., Devilbiss, D. M., Andrzejewski, M. E., Arnsten, A. F., Kelley, A. E., Schmeichel, B., ... & Spencer, R. C. (2006). Methylphenidate preferentially increases catecholamine neurotransmission within the prefrontal cortex at low doses that enhance cognitive function. *Biological psychiatry*, *60*(10), 1111-1120.

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation ofbehavioral state and state-dependent cognitive processes. *Brain research reviews*, *42*(1), 33-84.

Biederman, J. (1998). Attention-deficit/hyperactivity disorder: a life-span perspective. *The Journal of clinical psychiatry*, *59*, 4-16.

Biederman, J., Faraone, S. V., Taylor, A., Sienna, M., Williamson, S., & Fine, C. (1998). Diagnostic continuity between child and adolescent ADHD: findings from a longitudinal clinical sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, *37*(3), 305-313

Biederman, J., Mick, E., & Faraone, S. V. (2000). Age-dependent decline of symptoms of attention deficit hyperactivity disorder: impact of remission definition and symptom type. *American journal of psychiatry*, *157*(5), 816-818.

Biederman, J., Petty, C. R., Evans, M., Small, J., & Faraone, S. V. (2010). How persistent is ADHD? A controlled 10-year follow-up study of boys with ADHD. *Psychiatry research*, *177*(3), 299-304.

Biederman, J., Wilens, T., Mick, E., Faraone, S. V., Weber, W., Curtis, S., Thornell, A., Pfister, K., Jetton, J. G., & Soriano, J. (1997). Is ADHD a Risk Factor for Psychoactive Substance Use Disorders? Findings From a Four-Year Prospective Follow-up Study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *36*(1), 21–29.

Bobzean, S. A. M., DeNobrega, A. K., & Perrotti, L. I. (2014). Sex differences in the neurobiology of drug addiction. *Experimental Neurology*, *259*, 64–74.

Bock, J., Breuer, S., Poeggel, G., & Braun, K. (2017). Early life stress induces attention-deficit hyperactivity disorder (ADHD)-like behavioral and brain metabolic dysfunctions: functional imaging of methylphenidate treatment in a novel rodent model. *Brain Structure and Function*, *222*(2), 765-780.

Bonci, A., & Williams, J. T. (1997). Increased probability of GABA release during withdrawal from morphine. *Journal of Neuroscience*, *17*(2), 796-803.

Boutrel, B. (2008). A neuropeptide-centric view of psychostimulant addiction. *British journal of pharmacology*, *154*(2), 343-357.

Brandon, C. L., Marinelli, M., Baker, L. K., & White, F. J. (2001). Enhanced reactivity and vulnerability to cocaine following methylphenidate treatment in adolescent rats. *Neuropsychopharmacology*, *25*(5), 651.

Brecht, M.-L., O'Brien, A., von Mayrhauser, C., & Anglin, M. D. (2004). Methamphetamine use behaviors and gender differences. *Addictive Behaviors*, *29*(1), 89–106.

Brenhouse, H. C., Napierata, L., Kussmaul, L., Leussis, M., & Andersen, S. L. (2009). Juvenile methylphenidate exposure and factors that influence incentive processing. *Developmental neuroscience*, *31*(1-2), 95-106.

Brown, S. A., D'Amico, E. J., McCarthy, D. M., & Tapert, S. F. (2001). Four-year outcomes from adolescent alcohol and drug treatment. *Journal of Studies on Alcohol*, *62*(3), 381- 388.

Bruggisser, M., Bodmer, M., & Liechti, M. E. (2011). Severe toxicity due to injected but not oral or nasal abuse of methylphenidate tablets. *Swiss Med Wkly*, *141*, w13267.

Carpentier, P. J., de Jong, C. A. J., Dijkstra, B. A. G., Verbrugge, C. A. G., & Krabbe, P. F. M. (2005). A controlled trial of methylphenidate in adults with attention deficit/hyperactivity disorder and substance use disorders. *Addiction*, *100*(12), 1868–1874.

Cartier, J., Farabee, D., & Prendergast, M. L. (2006). Methamphetamine Use, Self-Reported Violent Crime, and Recidivism Among Offenders in California Who Abuse Substances. *Journal of Interpersonal Violence*, *21*(4),435–445.

Centers for Disease Control and Prevention. (2010). www.cdc.gov/ncbddd/adhd/data

Chait, L. D. (1994).Reinforcing and subjective effects of methylphenidate in humans.*Behavioural pharmacology*.

Charach, A., Yeung, E., Volpe, T., Goodale, T., & dosReis, S. (2014). Exploring stimulant treatment in ADHD: Narratives of young adolescents and their parents. *BMC Psychiatry*, *14*(1), 110.

Cheng, J., Xiong, Z., Duffney, L. J., Wei, J., Liu, A., Liu, S., Chen, G.-J., & Yan, Z. (2014). Methylphenidate Exerts Dose-Dependent Effects on Glutamate Receptors and Behaviors. *Biological Psychiatry*, *76*(12), 953–962.

Chiu, C. T., Ma, T., & Ho, K. (2006). Methamphetamine-induced behavioral sensitization in mice: alterations in μ-opioid receptor. *Journal of biomedical science*, *13*(6), 797-811.

Cho, A. K., & Melega, W. P. (2001). Patterns of methamphetamine abuse and their consequences. *Journal of addictive diseases*, *21*(1), 21-34.

Clark, D. B., Parker, A. M., & Lynch, K. G. (1999). Psychopathology and substance-related problems during early adolescence: A survival analysis. *Journal of clinical child psychology*, *28*(3), 333-341.

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

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., Atkinson, L. Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H.-C., Shokraneh, F., Xia, J., & Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *The Lancet Psychiatry*, *5*(9), 727–738

Courtney, K. E., & Ray, L. A. (2014). Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug and alcohol dependence*, *143*, 11-21.

Dalsgaard, S., Mortensen, P. B., Frydenberg, M., & Thomsen, P. H. (2014). ADHD, stimulant treatment in childhood and subsequent substance abuse in adulthood—a naturalistic long-term follow-up study. *Addictive Behaviors*, *39*(1), 325-328.

Dafny, N., & Yang, P. B. (2006). The role of age, genotype, sex, and route of acute and chronic administration of methylphenidate: A review of its locomotor effects. *Brain Research Bulletin*, *68*(6), 393–405.

Davidovitch, M., Koren, G., Fund, N., Shrem, M., & Porath, A. (2017). Challenges in defining the rates of ADHD diagnosis and treatment: trends over the last decade. *BMC pediatrics*, *17*(1), 218.

Daw, N. D., & Doya, K. (2006). The computational neurobiology of learning and reward. *Current Opinion in Neurobiology*, *16*(2), 199–204

Devilbiss, D. M., & Berridge, C. W. (2008). Cognition-Enhancing Doses of Methylphenidate Preferentially Increase Prefrontal Cortex Neuronal Responsiveness. *Biological Psychiatry*, *64*(7), 626–635

Ding, Y., Lin, H., Zhou, L., Yan, H., & He, N. (2014). Adverse childhood experiences and interaction with methamphetamine use frequency in the risk of methamphetamine-associated psychosis. *Drug and Alcohol Dependence, 142*, 295–300

Dluzen, D. E., & Liu, B. (2008). Gender differences in methamphetamine use and responses: A review. *Gender Medicine*, *5*(1), 24–35.

Dobkin, C., & Nicosia, N. (2009). The War on Drugs: Methamphetamine, Public Health, and Crime. *American Economic Review*, *99*(1), 324–349

Dougherty, D. M., Olvera, R. L., Acheson, A., Hill-Kapturczak, N., Ryan, S. R., & Mathias, C.W. (2016). Acute effects of methylphenidate on impulsivity and attentional behavior among adolescents comorbid for ADHD and conduct disorder. *Journal of Adolescence*, *53*, 222–230.

Dunlop, A. J., & Newman, L. K. (2016). ADHD and psychostimulants–overdiagnosis and overprescription. *Med J Aust*, *204*(4), 139.

DuPont, R. L., Coleman, J. J., Bucher, R. H., & Wilford, B. B. (2008). Characteristics and motives of college students who engage in nonmedical use of methylphenidate. *The American Journal on Addictions*, *17*(3), 167-171

Edwards, S., & Koob, G. F. (2013). Escalation of drug self-administration as a hallmark of persistent addiction liability. *Behavioural pharmacology*, *24*.
.

Engert, V., & Pruessner, J. C. (2008). Dopaminergic and noradrenergic contributions to functionality in ADHD: the role of methylphenidate. *Current neuropharmacology*, *6*(4), 322-328.

Ernst, M., Zametkin, A. J., Matochik, J. A., Jons, P. H., & Cohen, R. M. (1998). DOPA decarboxylase activity in attention deficit hyperactivity disorder adults. A [fluorine-18] fluorodopa positron emission tomographic study. *Journal of Neuroscience*, *18*(15), 5901- 5907.

Estroff, T. W., Schwartz, R. H., & Hoffmann, N. G. (1989). Adolescent cocaine abuse: addictive potential, behavioral and psychiatric effects. *Clinical pediatrics*, *28*(12), 550-555.

Faraone, S. V. (2018). The pharmacology of amphetamine and methylphenidate: relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. *Neuroscience & Biobehavioral Reviews*, *87*, 255-270.

Faraone, S. V., & Biederman, J. (1998). Neurobiology of attention-deficit hyperactivity disorder. *Biological psychiatry*, *44*(10), 951-958.

Faraone, S. V., Biederman, J., Jetton, J. G., & Tsuang, M. T. (1997). Attention deficit disorder and conduct disorder: longitudinal evidence for a familial subtype. *Psychological medicine*, *27*(2), 291-300.

Faraone, S. V., & Larsson, H. (2019). Genetics of attention deficit hyperactivity disorder. *Molecular Psychiatry*, *24*(4), 562–575

Fletcher, J. M., & Wolfe, B. L. (2009). Long-Term Consequences of Childhood ADHD on Criminal Activities. *SSRN Electronic Journal*

Flory, K., Milich, R., Lynam, D. R., Leukefeld, C., & Clayton, R. (2003). Relation between childhood disruptive behavior disorders and substance use and dependence symptoms in young adulthood: Individuals with symptoms of attention-deficit/hyperactivity disorder are uniquely at risk. *Psychology of Addictive Behaviors*, *17*(2), 151.

Freitag, C. M., Hänig, S., Schneider, A., Seitz, C., Palmason, H., Retz, W., & Meyer, J. (2012). Biological and psychosocial environmental risk factors influence symptom severity and psychiatric comorbidity in children with ADHD. *Journal of Neural Transmission*, *119*(1), 81–94

Ford, C. P., Mark, G. P., & Williams, J. T. (2006). Properties and opioid inhibition of mesolimbic dopamine neurons vary according to target location. *Journal of Neuroscience*, *26*(10), 2788-2797.

Gahr, M., & Plener, P. L. (2016). Methylphenidate abuse: An overview. In *Neuropathology of drug addictions and substance misuse* (pp. 651-659). Academic Press.

Gardner, E. L. (2000). What we have learned about addiction from animal models of drug self-administration. *American Journal on Addictions*, *9*(4), 285-313.

Gardner, E. L. (2011). Addiction and brain reward and antireward pathways. In *Chronic Pain and Addiction* (Vol. 30, pp. 22-60). Karger Publishers.

Genro, J. P., Kieling, C., Rohde, L. A., & Hutz, M. H. (2010). Attention-deficit/hyperactivity disorder and the dopaminergic hypotheses. *Expert review of neurotherapeutics*, *10*(4), 587-601.

Ginsberg, Y., Hirvikoski, T., & Lindefors, N. (2010). Attention Deficit Hyperactivity Disorder (ADHD) among longer-term prison inmates is a prevalent, persistent and disabling disorder. *BMC Psychiatry*, *10*(1), 112

GIULIANO, K., & GEYER, E. (2017). ADHD: Overdiagnosed and overtreated, or misdiagnosed and mistreated?. *Cleveland Clinic journal of medicine*, *84*(11), 873.

Grant, K. M., LeVan, T. D., Wells, S. M., Li, M., Stoltenberg, S. F., Gendelman, H. E., Carlo, G., & Bevins, R. A. (2012). Methamphetamine-Associated Psychosis. *Journal of Neuroimmune Pharmacology*, *7*(1), 113–139

Goeders, N. E., & Schmoutz, C. D. (2019). *U.S. Patent Application No. 15/997,020*.

Greenhill, L. L., Swanson, J. M., Vitiello, B., Davies, M., Clevenger, W., Wu, M., ... & Elliott, G. R. (2001). Impairment and deportment responses to different methylphenidate doses in children with ADHD: the MTA titration trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(2), 180-187.

Haile CN, Kosten TA. Differential effects of D1- and D2-like compounds on cocaine self-administration in Lewis and Fischer 344 inbred rats. J Pharmacol Exp Ther 2001;299:509–18

Håkansson, A., & Jesionowska, V. (2018). Associations between substance use and type of crime in prisoners with substance use problems – a focus on violence and fatal violence. *Substance Abuse and Rehabilitation*, *Volume 9*, 1–9.

Haker, H., Kawohl, W., Herwig, U., & Rössler, W. (2013). Mirror neuron activity during contagious yawning—An fMRI study. *Brain Imaging and Behavior*, *7*(1), 28–34

Hamed, A. M., Kauer, A. J., & Stevens, H. E. (2015). Why the Diagnosis of Attention Deficit Hyperactivity Disorder Matters. *Frontiers in Psychiatry*, *6*.

Hanisch, C., Konrad, K., Günther, T., & Herpertz-Dahlmann, B. (2004). Age-dependent neuropsychological deficits and effects of methylphenidate in children with attention-deficit/hyperactivity disorder: a comparison of pre-and grade-school children. *Journal of Neural Transmission*, *111*(7), 865-881.

Harrod, S. B., Dwoskin, L. P., Crooks, P. A., Klebaur, J. E., & Bardo, M. T. (2001). Lobeline attenuates d-methamphetamine self-administration in rats. *Journal of Pharmacology and Experimental Therapeutics*, *298*(1), 172-179.

Hart, E. L., Lahey, B. B., Loeber, R., Applegate, B., & Frick, P. J. (1995). Developmental change in attention-deficit hyperactivity disorder in boys: a four-year longitudinal study. *Journal of abnormal child psychology*, *23*(6), 729-749

Hirose, N., Murakawa, K., Takada, K., Oi, Y., Suzuki, T., Nagase, H., ... & Koshikawa, N.(2005). Interactions among mu-and delta-opioid receptors, especially putative delta1-and delta2-opioid receptors, promote dopamine release in the nucleus accumbens. *Neuroscience*, *135*(1), 213-225.

Humphreys, K. L., Eng, T., & Lee, S. S. (2013). Stimulant medication and substance use outcomes: a meta-analysis. *JAMA psychiatry*, *70*(7), 740-749.

Hornung, J. P. (2003). The human raphe nuclei and the serotonergic system. *Journal of chemical neuroanatomy*, *26*(4), 331-343.

Hser, Y.-I., Evans, E., & Huang, Y.-C. (2005). Treatment outcomes among women and men methamphetamine abusers in California. *Journal of Substance Abuse Treatment*, *28*(1), 77–85.

Imperio, C. G., McFalls, A. J., Hadad, N., Blanco-Berdugo, L., Masser, D. R., Colechio, E. M., ... & Grigson, P. S. (2018). Exposure to environmental enrichment attenuates addiction-like behavior and alters molecular effects of heroin self-administration in rats. *Neuropharmacology*, *139*, 26-40.

Irwin, K. (1995). Ideology, pregnancy and drugs: differences between crack-cocaine, heroin and methamphetamine users. *Contemporary Drug Problems*, *22*(4), 613-638.

Itzhak, Y., Martin, J. L., & Ali, S. F. (2002). Methamphetamine-induced dopaminergic neurotoxicity in mice: long-lasting sensitization to the locomotor stimulation and desensitization to the rewarding effects of methamphetamine. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *26*(6), 1177-1183

.

Jaboinski, J., Cabral, J. C. C., Campos, R., & Barros, D. M. (2015). Exposure to methylphenidate during infancy and adolescence in non-human animals and sensitization to abuse of psychostimulants later in life: a systematic review. *Trends in psychiatry and psychotherapy*, *37*(3), 107-117.

Kalivas, P. W. (1995). Interactions between dopamine and excitatory amino acids in behavioral sensitization to psychostimulants. *Drug and alcohol dependence*, *37*(2), 95-100.

Kasparek, T., Theiner, P., & Filova, A. (2015). Neurobiology of ADHD From Childhood to Adulthood: Findings of Imaging Methods. *Journal of Attention Disorders*, *19*(11), 931– 943.

Kaye, S., Darke, S., & Torok, M. (2013). Attention deficit hyperactivity disorder (ADHD) among illicit psychostimulant users: A hidden disorder?: ADHD among illicit psychostimulant users. *Addiction*, *108*(5), 923–931.

Kidd, P. M. (2000). Attention Deficit/Hyperactivity Disorder (ADHD) in Children: Rationale for Its Integrative Management. *Attention Deficit Hyperactivity Disorder*, *5*(5), 27.

Kirkpatrick, M. G., Gunderson, E. W., Johanson, C.-E., Levin, F. R., Foltin, R. W., & Hart, C. L. (2012). Comparison of intranasal methamphetamine and d-amphetamine self-administration by humans: Amphetamine self-administration. *Addiction*, *107*(4), 783–791.

Kieffer, B. L., & Gavériaux-Ruff, C. (2002). Exploring the opioid system by gene knockout. *Progress in neurobiology*, *66*(5), 285-306.

Kóbor, A., Takács, Á., Urbán, R., & Csépe, V. (2012). The latent classes of subclinical ADHD symptoms: Convergences of multiple informant reports. *Research in developmental disabilities*, *33*(5), 1677-1689.

Kollins, S. H. (2003). Comparing the abuse potential of methylphenidate versus other stimulants: a review of available evidence and relevance to the ADHD patient. *The Journal of clinical psychiatry*.

Kollins, S. H. (2008). ADHD, substance use disorders, and psychostimulant treatment: current literature and treatment guidelines. *Journal of attention disorders*, *12*(2), 115-125.

Kollins, S. H., MacDonald, E. K., & Rush, C. R. (2001). Assessing the abuse potential of methylphenidate in nonhuman and human subjects: a review. *Pharmacology Biochemistry and Behavior*, *68*(3), 611-627.

Konstenius, M., Jayaram-Lindström, N., Beck, O., & Franck, J. (2010). Sustained release methylphenidate for the treatment of ADHD in amphetamine abusers: A pilot study. *Drug and Alcohol Dependence*, *108*(1–2), 130–133.

Konrad, K., Günther, T., Hanisch, C., & Herpertz-Dahlmann, B. (2004). Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*(2), 191-198.

Konrad, K., Neufang, S., Fink, G. R., & Herpertz-Dahlmann, B. (2007). Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(12), 1633-1641.

Konrad, K., Günther, T., Hanisch, C., & Herpertz-Dahlmann, B. (2004). Differential effects of methylphenidate on attentional functions in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *43*(2), 191-198.

Konrad, K., Neufang, S., Fink, G. R., & Herpertz-Dahlmann, B. (2007). Long-term effects of methylphenidate on neural networks associated with executive attention in children with ADHD: results from a longitudinal functional MRI study. *Journal of the American Academy of Child & Adolescent Psychiatry*, *46*(12), 1633-1641.

Kosten TA, Miserendino MJD, Haile CN, DeCaprio JL, Jatlow PI, Nestler EJ. Acquisition and maintenance of intravenous cocaine selfadministration in Lewis and Fischer inbred rat strains. Brain Res 1997;778:418–29.

Koob, G. F., & Le Moal, M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science*, *278*(5335), 52-58.

Koob, G. F., & Le Moal, M. (2005). Plasticity of reward neurocircuitry and the'dark side'of drug addiction. *Nature neuroscience*, *8*(11), 1442-1444.

Koob, G. F., & Volkow, N. D. (2016). Neurobiology of addiction: a neurocircuitry analysis. *The Lancet Psychiatry*, *3*(8), 760-773.

Kuczenski, R., & Segal, D. S. (1997). Effects of methylphenidate on extracellular dopamine, serotonin, and norepinephrine: comparison with amphetamine. *Journal of neurochemistry*, *68*(5), 2032-2037.

Kuczenski, R., & Segal, D. S. (2002). Exposure of Adolescent Rats to Oral Methylphenidate: Preferential Effects on Extracellular Norepinephrine and Absence of Sensitization and Cross-Sensitization to Methamphetamine. *The Journal of Neuroscience*, *22*(16), 7264–7271.

Lambert, E., Normand, J., Stall, R., Aral, S., & Vlahov, D. (2005). Introduction: new dynamics of HIV risk among drug-using men who have sex with men. *Journal of urban health: bulletin of the New York Academy of Medicine*, *82*(Suppl 1), i1. Lamonica, A. K., & Boeri, M. (2013). *An Exploration of the Relationship between the Use of Methamphetamine and Prescription Drugs*. 17.

Leonard, B. E., McCartan, D., White, J., & King, D. J. (2004). Methylphenidate: A review of its neuropharmacological, neuropsychological and adverse clinical effects. *Human Psychopharmacology: Clinical and Experimental*, *19*(3), 151–180.

Linford-Hughes, A. R., Davies, S. J. C., Taylor, L. G., Williams, T. M., Daglish, M. R. C., Pandit, S., ... & Nutt, D. J. (2004). A PET study of opioid receptors in abstinent alcohol dependent patients. *Journal of Psychopharmacology*, *18*(3), A41-A41.

Linssen, A. M., Sambeth, A., Vuurman, E. F., & Riedel, W. J. (2014). Cognitive effects of methylphenidate in healthy volunteers: a review of single dose studies. *International journal of neuropsychopharmacology*, *17*(6), 961-977.

Lukas, S. E. (1997). Proceedings of the national consensus meeting on the use, abuse and sequelae of abuse of methamphetamine with implications for prevention, treatment and research. DHHS Publication SMA. 96–8013.

Lyoo, I. K., Yoon, S., Kim, T. S., Lim, S. M., Choi, Y., Kim, J. E., ... & Renshaw, P. F. (2015). Predisposition to and effects of methamphetamine use on the adolescent brain. *Molecular psychiatry*, *20*(12), 1516-1524.

Madras, B. K., Miller, G. M., & Fischman, A. J. (2002). The dopamine transporter: Relevance to attention deficit hyperactivity disorder (ADHD). *Behavioural Brain Research*, *130*(1–2), 57–63.

Mannuzza, S., Klein, R. G., & Addalli, K. A. (1991). Young adult mental status of hyperactive boys and their brothers: a prospective follow-up study. *Journal of the american academy of child & adolescent psychiatry*, *30*(5), 743-751.

Mannuzza, S., Klein, R. G., Truong, N. L., Moulton III, Ph D, J. L., Roizen, E. R., Howell, K. H., & Castellanos, F. X. (2008). Age of methylphenidate treatment initiation in children with ADHD and later substance abuse: prospective follow-up into adulthood. *American Journal of Psychiatry*, *165*(5), 604-609.

Mansour, A., Fox, C. A., Akil, H., & Watson, S. J. (1995). Opioid-receptor mRNA expression in the rat CNS: anatomical and functional implications. *Trends in neurosciences*, *18*(1), 22-29.

Martin, W. R., Sloan, J. W., Sapira, J. D., & Jasinski, D. R. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology & Therapeutics*, *12*(2part1), 245–258.

Martins, S., Tramontina, S., Polanczyk, G., Eizirik, M., Swanson, J. M., & Rohde, L. A. (2004). Weekend holidays during methylphenidate use in ADHD children: a randomized clinical trial. *Journal of child and adolescent psychopharmacology*, *14*(2), 195-206.

Matsumoto, T., Kamijo, A., Yamaguchi, A., Iseki, E., & Hirayasu, Y. (2005). Childhood histories of attention-deficit hyperactivity disorders in Japanese methamphetamine and inhalant abusers: Preliminary report. *Psychiatry and Clinical Neurosciences*, *59*(1), 102– 105.

McCambridge, J., & Strang, J. (2005). Deterioration over time in effect of motivational interviewing in reducing drug consumption and related risk among young people. *Addiction*, *100*(4), 470-478.

McKAY, K. E., & Halperin, J. M. (2001). ADHD, aggression, and antisocial behavior across the lifespan: interactions with neurochemical and cognitive function. *Annals of the New York Academy of Sciences*, *931*(1), 84-96.

McMillan, D. E., Hardwick, W. C., Li, M., Gunnell, M. G., Carroll, F. I., Abraham, P., & Owens, S. M. (2004). Effects of murine-derived anti-methamphetamine monoclonal antibodies on (+)-methamphetamine self-administration in the rat. *Journal of Pharmacology and Experimental Therapeutics*, *309*(3), 1248-1255.

Meririnne, E., Kankaanpää, A., & Seppälä, T. (2001). Rewarding properties of methylphenidate: sensitization by prior exposure to the drug and effects of dopamine D1- and D2-receptor antagonists. *Journal of Pharmacology and Experimental Therapeutics*, *298*(2), 539-550.

Milberger, S., Biederman, J., Faraone, S. V., Wilens, T., & Chu, M. P. (1997). Associations between ADHD and psychoactive substance use disorders: Findings from a longitudinal study of high-risk siblings of ADHD children. *American Journal on Addictions*, *6*(4), 318-329.

Miller, D. J., Derefinko, K. J., Lynam, D. R., Milich, R., & Fillmore, M. T. (2010). Impulsivity and Attention Deficit-Hyperactivity Disorder: Subtype Classification Using the UPPS Impulsive Behavior Scale. *Journal of Psychopathology and Behavioral Assessment*, *32*(3), 323–332.

Molina, B. S., Hinshaw, S. P., Arnold, L. E., Swanson, J. M., Pelham, W. E., Hechtman, L., ... & Greenhill, L. L. (2013). Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD)(MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*(3), 250-263.

Molina, B. S., Smith, B. H., & Pelham, W. E. (1999). Interactive effects of attention deficit hyperactivity disorder and conduct disorder on early adolescent substance use. *Psychology of Addictive Behaviors*, *13*(4), 348.Morton, W. A., & Stockton, G. G. (2000). Methylphenidate abuse and psychiatric side effects. *Primary care companion to the Journal of clinical psychiatry*, *2*(5), 159.

Morton, W. A., & Stock, G. G. (2000). Methylphenidate Abuse and Psychiatric Side Effects. *The Primary Care Companion to The Journal of Clinical Psychiatry*, *02*(05), 159–164.

Murakawa, K., Hirose, N., Takada, K., Suzuki, T., Nagase, H., Cools, A. R., & Koshikawa, N. (2004). Deltorphin II enhances extracellular levels of dopamine in the nucleus accumbens via opioid receptor-independent mechanisms. *European journal of pharmacology*, *491*(1), 31-36.

Nielsen, S., Bruno, R., & Schenk, S. (Eds.). (2017). *Non-medical and illicit use of psychoactive drugs* (Vol. 34). Springer International Publishing.

Nurco, D. N., Hanlon, T. E., & Kinlock, T. W. (1991). Recent research on the relationship between illicit drug use and crime. *Behavioral Sciences & the Law*, *9*(3), 221-242.

Obermeit, L. C., Cattie, J. E., Bolden, K. A., Marquine, M. J., Morgan, E. E., Franklin, D. R., Atkinson, J. H., Grant, I., & Woods, S. P. (2013). Attention-deficit/hyperactivity disorder among chronic methamphetamine users: Frequency, persistence, and adverse effects on everyday functioning. *Addictive Behaviors*, *38*(12), 2874–2878.

O'Connor, E. C., Chapman, K., Butler, P., & Mead, A. N. (2011). The predictive validity of the rat self-administration model for abuse liability. *Neuroscience & Biobehavioral Reviews*, *35*(3), 912-938.

Outram, S. M. (2010). The use of methylphenidate among students: the future of enhancement?. *Journal of Medical Ethics*, *36*(4), 198-202.

Palfrey, J. S., Levine, M. D., Walker, D. K., & Sullivan, M. (1985). The emergence of attention deficits in early childhood: A prospective study. *Journal of Developmental and Behavioral Pediatrics*, *6*(6), 339–348.

Parran, T. V., & Jasinski, D. R. (1991). Intravenous methylphenidate abuse: prototype for prescription drug abuse. *Archives of internal medicine*, *151*(4), 781-783.

Perepletchikova, F., Krystal, J. H., & Kaufman, J. (2008). Practitioner review: adolescent alcohol use disorders: assessment and treatment issues. *Journal of Child Psychology and Psychiatry*, *49*(11), 1131-1154.

Pierce, R. C., Duffy, P., & Kalivas, P. W. (1995). Sensitization to cocaine and dopamine autoreceptor subsensitivity in the nucleus accumbens. *Synapse*, *20*(1), 33-36.

Pierce, R. C., & Kalivas, P. W. (1997). A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain research reviews*, *25*(2), 192- 216

Pietras, C. J., Cherek, D. R., Lane, S. D., Tcheremissine, O. V., & Steinberg, J. L. (2003). Effectsof methylphenidate on impulsive choice in adult humans. *Psychopharmacology*, *170*(4), 390-398.

Prendergast, M. L., Messina, N. P., Hall, E. A., & Warda, U. S. (2011). The relative effectiveness of women-only and mixed-gender treatment for substance-abusing women. *Journal of Substance Abuse Treatment*, *40*(4), 336–348

Polanczyk, G., De Lima, M. S., Horta, B. L., Biederman, J., & Rohde, L. A. (2007). The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *American journal of psychiatry*, *164*(6), 942-948.

Prince, J. B., Morrison, N. R., & Wilens, T. E. (2015). Pharmacotherapy of ADHD in adults. *Attention-deficit hyperactivity disorder in adults and children*, 276.

Radfar, S. R., & Rawson, R. A. (2014). Current research on methamphetamine: epidemiology, medical and psychiatric effects, treatment, and harm reduction efforts. *Addiction & health*, *6*(3-4), 146.

Ramaekers, J. G., Evers, E. A., Theunissen, E. L., Kuypers, K. P. C., Goulas, A., & Stiers, P. (2013). Methylphenidate reduces functional connectivity of nucleus accumbens in brain reward circuit. *Psychopharmacology*, *229*(2), 219-226.

Rapport, M. D., Jones, J. T., DuPaul, G. J., Kelly, K. L., Gardner, M. J., Tucker, S. B., & Shea, M. S. (1987). Attention deficit disorder and methylphenidate: group and single- subject analyses of dose effects on attention in clinic and classroom settings. *Journal of Clinical Child Psychology*, *16*(4), 329-338.

Reinhardt, M. C., & Reinhardt, C. A. U. (2013). Attention deficit-hyperactivity disorder, comorbidities, and risk situations. *Jornal de Pediatria (Versão em Português)*, *89*(2), 124–130.

Ritz, M. C., & Kuhar, M. J. (1989). Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine.*Journal of Pharmacology and Experimental Therapeutics*, *248*(3), 1010-1017.

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 research reviews*, *11*(2), 157-198.

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

Robinson, T. E., & Berridge, K. C. (2000). The psychology and neurobiology of addiction: an incentive–sensitization view. *Addiction*, *95*(8s2), 91-117.

Rowland, A. S., Skipper, B. J., Umbach, D. M., Rabiner, D. L., Campbell, R. A., Naftel, A. J., & Sandler, D. P. (2015). The Prevalence of ADHD in a Population-Based Sample. *Journal of Attention Disorders*, *19*(9), 741–754

Salo, R., Fassbender, C., Iosif, A.-M., Ursu, S., Leamon, M. H., & Carter, C. (2013). Predictors of methamphetamine psychosis: History of ADHD-relevant childhood behaviors and drug exposure. *Psychiatry Research*, *210*(2), 529–535

Sandoval, V., Riddle, E. L., Hanson, G. R., & Fleckenstein, A. E. (2003). Methylphenidate alters vesicular monoamine transport and prevents methamphetamine-induced dopaminergic deficits. *Journal of Pharmacology and Experimental Therapeutics*, *304*(3), 1181-1187.

Sato, M. (1992). A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Annals of the New York Academy of Sciences*, *654*(1), 160-170.

Schrantee, A., Tamminga, H. G., Bouziane, C., Bottelier, M. A., Bron, E. E., Mutsaerts, H. J. M., ... & Klein, S. (2016). Age-dependent effects of methylphenidate on the human dopaminergic system in young vs adult patients with attention-

deficit/hyperactivity disorder: a randomized clinical trial. *JAMA psychiatry*, *73*(9), 955-962.

Schubiner, H., Tzelepis, A., Milberger, S., Lockhart, N., Kruger, M., Kelley, B. J., & Schoener, E. P. (2000). Prevalence of attention-deficit/hyperactivity disorder and conduct disorder among substance abusers. *The Journal of clinical psychiatry*.

Seidman, L. J. (2006). Neuropsychological functioning in people with ADHD across the lifespan. *Clinical psychology review*, *26*(4), 466-485.

Shanks, R. A., Ross, J. M., Doyle, H. H., Helton, A. K., Picou, B. N., Schulz, J., ... & Lloyd, S. A. (2015). Adolescent exposure to cocaine, amphetamine, and methylphenidate cross-sensitizes adults to methamphetamine with drug-and sex-specific effects. *Behavioural brain research*, *281*, 116-124.

Shoji, Y., Delfs, J., & Williams, J. T. (1999). Presynaptic inhibition of GABAB-mediated synaptic potentials in the ventral tegmental area during morphine withdrawal. *Journal of Neuroscience*, *19*(6), 2347- 2355.

Sibley, M. H., Swanson, J. M., Arnold, L. E., Hechtman, L. T., Owens, E. B., Stehli, A., ... & Jensen, P. S. (2017). Defining ADHD symptom persistence in adulthood: optimizing sensitivity and specificity. *Journal of child psychology and psychiatry*, *58*(6), 655-662.

Smith, Robert C., and John M. Davis.(1977) Comparative effects of d-amphetamine, l-amphetamine and methylphenidate on mood in man. *Psychopharmacology* 53.1: 1-12.

Sobolewski, M., Allen, J. L., Morris-Schaffer, K., Klocke, C., Conrad, K., & Cory-Slechta, D. A. (2016). A novel, ecologically relevant, highly preferred, and non-invasive means of oral substance administration for rodents. *Neurotoxicology and teratology*, *56*, 75-80.

Solomon, R. L., & Corbit, J. D. (1974). An opponent-process theory of motivation: I. Temporal dynamics of affect. *Psychological review*, *81*(2), 119.

Spencer, T. J., Biederman, J., & Mick, E. (2007). Attention-deficit/hyperactivity disorder: diagnosis, lifespan, comorbidities, and neurobiology. *Journal of pediatric psychology*, *32*(6), 631-642.

Sterling, P., Eyer, J., Fisher, S., & Reason, J. (1988). Handbook of life stress, cognition and health. *Allostasis; A new paradigm to explain arousal pathology. New York: Wiley*, 629-649.

Stevens, M. C., Pearlson, G. D., Calhoun, V. D., & Bessette, K. L. (2018). Functional neuroimaging evidence for distinct neurobiological pathways in attention-

deficit/hyperactivity disorder. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, *3*(8), 675-685.

Swanson, J., Baler, R. D., & Volkow, N. D. (2011). Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. *Neuropsychopharmacology*, *36*(1), 207-226.

Swanson, J. M., Wigal, T. L., & Volkow, N. D. (2011). Contrast of medical and nonmedical use of stimulant drugs, basis for the distinction, and risk of addiction: comment on Smith and Farah (2011).

Swanson, J., & Volkow, N. (2001). Pharmacokinetic and pharmacodynamic properties of methylphenidate in humans. *Stimulant drugs and ADHD*, 259-282.

Swendsen, J., Conway, K. P., Degenhardt, L., Dierker, L., Glantz, M., Jin, R., ... & Kessler, R. C. (2009). Socio-demographic risk factors for alcohol and drug dependence: the 10-year follow-up of the national comorbidity survey. *Addiction*, *104*(8), 1346-1355.

Swendsen, J., & Le Moal, M. (2011). Individual vulnerability to addiction. *Annals of the New York Academy of Sciences*, *1216*(1), 73-85.

Tannock, R., Ickowicz, A., & Schachar, R. (1995). Differential effects of methylphenidate on working memory in ADHD children with and without comorbid anxiety. *Journal of the American Academy of Child & Adolescent Psychiatry*, *34*(7), 886-896.

Teter, C. J., Falone, A. E., Cranford, J. A., Boyd, C. J., & McCabe, S. E. (2010). Nonmedical use of prescription stimulants and depressed mood among college students: Frequency and routes of administration. *Journal of Substance Abuse Treatment*, *38*(3), 292–298.

Teter, C. J., McCabe, S. E., Boyd, C. J., & Guthrie, S. K. (2003). Illicit methylphenidate use in an undergraduate student sample: prevalence and risk factors. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, *23*(5), 609-617.

Thomas, R., Sanders, S., Doust, J., Beller, E., & Glasziou, P. (2015). Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics*, *135*(4), e994- e1001.

Trigo, J. M., Martin-García, E., Berrendero, F., Robledo, P., & Maldonado, R. (2010). The endogenous opioid system: a common substrate in drug addiction. *Drug and alcohol dependence*, *108*(3), 183-194.

Urban, K. R., & Gao, W. J. (2015). Evolution of the study of methylphenidate and its actions on the adult versus juvenile brain. *Journal of attention disorders*, *19*(7), 603-619.

Urban, K. R., Waterhouse, B. D., & Gao, W. J. (2012). Distinct age-dependent effects of methylphenidate on developing and adult prefrontal neurons. *Biological psychiatry*, *72*(10), 880-888.

Valvassori, S. S., Frey, B. N., Martins, M. R., Réus, G. Z., Schimidtz, F., Inácio, C. G., ... & Quevedo, J. (2007). Sensitization and cross-sensitization after chronic treatment with methylphenidate in adolescent Wistar rats. *Behavioural pharmacology*, *18*(3), 205-212.

Valvassori, S. S., Frey, B. N., Martins, M. R., Réus, G. Z., Schimidtz, F., Inácio, C. G., ... & Quevedo, J. (2007). Sensitization and cross-sensitization after chronic treatment with methylphenidate in adolescent Wistar rats. *Behavioural pharmacology*, *18*(3), 205-212

van Dyck, C. H., Quinlan, D. M., Cretella, L. M., Staley, J. K., Malison, R. T., Baldwin, R. M., ... & Innis, R. B. (2002). Unaltered dopamine transporter availability in adult attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *159*(2), 309-312.

Verheul, R., & van den Brink, W. (2000). The role of personality pathology in the aetiology and treatment of substance use disorders. *Current Opinion in Psychiatry*, *13*(2), 163-169.

Vitiello, B., Severe, J. B., Greenhill, L. L., Arnold, L. E., Abikoff, H. B., Bukstein, O. G., ... & March, J. S. (2001). Methylphenidate dosage for children with ADHD over time under controlled conditions: lessons from the MTA. *Journal of the American Academy of Child & Adolescent Psychiatry*, *40*(2), 188-196.

Volkow, N. D., Fowler, J. S., Wang, G., Ding, Y., & Gatley, S. J. (2002). Mechanism of action of methylphenidate: Insights from PET imaging studies. *Journal of Attention Disorders*, *6*(1_suppl), 31–43

Volkow, N. D., & Swanson, J. M. (2008). Does childhood treatment of ADHD with stimulant medication affect substance abuse in adulthood?

Volkow, N. D., Wang, G. J., Fowler, J. S., Logan, J., Angrist, B., Hitzemann, R., ... & Pappas, N. (1997). Effects of methylphenidate on regional brain glucose metabolism in humans: relationship to dopamine D2 receptors. *American Journal of Psychiatry*, *154*(1), 50-55.

Volkow, N. D., Wang, G. J., Newcorn, J., Fowler, J. S., Telang, F., Solanto, M. V., ... & Schulz,K. (2007). Brain dopamine transporter levels in treatment and drug naive adults with ADHD. *Neuroimage*, *34*(3), 1182-1190

Volkow, N. D., Wang, G. J., Tomasi, D., Kollins, S. H., Wigal, T. L., Newcorn, J. H., ... & Swanson, J. M. (2012). Methylphenidate-elicited dopamine increases in ventral striatumare associated with long-term symptom improvement in adults with attention deficit hyperactivity disorder. *Journal of neuroscience*, *32*(3), 841-849.

Vrecko, S. (2015). Everyday drug diversions: A qualitative study of the illicit exchange and non-medical use of prescription stimulants on a university campus. *Social Science & Medicine*, *131*, 297-304.

Wada, K., & Fukui, S. (1991). Residual symptoms in methamphetamine psychosis. *J Mental Health*, *37*, 161-68.

Wanchoo, S. J., Swann, A. C., & Dafny, N. (2009). Descending glutamatergic pathways of PFC are involved in acute and chronic action of methylphenidate. *Brain research*, *1301*, 68- 79.

Wang, G. J., Volkow, N. D., Wigal, T., Kollins, S. H., Newcorn, J. H., Telang, F., ... & Fowler, J. S. (2013). Long-term stimulant treatment affects brain dopamine transporter level in patients with attention deficit hyperactive disorder. *PloS one*, *8*(5), e63023.

Wermuth, L. (2000a). Methamphetamine Use: Hazards and Social Influences. *Journal of DrugEducation*, *30*(4), 423–433

White, H. R., Xie, M., Thompson, W., Loeber, R., & Stouthamer-Loeber, M. (2001). Psychopathology as a predictor of adolescent drug use trajectories. *Psychology of Addictive Behaviors*, *15*(3), 210.

Woods, S. P., Lovejoy, D. W., & Ball, J. D. (2002). Neuropsychological characteristics of adults with ADHD: A comprehensive review of initial studies. *The Clinical Neuropsychologist*, *16*(1), 12-34.

Wilens, T. E., Biederman, J., Mick, E., Faraone, S. V., & Spencer, T. (1997). Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance use disorders. *The Journal of nervous and mental disease*, *185*(8), 475-482.

Wilens, T. E., Biederman, J., & Mick, E. (1998). Does ADHD affect the course of substance abuse? Findings from a sample of adults with and without ADHD. *American Journal on Addictions*, *7*(2), 156-163.

Wilens, T. E., Gignac, M., Swezey, A., Monuteaux, M. C., & Biederman, J. (2006). Characteristics of Adolescents and Young Adults With ADHD Who Divert or Misuse Their Prescribed Medications. *Journal of the American Academy of Child & Adolescent Psychiatry*, *45*(4), 408–414

Yang, P. B., Swann, A. C., & Dafny, N. (2003). Chronic pretreatment with methylphenidate induces cross-sensitization with amphetamine. *Life sciences*, *73*(22), 2899-2911.

Yang, P. B., Swann, A. C., & Dafny, N. (2006). Dose-response characteristics of methylphenidate on locomotor behavior and on sensory evoked potentials recorded from the VTA, NAc, and PFC in freely behaving rats. *Behavioral and Brain Functions*, *2*(1), 3.

Yang, P. B., Swann, A. C., & Dafny, N. (2007). Methylphenidate treated at the test cage dose-dependent sensitization or tolerance depend on the behavioral assay used. *Critical Reviews™ in Neurobiology*, *19*(1).

Young, S., Moss, D., Sedgwick, O., Fridman, M., & Hodgkins, P. (2015). A meta-analysis of the prevalence of attention deficit hyperactivity disorder in incarcerated populations.*Psychological Medicine*, *45*(2), 247–258

Young, Susan, Gudjonsson, G., Chitsabesan, P., Colley, B., Farrag, E., Forrester, A., Hollingdale, J., Kim, K., Lewis, A., Maginn, S., Mason, P., Ryan, S., Smith, J., Woodhouse, E., & Asherson, P. (2018). Identification and treatment of offenders with attention-deficit/hyperactivity disorder in the prison population: A practical approach based upon expert consensus. *BMC Psychiatry*, *18*(1), 281.

Zaczek, R., Battaglia, G., Contrera, J. F., Culp, S., & De Souza, E. B. (1989). Methylphenidate and pemoline do not cause depletion of rat brain monoamine markers similar to that observed with methamphetamine. *Toxicology and Applied Pharmacology*, *100*(2), 227–233.

Zito, J. M. (2000). Pharmacoepidemiology of methylphenidate and other medications for the treatment of ADHD. *AUTHOR Manderscheid, Ronald W., Ed.; Henderson, Marilyn J., Ed. TITLE Mental Health, United States, 2000. INSTITUTION Substance Abuse and Mental Health Services Administration*, *20*, 128.