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Stimulants and the Risk for Psychosis: A Study of Individuals at Clinical High Risk and the Relation of Symptoms with Use of Stimulant Medication

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Stimulants and the Risk for Psychosis: A Study of Individuals at Clinical High Risk and the Relation of Symptoms with Use of Stimulant Medication

By

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B.A., Washington University in Saint Louis, 2008

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An abstract of
A thesis submitted to the Faculty of the Graduate School of Emory University in partial fulfillment of the requirements for the degree of
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Abstract

Stimulants and the Risk for Psychosis: A Study of Individuals at Clinical High Risk and the Relation of Symptoms with Use of Stimulant Medication

By Arthur T. Ryan

Clinical high risk (CHR) individuals display attenuated versions of psychotic symptoms, and are at an increased risk of developing schizophrenia and other psychotic disorders when compared with the general population. Illicit psychostimulants, such as methamphetamine, are known to exacerbate the symptoms of individuals with schizophrenia. Prescription psychostimulants are chemically similar to illicit psychostimulants and are commonly used to treat the symptoms of Attention Deficit Hyperactivity Disorder (ADHD). No published report has examined the effects of prescription psychostimulants on individuals with CHR.

CHR individuals were administered the Structured Interview for Prodromal Syndromes (SIPS). Participants' prescription drug history was also recorded, along with their use of illicit drugs. Analyses were conducted to compare participants who had used prescription psychostimulants with those that had not, as well as those who had used illicit psychostimulants with those that had not. No significant differences were found between these groups on the positive, negative, disorganized, and general symptom scales of the SIPS. Analysis of the effect of duration of stimulant use also failed to yield significant results. Results suggest that prescription stimulants do not exacerbate the symptoms of CHR individuals and their use in the treatment of attentional problems in CHR individuals is not contraindicated.

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Schizophrenia and other psychotic disorders remain among the most costly mental illnesses in terms of lost productivity, health care provision, and related costs (Murray & Lopez, 1996). Over the past 20 years, research into the genesis of psychotic disorders has investigated how genetic factors and deviations from normal brain development may underlie these illnesses (Lewis & Levitt, 2002). As research findings have accumulated, it has become more apparent that the diagnostic boundaries among psychotic disorders specified by current taxonomies do not conform to evidence on etiologic factors. Thus schizophrenia, as defined in the DSM IV-TR, overlaps with other psychotic disorders (e g., mood disorders with psychotic features) with respect to structural and functional brain abnormalities, as well as genetic and environmental risk factors. Further, there is significant heterogeneity in both phenomenology and neurobiology within diagnostic categories of psychosis. As a result, investigators now assume that there are multiple etiologic subtypes of psychosis, although they may share a "final common pathway" with respect to neurocircuitry dysfunction.

It has been hoped that a better understanding the development of psychotic disorders will allow researchers to identify risk factors and prepare the way for earlier interventions to prevent or treat the illness (Correll, Hauser, Auther, & Cornblatt, 2010). The goal of the present study is to examine the relation of prescription and recreational stimulant use with the severity and progression of clinical signs of risk for psychotic disorders. Past research has indicated that stimulant use, potentially through its effects on the dopamine system, can trigger or exacerbate psychotic symptoms. Thus it is important to understand whether stimulants are linked with clinical signs of risk.

The Nature and Course of Psychosis

While Bleuler, who coined the word schizophrenia, noted that psychotic illness is often preceded by a period of decreased functioning and increasing clinical symptoms (Bleuler, 1950), this period was not studied extensively until relatively recently (Correll et al., 2010). These 'increasing clinical symptoms' include attenuated versions of the positive symptoms of schizophrenia (i.e., hallucinations, delusions, paranoid ideation, thought disorder, and grandiosity) and the negative symptoms of schizophrenia (e.g., avolition, problems with attention, and flattened affect). Research in the last 15 years has identified a set of criteria that identify an individual as having a highly increased risk for the development of a psychotic illness within the next few months or years. This risk syndrome has gone by various names, including the 'schizophrenia/psychosis prodrome,' 'ultra high risk,' psychosis risk syndrome,' and 'clinical high risk' (CHR). In this paper, the acronym CHR will be used.

Several distinct sets of diagnostic criteria may qualify an individual as having CHR, including: (1) attenuated positive symptoms (APS) that have begun or increased in intensity in the last year, (2) high genetic risk for psychosis (e.g., first or second degree relative with a psychotic disorder) with a recent decline in functioning, and/or (3) brief and self-limiting psychotic symptoms with a recent onset (Addington et al., 2007). The exact criteria for CHR varies across studies (e.g. what counts as a significant increase in symptoms), largely because researchers from several nations (e g., Australia, Germany, Mexico and the U.S.) independently initiated investigations of clinical (i.e., cognitive, behavioral, and affective signs and symptoms associated with mental illness) risk factors for psychosis. Despite the resulting differences in measures and symptom criteria,

individuals meeting varied CHR criteria in a number of large studies have consistently shown a significantly increased risk for developing a psychotic disorder, with rates of 'conversion' (i.e., the development of symptoms meeting criteria for a psychotic illness) ranging from 20% - 40% within a roughly two year period (McFarlane, 2011). This incidence rate is several hundred times higher than the estimated annual incidence rate of schizophrenia in the general population of .2 per 1000 individuals (Eaton, 1999).

While CHR is strongly associated with the development of schizophrenia, many individuals with CHR go on to develop other illnesses with psychotic features (e.g., bipolar disorder) suggesting that the CHR profile reflects a general risk for psychosis rather than for a particular disorder. This fact supports the growing consensus that all forms of psychotic illness share similarities in their etiology and development (O'Donovan, Craddock, & Owen, 2009). Individuals with CHR are also likely to exhibit clinically significant levels of distress, depression, and anxiety, as well as problems with neurocognitive, social, and role functioning.

Researchers have also identified several risk factors that increase the risk for psychosis in CHR individuals, including high levels of daily stress and cannabis use (Correll et al., 2010). Researchers who study individuals with CHR are hoping to better understand the cognitive, clinical, and biological changes that precipitate the development of psychosis, and why some individuals' conditions improve while others remain stable or deteriorate. It is hoped that this increased understanding will allow researchers to develop interventions to prevent the onset of psychotic illness in these at-risk individuals.

Stimulants and Psychosis

While the ability of stimulant medications to induce psychosis has been reported since at least 1967 (Ney, 1967), the clinical and neuropsychological effects of long term treatment with stimulant medication remain mostly unknown (Berman, Kuczenski, McCracken, & London, 2009). At the same time, chronic stimulant administration remains the best supported and most popular long-term treatment for the symptoms of ADHD (Faraone, Biederman, Spencer, & Aleardi, 2006). With the increasing clinical consensus that ADHD symptoms continue into adulthood, an increasing number of patients are using stimulants indefinitely to treat their continued symptoms (Kessler et al., 2006). In line with this, the use of medical stimulants has remained on an upward trend for the past several years, with between 1% and 2% of the United States population currently taking a stimulant medication (Gu, Dillon, & Burt, 2010). Similar rates of stimulant use are found in Western European countries and Australia (Berman et al., 2009). While it is likely that many of these long-term stimulant users experience significant relief of their attentional symptoms while they take their medication (Wilens, 2002), it is becoming more and more imperative that we understand both the biological and clinical consequences of long term stimulant use, especially among those with a diathesis for psychotic illness.

The current study seeks to evaluate the effects of stimulant use in a CHR sample (Woods et al., 2009). A significant portion of this sample has either used stimulant medication at some point during their lifetime or was using stimulants at the time of their first assessment. Examining the association of attenuated psychotic symptoms with

medical stimulant use in this sample, may shed light on the effects of stimulant medication use on APS symptoms.

Amphetamines, non-amphetamine behavioral stimulants, and their pharmacodynamic properties. Amphetamines are one of the most common classes of stimulants used for medicinal and recreational purposes. They are a group of chemicals related to one another by their similar chemical structure and biological properties. They are named after the first chemical synthesized in their group, amphetamine (Berman et al., 2009). Amphetamine produces its stimulatory effects by increasing synaptic levels of dopamine, norepinephrine, and serotonin through several chemical mechanisms. While amphetamine binds to all monoamine transporters, its behavioral stimulating effects are primarily due to its effects on dopamine and the dopamine transporter. Amphetamine prevents the dopamine transporter from clearing dopamine from the synaptic cleft. At the same time, it facilitates the transportation of dopamine from the cytoplasm of the cell into the synapse and extracellular space. Amphetamine also disrupts the storage of dopamine in the vesicles: this allows dopamine to build up in the cytoplasm and eventually be transferred to the synapse. Molecular mechanisms by which amphetamine may increase monoamine release include exchange diffusion, channel-like transport, phosphorylation, and transporter trafficking. Amphetamine appears to amplify both tonic (i.e., slow base rate) and phasic (i.e., concentrated burst) dopamine release. In addition to affecting the dopamine system, amphetamines are also believed to have noradrenergic effects at clinical dosages.

Forms of amphetamine and molecules derived from it can have different biological and behavioral effects based on small differences in their molecular shape and

composition (Brunton, Lazo, & Parker, 2006). Amphetamine exists as two enatiomers. Enatiomers are forms of a chemical that share the same molecular formula and chemical bonds, and only differ in that they are mirror reflections of one another. The "left handed" form is known as levoamphetamine and the "right handed" as dextroamphetamine (Brunton et al., 2006). At low doses, levoamphetamine produces greater arousal than dextroamphetamine by acting primarily on the norepinephrine system. At higher doses, however, dextroamphetamine has stimulant properties that are three to four times greater then levoamphetamine and stem primarily from its effects on the dopamine system. The most popular preparations of prescription amphetamines, such as Adderall, include a mixture of levo and dextro forms of amphetamine. Methamphetamine differs molecularly from amphetamine in that a methyl group is attached to the molecule, making it more lipid soluble (and thus better able to cross the blood-brain barrier) and more resistant to degradation by monoamine oxidase. This makes it an even more potent stimulant than dextroamphetamine with even fewer peripheral effects (Brunton et al., 2006).

Methylphenidate (Ritalin) belongs to a class of drugs known as non-amphetamine behavioral stimulants. Non-amphetamine behavioral stimulants lack the molecular nucleus that is shared by all amphetamines, but have similar pharmacodynamic effects to amphetamines, namely potentiating the action of the neurotransmitter dopamine in the nervous system (Julien, Advokat, & Comaty, 2011). Methylphenidate increases the synaptic concentration of dopamine by blocking presynaptic dopamine transporters and, probably, by increasing the release of dopamine, though to a lesser extent than that seen with amphetamines.

Several amphetamines and non-amphetamine behavioral stimulant drugs are used for the treatment of ADHD and have proven to be highly effective in treating the attentional symptoms associated with the disorder. Stimulant treatment for ADHD in children has been shown to improve cognitive functioning, behavioral symptoms, academic performance, and social functioning in between 60% and 80% of individuals (Julien et al., 2011). Continued regular use of stimulant treatment is associated with continued treatment effectiveness (MTA Cooperative Group, 2004), thus making continued stimulant treatment the standard of care for many children. Several types of amphetamines are approved for use in treating children with ADHD, including mixed amphetamine salts (Adderall), dextroamphetamine (Dexedrine, DextroStat), and methamphetamine (Desoxyn). The most popular medication for the treatment of ADHD, however, is methylphenidate (Julien et al., 2011). While amphetamines and non-amphetamine behavioral stimulants are generally considered safe for long term use in children, their abuse can lead to severe physiological and psychological dependence (Berman et al., 2009). Amphetamines and NABs are the most commonly prescribed and among the most commonly abused psychoactive drugs among young people, with 8.1% of 12-grade students abusing illicit amphetamines (Johnston, Bachman, & Schulenberg, 2006).

Stimulant psychosis and the dopamine hypothesis of schizophrenia. The dopamine hypothesis of schizophrenia remains the most widely accepted model for the "final common pathway for the genesis of the positive symptoms in schizophrenia" (Howes & Kapur, 2009). Two core research findings have led to the predominance of the dopamine hypothesis. The first is that dopamine agonists (e.g., amphetamines) can induce

psychotic symptoms in both healthy individuals and those with schizophrenia. The second is the effectiveness of dopamine antagonists in treating the positive symptoms of psychotic disorders**.** Patients suffering from psychotic symptoms have been shown to have higher levels of pre-synaptic dopamine, increased striatal dopamine release, and higher levels of endogenous synaptic dopamine during psychosis, while people at high risk for schizophrenia also show elevated levels of dopamine signaling, at levels intermediate between those of healthy controls and those with active psychosis (Howes et al., 2009). Stimulants have been shown to both increase levels of striatal dopamine and precipitate frank psychotic symptoms in healthy controls, schizophrenic patients, and individuals with CHR (Howes & Kapur, 2009). Research has also shown that methylphenidate can induce stimulant psychosis similarly to amphetamines (Curran, Byrappa, & McBride, 2004), though larger doses may be necessary given methylphenidate's comparatively weaker ability to potentiate dopamine release as compared with amphetamines.

Stimulant Sensitization. Studies of stimulant abuse have also shown that small, repeated doses of psychostimulants can potentiate the presynaptic dopamine system: the result is that a smaller amount of stimulant is required to precipitate psychotic symptoms during future administrations of psychostimulants (Sato, 1992). Sensitization to stimulant administration (i.e. increased neurochemical and behavioral responses to repeated administration of stimulants) has been reproduced several times in animal models (Curran et al., 2004), but few studies have investigated this phenomenon in humans. An exception is a 2006 study in which Boileu et al. found that three oral administrations of amphetamine delivered during a six day period increased stimulant-related behavior (e.g.,

eye blink rate) and self-report responses (i.e., visual analog scale ratings of energy and alertness) to two subsequent administrations of amphetamine delivered two weeks and a full year later. In order to measure the amount of intrasynaptic dopamine in the striatum, Boileu (2006) used positron emission tomography (PET) along with the $D_{2/3}$ receptor ligand [^{11}C]raclopride, a substance whose binding potential decreases in proportion to the amount of intersynaptic dopamine that is present (Laruelle, 2000). Intrasynaptic dopamine was shown to increase in striatal structures during the 4th and 5th administrations relative to earlier administrations. Increased dopamine release in certain sub-structures of the striatum was significantly correlated with stimulant-related behaviors, such as alertness and euphoria.

Boileau et al.'s labratory findings support a large literature of naturalistic studies suggesting that stimulant abuse results in stimulant sensitization in humans. Studies of chronic abusers of stimulants have found increased dopamine release and behavioral sensitization over time (Collip, Myin-Germeys, & Van Os, 2008), while the majority of long term cocaine and methamphetamine users exhibit psychotic symptoms in response to smaller doses of the drug over time (Curran et al., 2004).

In order to investigate how use of the amphetamine derivative 3,4-Methylenedioxymethamphetamine (MDMA) affected dopaminergic functioning in former abusers of the drug, Tai et al. (2011) used another radiotracer ligand, ^{18}F-DOPA, in a PET study. After administration, ^{18}F-DOPA is absorbed by monoamine neurons, converted to ^{18}F-dopamine within the neuron, and then trapped in vesicular storage. The amount of ^{18}F-DOPA that is captured in vesicular storage is a well-validated measure of presynaptic dopamine functioning and has been used successfully in studies of

presynaptic dopamine system dysfunction in Parkinson's disease (e.g., Brooks et al., 1990), as well as in documenting the hyperdopaminergic state found among individuals with schizophrenia (Howes et al., 2007). In Tai et al.'s study, they found that former chronic users had a 9% increased level of dopamine uptake in the putamen compared with non-users after an average of 3.2 years of abstinence: this increased level of dopamine uptake is of similar magnitude to the increased uptake found in CHR individuals (Howes et al., 2007). Notably, dopamine uptake levels in drug naïve individuals did not predict who would go on to abuse MDMA (i.e., it was not the case that individuals with preexisting higher levels of dopamine uptake were simply more likely to abuse the drug). This suggests a causal role of MDMA use in the increasing level of dopamine uptake in the putamen found among drug abusing individuals (de Win et al., 2008).

Convergent evidence for the importance of the sensitization of the dopamine system for the development of schizophrenia has come from research into other environmental risk factors for schizophrenia and their effects on the dopamine system (Collip et al., 2008). Howes and others have argued that that, while the environmental risk factors which increase the risk for schizophrenia may act on a variety of processes (e.g., epi-genetic, hormonal, etc.), the final pathway by which these risk factors contribute to the onset of psychosis is through their sensitization of the dopamine system (Howes et al., 2004). It has been hypothesized that this sensitization is the substrate for the susceptibility to the psychosis-inducing effects of stress and dopamine-agonist drugs found in those with at increased genetic risk for schizophrenia (Lieberman, Sheitman, & Kinon, 1997).

Evidence has emerged to support the hypothesis that sensitization of the dopamine system is the final causal pathway by which various risk factors increase the chances of developing a psychotic illness. Individuals with dysregulated dopaminergic systems are more sensitive to the psychogenic effects of environmental stressors (Myin-Germeys, Marcelis, Krabbendam, Delespaul, & van Os, 2005), while individuals exposed to environmental risk factors (such as poor maternal care) are more likely to have dysregulated dopaminergic systems (Pruessner, Champagne, Meaney, & Dagher, 2004). Large scale studies involving thousands of participants (Hanssen, Bak, Bijl, Vollebergh, & van Os, 2005; Poulton et al., 2000; Wiles et al., 2006) have shown that participants exposed to these risk factors show increased persistence of normally transient developmental expressions of subclinical psychotic experiences and a subsequent increased rate of transition to psychotic disorders. It appears that some of these changes in the sensitivity of the dopamine system in response to stress may be mediated by dysregulation of the HPA axis and the changes that this dysregulation brings to brain development and functioning (Walker, Mittal, & Tessner, 2008). In animal models, environmental factors such as non-optimal maternal care (Brake, Zhang, Diorio, Meaney, & Gratton, 2004) and dopamine agonists (Pani, Porcella, & Gessa, 2000) have been shown to cause profound and long lasting changes in the responsiveness of the mesocoticolimbic system's dopamine neurons to stress and psychostimulants. Finally, elevated levels of dopamine release seem to be specific to psychotic symptoms, rather than an indicator of general psychopathology: increased striatal dopamine elevation is not found in individuals with mania, depression, and other psychiatric disorders when psychosis is not present (Howes & Kapur, 2009).

While the precise mechanisms and neurocircuitry underlying the sensitization of the dopamine system remains unknown, evidence has begun to accumulate which may lead to a better fundamental understanding of this process (Collip et al., 2008). A variety of studies have shown that the prefrontal cortex plays a role in regulating striatal levels of dopamine (Deutch, Clark, & Roth, 1990). Environmental factors may suppress the activity of the prefrontal cortex, inhibiting its ability to down-regulate levels of dopamine signaling in the striatum. This loss of down regulation may thus facilitate the onset of psychotic symptoms (Pani et al., 2000). Genetic variation may predispose people toward this loss of prefrontal control, and may be the casual mechanism by which certain catechol-O-methyl transferase polymorphisms and cannabis use interact to increase the odds of developing schizophrenia (Caspi et al., 2005). Other possible genetic risk factors for the loss of prefrontal cortex down-regulation include alleles of DISC1 and RGS4, which may lead to excessive levels of catecholamine (e.g., dopamine) release during stress due to the weaker regulation of intercellular pathways (Arnsten, 2007).

Animal models have suggested that glucocorticoids may affect stress-induced sensitization of mesencephalic dopaminergic transmission to drugs of abuse, including stimulants (Deroche et al., 1995). Prenatal stress, already associated with increased risk for schizophrenia (van Os & Selten, 1998), may cause changes in the sensitivity of the nucleus accumbens and in the capacity to develop amphetamine-induced dopamine sensitivity later in life. This increased sensitivity may be mediated by impaired control of corticosterone secretion in the prenatally stressed animal (Sorg & Kalivas, 1991). The subsequent chronic elevation of corticosterone levels may increase the rate and extent of the normal neurodevelopmental process of neural pruning (Walker et al., 2008): this

aberrant developmental process may result in some of the anatomical differences found in the brains of individuals with schizophrenia.

Finally, epigenetics may have a role to play in drug-induced sensitization to schizophrenia. Stimulants have been shown to affect DNA methylation (Tsankova, Renthal, Kumar, & Nestler, 2010). Multiple studies have shown that changes in mRNA levels in areas related to dopaminergic neurotransmission, including the ventral tegmental area and the nucleus accumbens can be affected by dopamine agonist drugs (Freeman et al., 2002; McClung & Nestler, 2003). Some of these changes in DNA methylation may up-regulate dopamine transmission in the ventral tegmental area and the nucleus accumbens.

Dopamine is not the only neurotransmitter thought to play a role in the development of psychosis. The glutamenergic hypothesis of schizophrenia also has a thriving literature supporting the importance of the glutamenergic system in the development of the negative and positive symptoms of schizophrenia (Coyle, 2006). Similarly to psychostimulants and the dopamine hypothesis, much of the initial interest in the glutamenergic hypothesis was spurred by the finding more than 50 years ago that dissociative anesthetics, such as ketamine and phencyclidine, could induce a psychotic syndrome very similar to schizophrenia (Itil, Keskiner, Kiremitci, & Holden, 1967; Luby, Cohen, Rosenbaum, Gottlieb, & Kelley, 1959). Later findings showed that the negative symptoms and cognitive deficits found in individuals with schizophrenia could be induced in normal controls using low dose infusions of ketamine (Krystal et al., 1994).

Glutamate is the most common excitatory neurotransmitter in the brain. Its effects on post-synaptic cells are mediated by three families of receptors: AMPA, kainite, and NMDA. The psychotomimetic properties of dissociative anastetics are thought to be due to their blockage of N-Methyl-d-aspartic acid (NMDA) receptors. This antagonism appears to disrupt the normal functioning of glutamate on post-synaptic cells. Glutamate's action on post-synaptic cells can normally lead to dendrite spine proliferation and neurotrophism (Lladó et al., 1999), two processes key to cognitive functioning, especially memory formation. Additionally, this antagonism can lead to a build-up of extra cellular glutamate, a known cause cause oxidative stress and excitotoxicity (Coyle, Tsai, & Goff, 2002).

Chemical and genetic expression measurements of proteins important to the proper functioning of the glutamate system have suggested that individuals with schizophrenia, first episode psychosis, high genetic risk, and PRS, have reduced levels of these proteins as compared with healthy controls (Correll et al., 2010; Coyle, 2006). Several trials of pharmaceutical agents which could theoretically help to restore the normal functioning of the glutamate system (e.g. glycine, D-serine, sarcosine) have shown them to be effective in treating some of the negative symptoms and cognitive deficits associated with psychosis. Trials with CHR individuals are underway, though findings have been mixed and more work is needed to discover which agents are most effective (Correll et al., 2010).

While the glutamate hypothesis is sometimes framed as a competitor to the dopamine hypothesis, the consensus among researchers is that both the dopaminergic and glutamenergic systems play a role in the underlying etiology of psychotic illness and that

their functioning is intimately linked (Coyle, 2006). For example, dopamine release in response to ketamine alone is not found in healthy volunteers (Kegeles et al., 2002), but ketamine has been shown to increase amphetamine-induced dopamine release in healthy volunteers to levels normally seen in individuals with schizophrenia (Kegeles et al., 2000). While it may be the case that the positive symptoms of psychosis are associated more with dysfunction in the dopamine system, while negative symptoms and cognitive deficits are associated more with dysfunction in the glutamate system, the clear interconnectedness of these neurotransmitter systems in the brain suggest that dysregulation in one can precipitate dysregulation in the other. An understanding of the neurological dysfunction underlying the etiologies of psychoses will likely require an understanding of both systems and their interactions.

The Effects of Amphetamine Exposure at Different Stages of Development. Pre-adolescence and adolescence is a time of significant neurodevelopmental maturation and change (Spear, 2000). The changes that are especially relevant to the study of stimulants and psychosis include the pruning of neocortical synapses (Holland & Gallagher, 1999), changes in the density of dopamine receptors in various parts of the brain (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988), and the substantial reorganization of mesocorticolimbic dopaminergic circuits (Van Eden, Kros, & Uylings, 1990). It has been suggested that the changes in dopaminergic circuits within the brain represents a shift in the balance between subcortical and cortical dopamine systems toward the predominance of cortical control of these dopamine circuits and enhanced dopaminergic tone in the prefrontal cortex (Spear, 2000). All of this suggests that

dopaminergic drugs, such as amphetamines, are likely to have differing effects dependant on the stage of development at which they are used.

Researchers using animal models have noted differing effects of amphetamine exposure dependant on the developmental stage of their subjects. Rats at postnatal day (PND) 35-55 are thought to be developmentally comparable to humans of about 12-18 years (Rice & Barone Jr, 2000). Adolescent rodents are less sensitive to the locomotor and stereotypic effects of amphetamine (Laviola, Adriani, Terranova, & Gerra, 1999). There is some evidence for a transition to susceptibility to methamphetamine induced neurotoxicity around PND-40. Rats treated with methamphetamine at PND- 90 exhibited deficits in striatal dopamine functioning seven days later while PND- 40 rats did not (Kokoshka, Fleckenstein, Wilkins, & Hanson, 2000). Plasma and striatal levels of methamphetamine an hour after administration were roughly double in the PND- 90 group, possibly mediating this neurotoxic effect. Changes in the pharmacokinetics of amphetamines with age also occurs in humans: e.g., the half life for d-amphetamine is 10 hours in adults, 11 hours in adolescents, and 9 hours in children aged 6-12 (FDA, 2007). The pattern of drug exposure can also be critical to the outcome of drug exposure experiments in animal models. For example, six biweekly injections of methamphetamine starting at PND-40 blocked the neurotoxic effects of a binge of methamphetamine administered at PND-90 while, contrastingly, a single methamphetamine binge at PND-40 did not prevent the neurotoxic effects of the methamphetamine binge delivered at PND-90 (Riddle, Kokoshka, Wilkins, Hanson, & Fleckenstein, 2002). Finally, very young animal models may also be resistant to the neurotoxic effects of stimulant treatment. For example, pre-weaning rats (generally 28 days old or younger) are more

resistant to the neurotoxic effects of methamphetamine treatment as compared with adult rats (Lucot, Wagner, Schuster, & Seiden, 1982).

One should not attempt to directly apply the findings of animal model studies to research and treatment of human beings. There are clear and important differences between a rat brain and human brain, and it is unlikely that researchers will find a one to one correlation between the effects of stimulant exposure on rats and humans. However, effects found in animal models are likely to exist in one form or another in humans. As such, one must carefully consider the possibility that the effects of stimulant exposure can depend on what developmental stage they are administered at and the pattern of their administration (i.e. binge vs. regular dosing). Some studies in the human literature have begun to support the importance of these factors. For example, individuals who began stimulant treatment during elementary school were no more likely to report illicit prescription stimulant use during their college years than individuals who were never proscribed stimulants, while individuals proscribed stimulants during secondary school and college were respectively three and seven times more likely to abuse prescription stimulants than the non-prescribed controls (Wilens, Faraone, Biederman, & Gunawardene, 2003). In another study (Mannuzza et al., 2008), prospectively-followed individuals with ADHD who initiated stimulant treatment after age 7 had rates of substance abuse disorders as adults that were roughly twice as high (44%) as individuals with ADHD who had initiated treatment before age 8 (27%), a rate similar to age-matched controls (29%). Since the above described studies are observational, one cannot conclude that the neurodevelopmental state at the initiation of stimulant treatment caused

the observed differences, however they do provide a rationale for more research into how neurodevelopmental factors influence response to stimulant treatment.

Retrospective Studies Linking Medicinal Stimulant use and Psychosis. Only a handful of studies have retrospectively examined the onset and duration of stimulant treatment and its relationship with the onset of psychosis in youth suffering from psychotic disorders (Ross, 2006). Karatekin, White, and Bingham (2010) reported that 59% of their sample of 42 individuals with childhood-onset schizophrenia had been prescribed psychostimulant medication. Most interestingly, participants who had been exposed to psychostimulants had a significantly younger age at onset of psychotic symptoms (11.2 years) than those who had not (13.7 years). Also of note, the childhood-onset schizophrenia participants with comorbid ADHD symptoms did not differ significantly from those without ADHD symptoms on well validated measures of behavioral problems (the Child Behavioral Checklist and the Caregiver-Teacher Report Form). This suggests that the earlier age of onset in the stimulant using group was not merely a product of greater psychopathology and more severe attentional deficits resulting in an increased likelihood of stimulant medication treatment. While childhood-onset schizophrenia is rarer than adolescent or later onset schizophrenia, individuals with childhood-onset schizophrenia resemble individuals with later onset schizophrenia on a variety of important factors, including symptom presentation, anatomical findings, response to dopamine antagonists, and dopaminergic system dysregulation (Schaeffer & Ross, 2002) suggesting that these findings may also apply to other populations with or at-risk for psychosis.

In another study of individuals with childhood-onset psychosis, Schaeffer and Ross (2002) found that thirteen (77%) of their participants had been prescribed a stimulant medication and that eight (47%) had received a formal diagnosis of ADHD. Perhaps most interestingly, only three (23%) of the subjects receiving stimulant medication had displayed "odd behavior" prior to the prescription of stimulant medication, and only one (7%) had psychotic symptoms prior to taking stimulant medications. In another retrospective study, Cherland and Fitzpatrick (1999) reviewed the case files of 98 children treated for ADHD with psychostimulants at an outpatient clinic. They found that nine children (9%) developed psychotic symptoms during treatment, with treatment lasting 21 months on average. Two of those nine children retained their psychotic symptoms after the cessation of stimulant treatment and both were later diagnosed with bipolar disorder.

Several studies have attempted to estimate the base rates of psychotic reactions in children treated with stimulants using clinical drug trial data. Ross (2006) estimated the rate by examining an FDA review of several pharmaceutical-company sponsored trials of stimulant medication in children, specifically looking at the rates of 'toxicosis events' that occurred among participants in these trials. Toxicosis events refers to a wide range of negative reactions in drug trials: sadly, more detailed descriptions for the vast majority of these events are unavailable as the most common outcome reported was "not reported" or "unavailable." Despite this difficulty, Ross attempted to evaluate which toxicosis events were likely to reflect psychotic reactions when data regarding the outcome were available. Summarized across trials, the number of individuals with toxicosis events that could have reflected psychotic reactions were: zero participants out of 3,990 in blind

placebo conditions, 13 out of 5,717 participants (0.22%) in blind therapeutic dose conditions, and 45 out of 15,999 participants (0.28%) in open-label trials. Ross also reviewed 60 cases of stimulant psychosis in a separate FDA database, finding that psychotic symptoms ceased in 92% of these cases after a reduction or cessation of stimulant treatment, while 8% continued to display psychotic symptoms after the cessation of stimulants and were later diagnosed with bipolar disorder or schizophrenia. Ross concluded that the rate of stimulant-related psychosis in individuals treated with stimulants is about .25%.

A more recent review conducted by Mosholder et al. (2009) examined the rate of psychosis and/or mania per 100 patient years of treatment using the same data set employed by Ross, along with spontaneous reports of psychosis and mania made to the FDA. They found 1.42 psychosis/mania events per 100 years of patient treatment in double blind placebo trials of stimulants, with 0 psychosis/mania events in placebo groups. Their examination of spontaneous case reports revealed 865 cases of stimulant medication related mania/psychosis. The vast majority of these cases (796 of the 865) were in patients who had no previous history of psychosis or mania and the majority of cases were independently confirmed by a physician. As Mosholder et al. point out, patients in clinical trials are selected specifically to have a high likelihood for treatment success (e.g., few/no comorbid conditions, previous positive response to stimulant treatment, etc.). In addition, children who experience negative side effects from medication in a clinical trial may drop out of the study before a full description of those negative effects can be noted. As such, clinical trials may underestimate the incidence of adverse effects. These factors may help to explain the large difference between Ross's

estimate of the rate of psychosis events (0.25%) and the rate that Cherland and Fitzpatrick observed in their outpatient clinic (9%), though this could also have been due to the specifics of the Cherland and Fitzpatrick's sample.

Mosholder et al. (2009) also note the extreme difficulty in drawing conclusions from the spontaneous case reports of mania/psychosis events, given that negative reactions often go unreported. At the same time, the number of active prescriptions for each type of stimulant is difficult to acquire, thus making an estimate of a base rate of stimulant psychosis in the population nearly impossible. Finally, it should be noted that it is difficult to interpret the statistics about 'positive dechallenge' from spontaneous case reports. Positive dechallenge is when the cessation of stimulant treatment results in a cessation of psychotic/manic symptoms. This occurred in 32% of the spontaneous case reports of psychosis and mania. While pharmacological researchers have usually seen the success of positive dechallenge as confirmation that stimulants were responsible for the manic/psychotic symptoms, research into stimulant psychosis has shown that psychotic symptoms induced by stimulants can persist well after stimulant medications have been withdrawn (Harris & Batki, 2000). Thus, those who did not respond to positive dechallenge could have had preexisting manic or psychotic symptoms, or, alternatively the deleterious effects of stimulant medication could have simply continued well after the medication was withdrawn.

This brief review suggests that well-controlled prospective longitudinal studies are required to produce a more reliable estimate of the rate of stimulant induced psychosis in patients taking stimulant medications in real world conditions. However, even based on Ross's conservative estimate of .25% for the rate of stimulant psychosis in

children taking prescriptions stimulants, a significant number of children will develop psychotic side effects during stimulant treatment in the U.S. An estimated 4,418,000 children used medical stimulants in 2003 (Visser & Lesesne, 2005), resulting in an estimate of 11,045 children with stimulant induced psychosis in that year. Given the upward trend in stimulant prescription rates, the increasing number of adults who are prescribed stimulants, and the increasing rates of illicit stimulant use in all demographics, the actual number of individuals with stimulant induced psychosis may be higher.

Several studies of prescription stimulant misuse and abuse among children and young adults have revealed markedly high rates of misuse: 54% of undergraduates at a Midwestern college were approached to sell, give, or barter their prescription stimulants (McCabe, Teter, & Boyd, 2006). In a separate survey of students at a northeastern university, 40% of students who were misusing or abusing stimulants crushed and snorted the drug (White, Becker-Blease, & Grace-Bishop, 2006). Taken together, these facts suggest that official rates of prescription stimulant use in the population may be significantly underestimating the number of young people who use stimulants, and that individuals who are misusing and abusing these drugs may be taking them in much larger dosages than would be prescribed and via methods (e.g. insufflations) which increase the speed at which the drug is absorbed. This statistics should be cause for concern, given the documented potential for negative side effects arising from their misuse.

Other Drugs and Their Relationship to the Symptoms and Development of Psychosis

Recent research has investigated how other licit and illicit drugs may function as risk or protective factors in the development of psychosis. A flurry of recent research has investigated the psychosis inducing properties of cannabis. Moore et al. (2007) conducted a recent meta-analysis of all available methodologically rigorous longitudinal studies of the association between cannabis use and later psychosis. After correcting for reverse causation (e.g., excluding those with psychotic symptoms at baseline assessment) and intoxication effects, their analysis yielded a pooled odds ratio of 1.41 (95% CI 1.20-1.65) for development of psychosis among individuals who had any marijuana use during their lifetime and 2.09 (95% CI 1.54-2.84) among the most frequent cannabis user categories. As the authors of the meta-analysis point out, given the 40% rate of lifetime cannabis use in the UK, a full 14% of psychotic outcomes in young adults could potentially be prevented if cannabis were not consumed. While, of course, no observational study can prove causation, and thus one cannot be sure that preventing cannabis exposure would in fact reduce the incidence of psychosis by 14%, this is still quite a substantial figure and definitely encourages further research into the link between cannabis and the development of psychosis.

Intravenous administration of the Delta-9-Tetrahydropcannabinol (Δ-9-THC) has been shown to induce positive, negative, and cognitive symptoms of psychosis, including suspiciousness, paranoid and grandiose delusions, conceptual disorganization, illusions, depersonalization, distorted sensory perceptions, feeling of unreality, blunted affect, reduced rapport, and emotional withdrawal (D'Souza et al., 2004). Δ-9-THC's

psychotropic effects are mediated by its agonistic effect of CB-1 receptors (Matsuda, Lolait, Brownstein, Young, & Bonner, 1990). CB-1 receptors are distributed with high density in the frontal regions of the cerebral cortex, basal ganglia, hippocampus, anterior cingulated cortex, and cerebellum (Egertová & Elphick, 2000). The induction of positive symptoms by Δ-9-THC may be due to their increase of mesolimbic dopaminergic activity (Pistis et al., 2002). Δ-9-THC induction of cognitive and negative symptoms of schizophrenia may be due to its inhibition of GABA release by interneurons in the hippocampus, which are believed to be important for the synchronization of pyramidal cell activity, a process thought to be critical to associative and sensory-gating functions (Wilson, 2002). Abnormalities with synchronization have been reported in individuals with schizophrenia (Spencer et al., 2003). Δ-9-THC has also been shown to elevate plasma cortisol levels via CB-1 receptor activation within the paraventricular nuclei (Murphy, Muñoz, Adrian, & Villanúa, 1998). Elevated levels of plasma cortisol are a well replicated finding among individuals with schizophrenia (Ritsner et al., 2004) and those who are at risk for psychosis (Walker, McMillan, & Mittal, 2007). It is thought that the increased risk for psychosis among chronic users of cannabis may be due to a behavioral sensitization effect to repeated cannabinoid exposure, an effect which has been demonstrated in animal models (Rubino, Vigano, Massi, & Parolaro, 2003).

Antipsychotics and antidepressants have been used to treat the positive and general symptoms (e.g., depressed mood) associated with schizophrenia. Thus, researchers have been interested in whether these medications can be used to treat the distressing symptoms experienced by CHR individuals. In general, antipsychotics have been shown to be are effective in reducing the number of conversions to psychotic

disorders among CHR individuals during a 6 month period (McGlashan et al., 2006; McGorry et al., 2002). However, subsequent follow up studies have shown that this preventative effect attenuates over time, and it is unclear if antipsychotics can be used to prevent psychosis in the long term especially given their significant side effects and high rates of treatment nonadherence among patients (McGlashan et al., 2006; Phillips et al., 2007). In naturalistic studies, CHR individuals prescribed antipsychotics have shown a more rapid decrease in positive symptoms at follow-up and a lower average positive symptom rating at follow-up despite their initially higher positive symptom ratings, however once again it is unclear whether these reductions will be maintained in the long run or prevent the onset of a psychotic disorder (Walker et al., 2009).

Anti-depressants are an attractive potential intervention strategy for individuals with CHR given their much milder side effect profile as compared with anti-psychotics and their effectiveness in treating the depressed mood and anxiety that often accompany the CHR state. Evidence for the effectiveness of antidepressants in reducing the positive symptoms of psychosis is mixed with one non-randomized study finding that antidepressant treatment significantly reduced 3 of the 5 dimensions of positive symptoms over a 6-month follow-up period, similar to the rate found among antipsychotic users (Cornblatt et al., 2007a). Similar results were found in a naturalistic study by Fusar-Poli et al. (2007a). However, a larger naturalistic study of the participants in the NAPLS study found no significant effects for anti-depressants in the reduction of positive symptoms as compared with untreated individuals, though this may have been because participants in this study had been taking anti-depressants for a longer time and already experienced any benefit they were likely to yield (Walker et al., 2009). If anti-

depressants do result in a long term reduction in positive symptoms and conversion to psychotic disorders, it is likely to stem from their reduction of neurohormonal stress responses which may contribute to the premature cell death seen in individuals with schizophrenia (Berton et al., 2006). Given the current state of the literature, it is unclear whether antidepressants and antipsychotics can lead to long term reduction in positive symptoms or conversion to psychotic disorders in individuals at-risk for psychosis; as such, it is important that clinicians carefully weight their potential benefits against their established side effects (Corcoran, Malaspina, & Hercher, 2005).

Attention in Schizophrenia and the Prodrome

Problems with attention are among the most widely replicated deficits associated with schizophrenia and other psychoses, and those at risk for psychosis (Luck & Gold, 2008). Attention, as it is colloquially understood, involves a wide variety of cognitive processes, and the extent to which they are impaired in individuals with schizophrenia varies. These impaired cognitive processes include: A) vigilance and sustained attention, which allows individuals to maintain focus for extended periods of time and respond (or withhold their response) to a series of presented stimuli (Chen & Faraone, 2000), B) sensory gating, which allows individuals to adjust their response to repeated stimuli, e.g., modulating their startle response to a loud noise when it is regularly preceded by a quieter noise (Braff, 1993), C) filtering out extraneous sensory information, such as in a backwards masking paradigm where an individual must ignore a masking stimulus presented after the target stimulus (Green, Nuechterlein, & Mintz, 1994), and D) maintaining a mental set over time or when interrupted, such as remembering at what point you are in the set of tasks necessary to prepare a meal (Nestor et al., 1992). Overall,

individuals with schizophrenia show the greatest deficits when tasks place a heavy load on attentional resources: on tasks with a smaller attentional load, individuals with schizophrenia can show similar performance to healthy controls (Nuechterlein & Dawson, 1984).

Large studies of CHR individuals have shown that their rate of attentional deficits is intermediate of healthy controls and individuals with first episode psychosis (Simon et al., 2007). Studies have also shown that attentional deficits are present in those at high genetic risk for schizophrenia and those with schizophrenia spectrum disorders, such as schizotypal personality disorder (Brewer et al., 2006; Francey et al., 2005). The elevated rate of attention problems in prepsychotic individuals likley contributes to their higher rate of prescription stimulant use.

The data on whether attentional measures can predict which CHR individuals will develop a psychotic disorder is mixed (Correll et al., 2010). While problems with attention may reflect a general cognitive deficit associated with the diathesis, development, and manifestation of schizophrenia, several studies have shown specific associations between the development of schizophrenia and attention measures (Oner & Munir, 2007). Additionally, while attentional difficulties may be neither a necessary nor sufficient predictor of the conversion to psychosis (Brewer et al., 2006), their ubiquity among those at high risk for psychosis suggest that some of these high-risk individuals and their parents are likely to seek treatment for these attention difficulties. This is likely reflected in the high rates of stimulant medication prescription in childhood-onset psychosis samples (Karatekin et al., 2010; Schaeffer & Ross, 2002).

The Overlap of ADHD and the Symptoms of CHR

Many individuals who develop schizophrenia have a history of ADHD symptoms and/or an earlier ADHD diagnosis (Alaghband-Rad, McKenna, Gordon, & Albus, 1995; Marenco & Weinberger, 2000; Schaeffer & Ross, 2002). ADHD is also diagnosed in a large proportion of children with high genetic risk for schizophrenia (Keshavan, Diwadkar, Montrose, Rajarethinam, & Sweeney, 2005). Studies have shown that CHR and childhood-onset schizophrenia individuals who have comorbid ADHD symptomatology have been shown to fare worse on clinical, developmental, and cognitive measures (Elman et al., 1998; Öner & Munir, 2005), though there have been exceptions (Karatekin et al., 2010).

The relationship between ADHD and schizophrenia is debated in the literature. Some have argued that individuals with a comorbid diagnosis of ADHD and schizophrenia represent a distinct and severe subgroup while others have suggested that attentional symptoms associated with psychosis are simply products of the general cognitive and clinical impairment associated with psychosis and are not 'true' ADHD (Karatekin et al., 2010). Given that attentional deficits are observed within those at high genetic risk for schizophrenia who do not otherwise manifest the clinical symptoms of the disorder (Oner & Munir, 2007), it does not appear that attentional difficulties can be completely explained as sequelae of the more florid psychopathology of schizophrenia.

One of the clearest differences between individuals with schizophrenia and ADHD is their response to psychopharmacological treatment. While ADHD's attentional and disorganizational symptoms typically show improvement in response to

psychostimulant medication, those with psychosis or at high risk for psychosis usually experience a worsening of their symptoms in response to such medication (Barch & Carter, 2005; Barr, 2001; Curran et al., 2004). Similarly, neuroleptics have not proven very effective in the treatment of the attentional deficits associated with ADHD (Bond, 1987; Gualtieri & Hicks, 1985).

While neuroleptics have proven to be relatively ineffective in treating the negative symptoms of schizophrenia, including problems with attention (Geddes, Freemantle, Harrison, & Bebbington, 2000), the combination of neuroleptics and stimulants has shown some promise in treating the attentional symptoms of some schizophrenia patients without precipitating an increase in positive symptoms (Barch, 2010). It may be that neuroleptics counter the excitatory effects of psychostimulants on the limbic system while allowing them to continue their stimulation of the frontocortical regions that are also impaired in schizophrenia, but this theory awaits further neurological and clinical testing.

Summing across the neurological and clinical evidence, patients suffering from schizophrenia and ADHD share certain similar dysfunctions in neurotransmitter systems and in frontocortical brain regions, and these dysfunctions may underlie the similar deficits in attention found in patients suffering from the two disorders and as well as those at high risk for schizophrenia (Barr, 2001). Frontocortical abnormalities in those who have a biological diathesis for psychosis may manifest at earlier ages as difficulties with attention, while the biological vulnerabilities associated than the more florid symptoms seem to be associated with other brain regions, especially those comprising the limbic system. The abnormalities found in non-frontal regions may arise primarily during

development in adolescence and early adulthood, and especially with the process of neural pruning that takes place during this time (Rapoport, Addington, Frangou, & Psych, 2005). In contrast to the multi-regional dysfunction found in individuals with schizophrenia, individuals with ADHD seem to have their dysfunction restricted to specific areas in frontocortical brain regions, and thus do not go on to develop the wider range of clinical symptomatology associated with schizophrenia.

The symptom overlap between early stage psychotic disorders and ADHD, along with a general lack of training in psychosis assessment among childhood mental health providers, has consequences for both diagnostic validity and stimulant prescription in youth. As previously noted, the early stages of schizophrenia and ADHD have a variety of symptoms in common, including attentional deficits, early neurodevelopmental disturbances, difficulties with social interactions, and even thought disorder (Caplan, Guthrie, Tang, Nuechterlein, & Asarnow, 2001). Additionally, the problem behaviors in school that are most likely to initiate an ADHD evaluation (e.g., poor social skills, attention problems, distractibility) are those that can also precede the development of schizophrenia. As Cherland and Fitzpatrick note in their review of childhood-onset schizophrenia cases (1999), among a wide range of mental healthcare providers, only child and adolescent psychiatrists gave a diagnosis of schizophrenia to the participants in their sample, while retrospective parental report made it clear that many of the other providers were unfamiliar with psychotic symptomatology. This lack of knowledge regarding psychosis likely contributed to both the high rate of prescription stimulant use and the average delay of two years between the onset of psychotic symptoms and the diagnosis with schizophrenia found among the children in their study.

As adult ADHD becomes a more widely accepted diagnosis, this possible misdiagnosis of early-stage schizophrenia may extend up the age range and lead to the further prescription of stimulant medications to those for whom they are inappropriate. As early diagnosis and treatment of schizophrenia has been cited as a major factor in promoting a positive prognosis (McGlashan, 1999) this misdiagnosis can have serious long term consequences. While diagnostic tools such as visual scan path analysis are being developed in order to better differentiate those with ADHD and schizophrenia at earlier points in the illness (Marsh & Williams, 2006), greater awareness among mental healthcare providers of psychotic illness and risk factors for its onset are also likely to be important tools in providing the most effective clinical interventions to at-risk individuals.

In summary, while several lines of research support the psychosis-precipitating properties of psychostimulants, and their potential to sensitize the dopamine system, there is a lack of research on prescription psychostimulant use in populations at risk for psychosis. Given data showing that the number and length of lifetime psychotic episodes are linked with poorer prognosis (Norman & Malla, 2001), and the current focus upon the early detection and prevention of serious psychopathological disorders (McGorry, Killackey, E, & Yung, 2008), many research programs have sought to identify clinical risk factors that could predict the development of psychosis. Hopefully, such research will shed light on the genesis of serious psychopathology and identify the most predictive risk factors so that those at risk may be detected at the earliest-possible stage and interventions can be implemented to minimize deterioration and disability.

Study Goals and Hypotheses

As described above, several independent lines of research suggest that psychostimulant use may be a risk factor for the precipitation of psychosis in those with a biological diathesis. The extensive literature on stimulant psychosis has shown that, in both naturalistic and laboratory conditions, psychotic states which closely mirror those of schizophrenia and other psychotic disorders can be induced using psychostimulants. Studies have also documented altered levels of dopamine release and uptake at key sites in the brain which correlate strongly with diagnostic status and symptomatology. Both animal and human studies have suggested that psychostimulant use may sensitize the dopamine system to release more dopamine in response to later chemical or environmental stressors. Finally, some of the symptoms and behaviors associated with risk for developing a psychotic disorder, such as impaired attention, are the same as those that would encourage the prescription of psychostimulants.

To date, there have been no studies examining the relationship between prescription psychostimulant use and attenuated positive symptoms among individuals with CHR. The proposed study seeks to address this issue by examining the relationship of prescription and nonprescription stimulant use with attenuated positive symptoms in a large, well characterized sample of at-risk individuals. The following hypotheses will be tested:

Hypothesis One. It is predicted that CHR individuals who have used prescription amphetamines, prescription non-amphetamine behavioral stimulants, and/or illicit stimulants during their lifetime will receive higher mean clinician ratings of attenuated

positive symptoms (i.e. unusual thought content/delusional ideas, suspiciousness/persecutory ideas, grandiose ideas, and perceptual abnormalities/hallucinations) as measured by the Structured Interview for Prodromal Syndromes (SIPS), when compared with CHR individuals who did not use psychostimulants.

Hypothesis Two. It is predicted that among CHR individuals who have used prescription amphetamines and/or non-amphetamine behavioral stimulants that those who have used psychostimulants for longer durations will receive higher mean clinician ratings of attenuated positive symptoms as measured by the SIPS.

Hypothesis Three. It is predicted that among CHR individuals who have used illicit psychostimulants during their lifetime, those who meet criteria for either abuse or dependence will receive higher mean clinician ratings of attenuated positive symptoms as measured by the SIPS.

Method

Participants and Procedure

Individuals with CHR syndromes. The NAPLS consortium is a group of eight research sites located across the United States and Canada that recruited samples of CHR individuals as well as normal controls in order to identify risk factors for the development of psychosis. In order to maximize statistical power for predicting psychosis, these sites pooled their data on CHR and control subjects. The present study is based on data aggregated across the eight sites, Zucker Hillside Hospital, University of California San Diego, Emory University, University of California Los Angeles, University of North

Caroline, Yale University, University of Toronto, and Harvard University (Addington et al., 2007).

After being identified, individuals were longitudinally followed for a period of at least two years so that changes in their clinical course, neuropsychological functioning, and biological measures (e.g., cortisol) could be assessed. Eight sites collected data on 860 nonpsychotic subjects between 1998 and 2005 (Woods et al., 2009). Subjects in the "prodromal" group (n = 377, referred to here as CHR individuals) met criteria for one or more prodromal syndromes as defined by the SIPS (described below). These criteria were: (1) recent onset or worsening of attenuated positive psychotic symptoms (2) recent onset of brief, self limiting periods of psychotic symptoms, (3) recent deterioration in functioning as measured by a 30% drop on the Global Assessment of Functioning scale and either A) schizotypal personality disorder (SPD) or B) a first-degree relative with psychosis. Also included were two individuals whose drop in functioning had not made the 30% cut-off or had occurred more than 12 months ago, given that it is expected that psychostimulants would have similar effects upon them. Demographic characteristics for the overall sample are listed in Table 1.

Measures

The Structured Interview for Prodromal Symptoms (SIPS). The SIPS is a semi-structured diagnostic interview designed to assess and diagnose the severity of prodromal symptoms of schizophrenia (McGlashan et al., 2001). It is composed of 19 symptom-items, each rated on a 0-6 scale. A score of 0 indicates the absence of a symptom while scores of 1-2 indicate the presence of a symptom at sub-prodromal

intensity. Scores between 3 and 5 are considered to be within the prodromal range and a score of 6 is in the psychotic range. Each symptom item is assessed with several questions, allowing the interviewer to explore various aspects of each symptom (e.g. the perceptual abnormality symptom item includes questions related to both visual and auditory perceptual abnormalities) The 29 symptom-items are grouped into four symptom scales: positive, negative, disorganized, and general symptoms.

The positive symptom scale consists of items that assess unusual thought content and delusional ideas, suspiciousness and persecutory ideas, grandiosity, perceptual abnormalities and hallucinations, and disorganized communication. The negative symptom scale includes items that assess social anhedonia, avolition, reduced expression of emotion, decreased experience of emotion and self, reduced ideational richness, and deterioration of role functioning. Items on the disorganized symptom scale assess odd behavior or appearance, bizarre thinking, trouble with focus and attention, and impairment in personal hygiene. Finally, the general symptom scale contains items that assess sleep disturbance, dysphoric mood, motor disturbances, and impaired tolerance to stress.

Medication Log. The interviews conducted with NAPLS participants included a medication log which interviewers completed using a semi-structured interview. Participants were asked to report any current or lifetime psychotropic medication usage, the duration that they used each of those medications, and how long it had been since they last used the medication. Participants' retrospective recall of these medications was supplemented with paperwork from their pharmacies and treatment providers, as well as the reports of their caretakers/family members when possible.

Illicit Drug Use Measures. Patients were assessed for lifetime substance use, abuse, or dependence using either the Structured Clinical Interview for DSM-IV (SCID-IV) (First, Spitzer, Gibbon, & Williams, 1995) or the Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children (KSADS-E) (Ambrosini, 2000) two well validated, semi-structured interviews for psychiatric diagnosis.

Results

Participants were grouped into categories based on their history of stimulant use: several participants met criteria for multiple categories and were included in all relevant analyses. See Table 1 for the number of subjects in each stimulant-use category. Participants were placed into the 'Prescription Stimulant Use' group if they reported any lifetime use of a prescription stimulant during their lifetime (i.e., prescription amphetamine or prescription non-amphetamine behavioral stimulant). Participants were categorized in the 'No Prescription Stimulant Use' group if they reported never having used any prescription in their lifetime. Participants were placed in the 'No Illicit Stimulant Use' group if they reported no lifetime use of methamphetamine or cocaine during the SCID-IV interview. Participants were placed in the 'Illicit Stimulant Use without Impairment' group if they reported any lifetime use of methamphetamine or cocaine during their SCID-IV interview, but never met abuse or dependence criteria for either of those drugs. Participants were placed in the 'Illicit Stimulant Use with Impairment' group if they reported any lifetime use of methamphetamine or cocaine and met abuse or dependence criteria for either or both of those drugs. The age and gender ratios of the various groups are listed in Table 1.

Analyses were performed to determine if the groups differed in their gender ratios or ages. An independent samples t-test was conducted to compare the mean age in the 'Prescription Stimulant Use' and the 'No Prescription Stimulant Use' groups. As Levene's test for equality of variance between the groups was significant F (1, 400) = 6.69, p = 0.1), equal variances were not assumed. There was a significant difference in the mean age of the 'Prescription Stimulant Use' (M=16.13, SD= 3.34) and the 'No Prescription Stimulant Use' (M=18.38, SD= 4.79) groups; t (98.53) = 4.386, p < .001. Younger subjects were more likely to have used prescription stimulants. Follow-up analyses of prescription medication groups were conducted using age as a covariate.

A chi-square test was conducted to determine if the two groups significantly differed in their gender ratios. The groups did differ significantly by gender, χ^2 (1, N=402) = 11.60, p < .001. Males were more likely to belong to the 'Prescription Stimulant Use' group. Thus, follow-up analyses were conducted using gender as a covariate.

A one way ANOVA was conducted to determine whether the 'Illicit Stimulant Use with Impairment', 'Illicit Stimulant Use without Impairment', and 'No Illicit Stimulant Use' groups differed in their mean ages. There was a significant relation of group membership with mean age [F(2, 370) = 10.527, p < .001]. Post hoc comparisons using independent means t-tests revealed significant differences between the 'No Illicit Stimulant Use' group (M= 17.69, SD = 4.47) and both the 'Illicit Stimulant Use with Impairment' group (M=21.39, SD= 4.62) and the 'Illicit Stimulant Use without Impairment' group (M=21.03, SD= 6.34). However, there was no significant difference between the two illicit stimulant using groups. A chi-square test was conducted to test for

group differences in gender ratios. The groups did not differ significantly in gender ratios χ^2 (2, N=373) = 1.63, p = .442.

In order to test hypothesis one, multivariate analyses of variance (MANOVAs) were conducted to determine if CHR individuals in the 'Prescription Stimulant Use' and/or 'Illicit Stimulant Abuse' category had higher ratings on the five positive symptom dimensions than CHR individuals in the 'No Lifetime Prescription Stimulant Use' and the 'No Lifetime Illicit Stimulant Use' categories respectively. Exploratory MANOVAs were conducted to test for group differences in scores on the negative, disorganized, and general symptom dimensions. In addition, the same analyses listed above were conducted on participants in the 'Prescription Stimulant Use' and 'No Prescription Stimulant Use' groups who were 16 years old or younger. This was done in order to determine if prescription stimulant use had different effects on younger participants.

Follow-up exploratory analyses were conducted to determine whether illicit and prescription stimulant use were more strongly associated with positive symptoms. Potentially confounding variables (e g., attention measures, SES, and antipsychotic use) were included in follow-up exploratory analyses to determine what effect they had upon the previously described tests. In addition, similar MANOVA was conducted on participants in the 'Prescription Stimulant Use' and 'No Prescription Stimulant Use' group who were 16 years old or younger to see if prescription stimulant use had different effects on younger participants.

In order to test hypothesis two, a linear regression analysis was conducted to determine whether lifetime duration of prescription stimulant is a significant predictor of

positive, negative, disorganized, and general symptom scores. Only participants with lifetime duration of prescription stimulant use data were included in this analysis. Follow-up analyses including relevant covariates (e.g., the specific type of stimulant used, SES, and antipsychotic) were conducted if preliminary analyses indicated that this was appropriate.

In order to test hypothesis three, a MANOVA was conducted to test for symptom differences among CHR individuals in the 'Illicit Stimulant Use with Impairment,' 'No Illicit Stimulant Use,' and 'Illicit Stimulant Use without Impairment' categories. Follow up analyses with potentially confounding variables (e g., type of illicit stimulant, SES, and antipsychotics) were conducted when appropriate.

Hypothesis 1

The MANOVA of SIPS positive symptom scores indicated no significant relation of symptoms ratings with any lifetime use of stimulant medication, $F (5, 397) = 1.268$, $p = .277$. The second MANOVA of SIPS positive symptoms yielded no significant effect for any lifetime illegal stimulant use, $F (5, 393) = 1.341$, $p = .246$. Their interaction when they were both included in a separate multivariate model was also non-significant, $F (5,391) = .420$, $p = .835$. Raw group means for the prescription stimulant groups on each symptom dimension, grouped into the 4 symptom scales, are illustrated in Figures 1-4 while the illicit stimulant groups are illustrated in Figures 5-8.

Examination of the individual positive symptom dimensions showed that scores for delusional ideas and perceptual abnormalities appeared elevated among illicit stimulant users, while ratings of delusional ideas among prescription stimulant users

appeared lower. Thus, follow-up univariate analyses were conducted on for these three symptom ratings. Illicit stimulant users had significantly higher ratings on the delusional ideas symptom dimension than non-users, $F(1, 397) = 4.613$, $p = .032$. However, the higher perceptual abnormality scores in the illicit stimulant group proved non-significant, $F(1,397) = 2.727$, $p=.099$. In another follow-up analysis, prescription stimulant users had significantly lower delusional idea ratings than individuals in the 'No Lifetime Prescription Stimulant Use' category $F(1,397) = 4.687$, $p=.031$.

Follow-up analyses employing only individuals 16 years old and younger all failed to reach significance ($p<.05$). Additional follow-up analyses employing age, gender, mother's education, antipsychotic use, and antidepressant use as covariates also failed to yield significant omnibus effects of lifetime prescription stimulant use, lifetime illegal stimulant use, and their interaction (all $p > .05$). Exploratory MANOVA analyses for negative, disorganized, and general symptom scores also indicated no significant omnibus effects of lifetime prescription stimulant use, lifetime illicit stimulant use, and their interaction (all $p > .05$).

Hypothesis 2

Linear regression analysis indicated that total duration of lifetime prescription stimulant use did not predict the sum of ratings on the positive symptom dimensions, $\beta = .072$, $t(29) = .389$, $p = .700$. Follow-up multiple regression analyses which included the covariates of age, mother's education, antidepressant use, and antipsychotic use all failed to reach significance (all $p > .05$). Follow up exploratory analyses examining whether

total duration of lifetime prescription stimulant use could predict each of the positive symptom dimensions yielded no significant results (all $p > .05$).

Hypothesis 3

The MANOVA for attenuated positive symptom scores among CHR individuals indicated no significant omnibus effects for the severity of illicit stimulant use among lifetime illicit stimulant users (i.e., some lifetime use without impairment vs. lifetime abuse/dependence), $F(5, 35) = .327$, $p = .893$. A follow up analysis which included individuals in the 'No Lifetime Illicit Stimulant Use' category was also not significant ($p > .05$). Exploratory MANOVA analyses for negative and disorganized general symptom domains indicated no significant omnibus effect of severity of illicit stimulant use (all $p > .05$). An exploratory MANOVA analysis of general symptoms yielded a significant result only when using Roy's Largest Root as the test statistic, F (4, 360) = 3.027, p=.018. Follow-up univariate tests indicated that illicit stimulant use without impairment was associated with lower ratings of depressed mood at baseline assessment, F (2, 362) = 3.093, p= .047. An exploratory MANOVA which analyzed each type of illicit stimulant (i.e., methamphetamine and cocaine) separately yielded no significant difference ($p > .05$)

Discussion

Findings

The goal of this study was to investigate the association between stimulant use and attenuated positive symptoms in a group of individuals with increased risk for a psychotic disorder. While previous literature suggested that stimulant use might be associated with increased positive symptoms, no such association was found in the

present study. Notably, the results remained non-significant even with the inclusion of covariates, including age, gender, SES, etc. Another set of analyses using only CHR subjects age 16 or younger also failed to yield significant results. Also, follow up univariate analyses were generally non-significant, addressing the concern that perhaps these non-significant results could be due to psychostimulants affecting only a specific positive symptom dimension. The exceptions were a significant elevation on the delusional ideas dimension among individuals who had used illicit psychostimulants, and a significant decrease in delusional idea ratings among prescription stimulant users. The importance of these significant findings must be tempered by the fact that it is one of many exploratory univariate analyses that were run without alpha level correction for multiple tests. However, they did follow the general trend towards reduced positive symptoms among prescription stimulant users and increased positive symptoms among illicit stimulant users. It was also noteworthy that there was a significant decrease in depressive symptoms among illicit stimulant users who never met criteria for abuse or dependence: this may have reflected the mood enhancing effects of these drugs and/or that depressed individuals are less likely to procure these drugs and use them recreationally. These findings are encouraging in that they are not consistent with an exacerbation of prodromal symptoms by prescription stimulants in CHR individuals.

While these results conflicts with some of the current literature regarding stimulants and the risk for psychosis, other previous studies may help explain these findings. Studies of animal models of stimulant sensitization have shown striking differences between different organisms tolerances of repeated doses of psychostimulants (Berman et al., 2009). For example, repeated administration of low doses of

amphetamine to rats (equivalent to doses in the therapeutic range for humans) does not produce neurotoxicity (Segal & Kuczenski, 1997), while equivalent doses administered to non-human primates for 4 weeks resulted in a 30-50% reduction in striatal dopamine, its membrane transporter, and it's vesicular transporter (Ricaurte et al., 2005). As reviewed by Curran et al. (2004), evidence for stimulant sensitization in humans is mixed, and though better studies have emerged in the intervening years such as those using PET scans to observe the effects of stimulants in vivo, the study of stimulant sensitization in real world situations remains difficult due to confounds such as polysubstance abuse and the ethical limits imposed when working with a vulnerable population. The differing effects of stimulants according to their dosage and method of administration may be reflected in the finding of increased delusional idea ratings for illicit stimulant users contrasting with the significantly *lower* delusional ideas ratings among prescription stimulant users.

These null findings raise the possibility that it may be safe to carefully employ psychostimulants in the treatment of CHR individuals. This supports previous studies that have shown that stimulants may have positive effects on cognition in schizophrenia (Barch & Carter, 2005), at least in the short term and when combined with neuroleptics. It may well be the case that stimulants, in carefully titrated dosages, and possibly combined with other psychotropics, have no long term negative effects on those with CHR and even those with a psychotic illness. They may even represent a viable intervention strategy in treating the negative symptoms of schizophrenia which so far have remained largely refractory to interventions (Barch, 2010). However, given the circumstantial evidence of negative sequelae from studies of chronic stimulant users,

animal models, and experimental administrations of stimulants, it remains imperative that clinicians carefully monitor their patients who are taking prescription stimulants, especially those that present clinical signs of increased risk for psychosis.

Limitations

The present study had several limitations that bear mentioning. The first is the issue of sample size. While the sample size of individuals with CHR in the NAPLS I study was large, especially compared with previous studies of individuals with CHR, the proportion using prescription stimulants was small (i.e. 52/402 CHR individuals with any lifetime prescription stimulant use and 18/402 CHR individuals using them at baseline). This smaller proportion of individuals with any history of stimulant provided modest statistical power for detecting group differences. Additionally, many of the individuals who reported some lifetime stimulant use had only used stimulants for a brief duration (e.g., a couple of months) and some time ago. This does not seem to be unique to the individuals enrolled in the study, however, as the majority of patients who begin stimulant medication treatment persist in that treatment for less than six months (Perwien, Hall, Swensen, & Swindle, 2004).

In addition, some participants were unable to provide information regarding the duration and time since discontinuation of stimulant treatment. This is to be expected, given limitations on retrospective recall of medication information, especially for individuals with significant psychiatric symptoms (Coughlin, 1990). The data on illicit stimulant use may have had similar limitations. Also, as a smaller group of participants were using psychostimulants at baseline, this study might have had a diminished ability

to detect any psychostimulant sensitization if it existed, as such sensitization is likely to fade over time (Berman et al., 2009). The lack of temporal data regarding illicit stimulant use is similarly limiting.

Future Research

Future research could address some of the limitations of this study and begin to provide evidence that psychostimulants can be safely employed among CHR individuals under certain conditions. Future studies could employ a more sensitive outcome measure than the SIPS. While effective in predicting the onset of psychosis, the prodromal ratings on the SIPS are scores of 3, 4 and 5, and the increase from 4 to 5 is made primarily on the basis of how much insight the individual maintains. Studies employing other outcome measures with a wider range of ratings, such as the O-LIFE scale of schizotypal symptoms (Mason, Linney, & Claridge, 2005), might be better suited to detecting smaller shifts in the intensity of prodromal symptoms. Future studies could also use age of onset of prodromal symptoms as their outcome measure rather than symptom ratings. An example of such a study is Karatekin et al.'s (2010) study showing that children who had been prescribed stimulants had an earlier age of onset for schizophrenia as compared with children who had not received stimulant medication. As his study was retrospective and focused on childhood onset schizophrenia, it's hard to know whether his results will generalize to the wider CHR population: prospective studies of a less symptomatic population would be useful.

Future large longitudinal studies, such as the second iteration of the NAPLS study (Addington & Heinssen, 2012), may be able to address some of the limitations I have

mentioned. By including instruments designed to assess recent illicit drug use, by increasing the number of participants with complete medication duration and discontinuation information, and by including a battery of instruments designed to assess neuropsychological and social cognitive function, NAPLS II will have greater power to detect smaller effects and note changes in cognitive as well as clinical variables. Hopefully, the information gained in the present study and future ones will allow future clinicians to more confidently assess the risks and benefits of clinical interventions they might deliver to CHR individuals, and enable them to have a greater positive effect on CHR individuals' clinical symptoms and functional outcomes.

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Table 1

Demographic Characteristics by Stimulant Use Status

	Total	Females	Males	Mean Age (SD)
Any Lifetime Stimulant Use	93	26	67	18.09 (5.06)
No Lifetime Stimulant Use	305	124	181	18.06 (4.54)
Lifetime Prescription Stimulant Use	52	10	42	16.13 (3.43)
No Lifetime Prescription Stimulant Use	344	204	127	18.40 (4.84)
Age 16 or younger and Lifetime Prescription Stimulant Use	32	9	23	13.84 (1.30)
Age 16 or younger and No Lifetime Prescription Stimulant Use	134	53	81	14.23 (1.434)
Lifetime Illicit Stimulant Use	41	16	25	21.19 (5.58)
No Lifetime Illicit Stimulant Use	331	127	204	17.70 (4.47)
Prescription Stimulant Users with Duration Information	31	6	25	15.89 (3.20)

Table 1: Number of CHR individuals with positive symptom data in each of the stimulant using and non-stimulant using categories. Ages significantly varied between the Any Lifetime Stimulant Use group and the No Lifetime Stimulant Use Group, as well as the Lifetime Prescription Stimulant Use Group and the No Lifetime Prescription Stimulant Use Group.

Figure 1

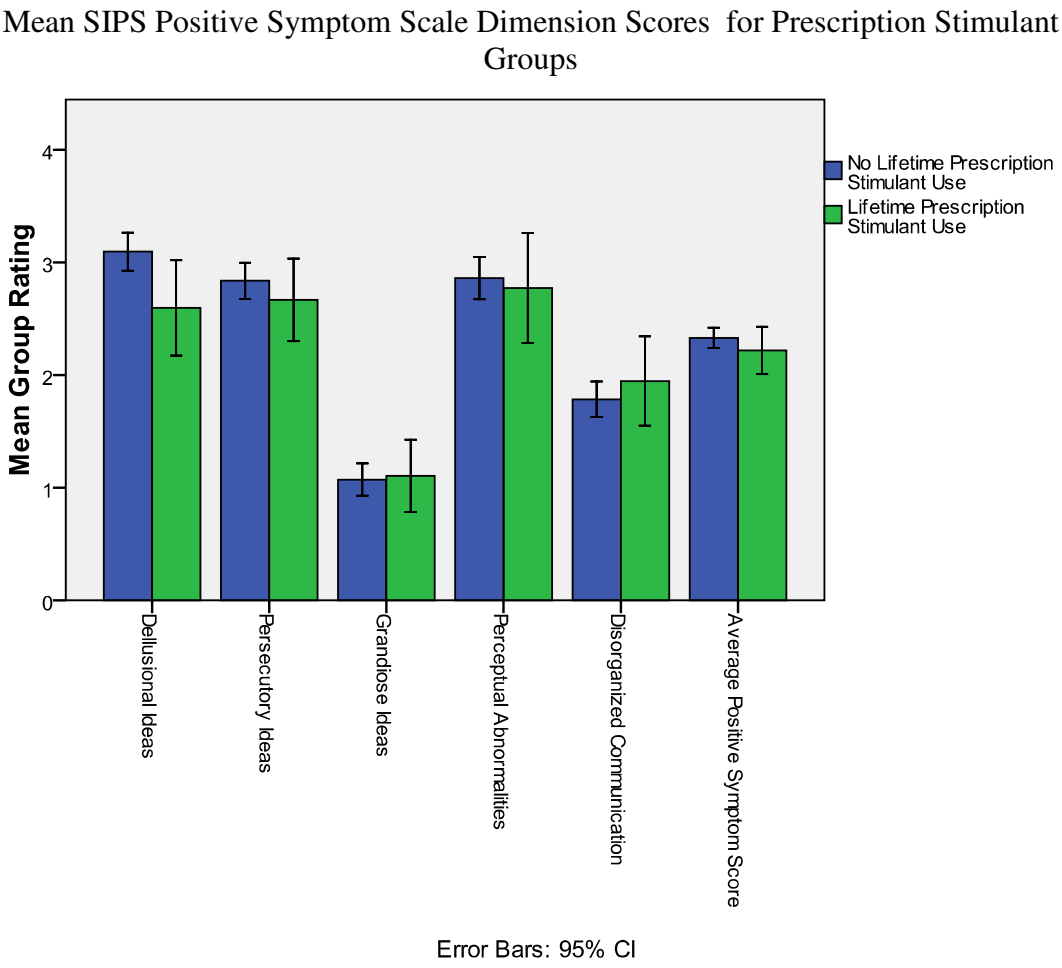

Figure 1: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the two groups. In follow up univariate analyses, lifetime prescription stimulant users were found to have significantly ($p < .05$) lower delusional ideas scores than the non-prescription stimulant using group.

Figure 2

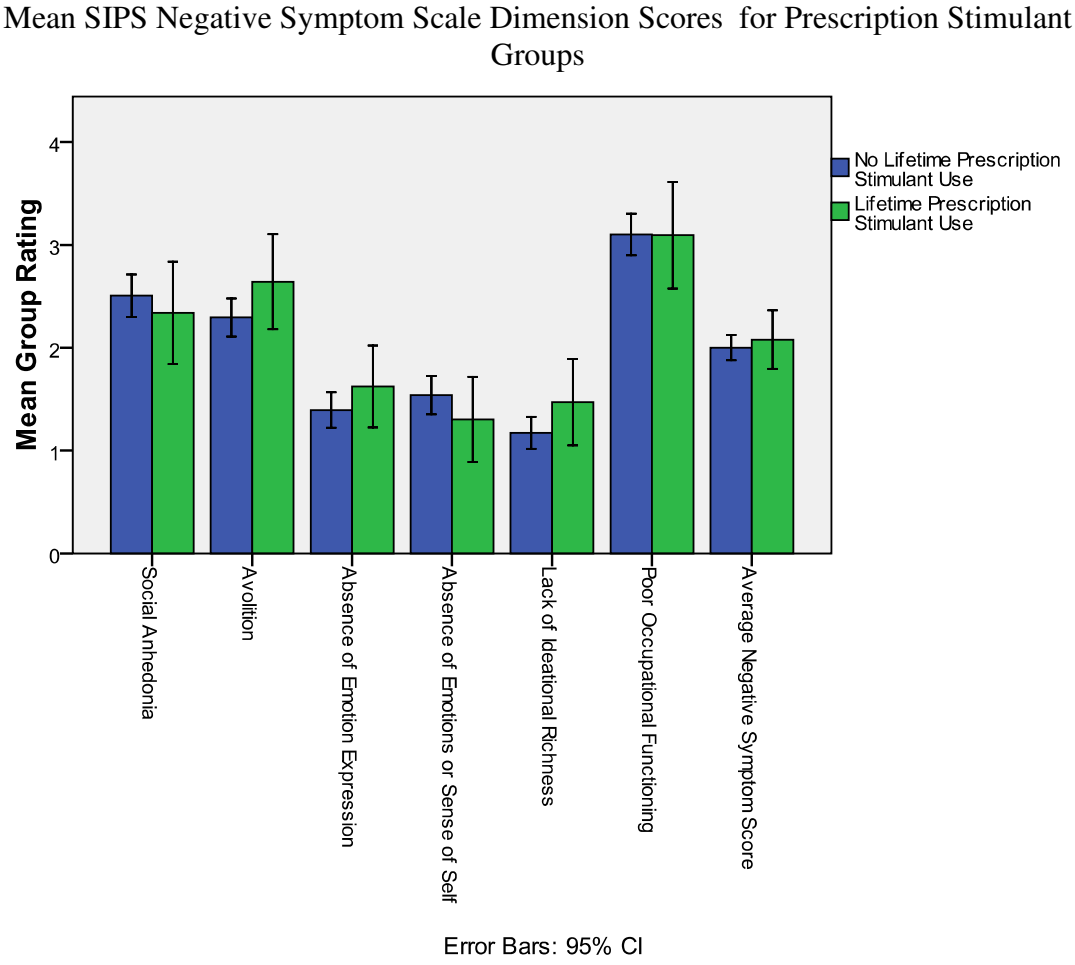

Figure 2: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the two groups.

Figure 3

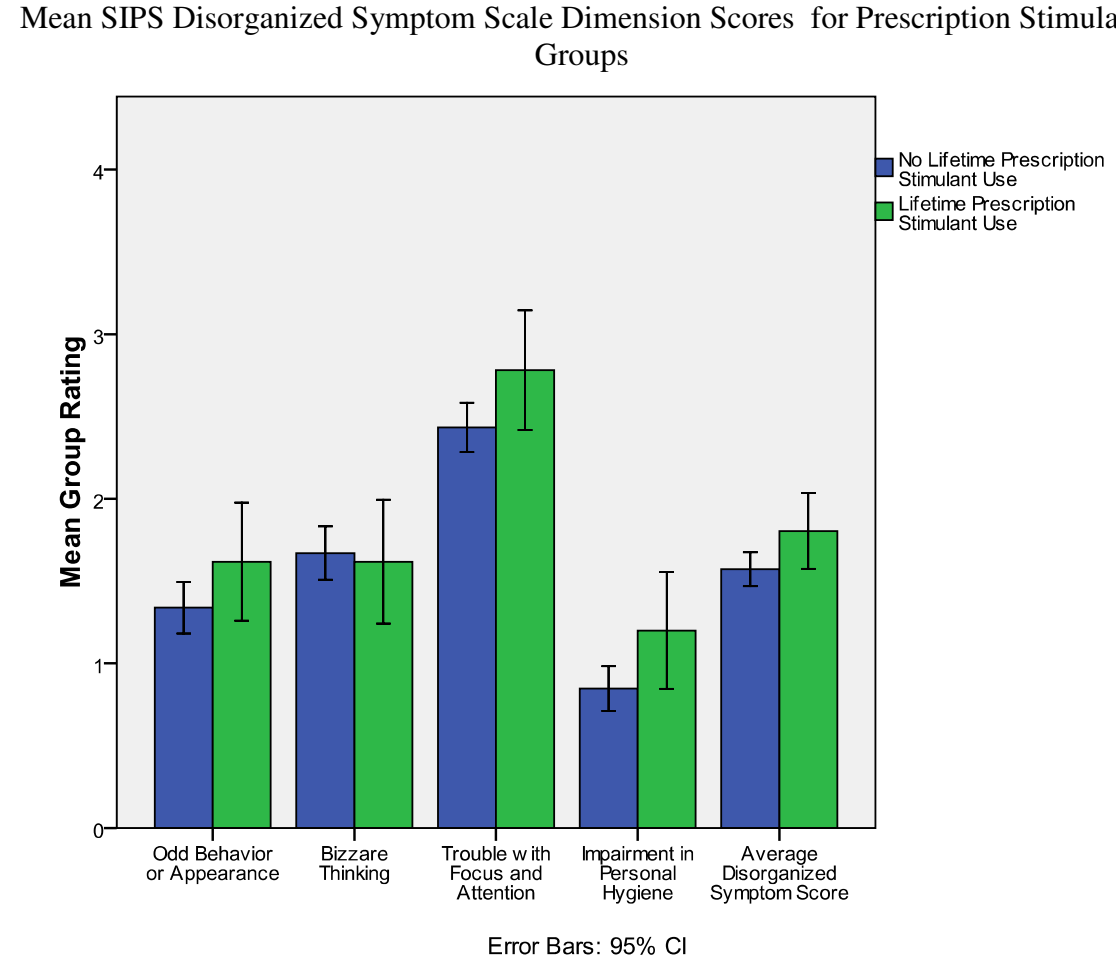

Figure 3: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the two groups.

Figure 4

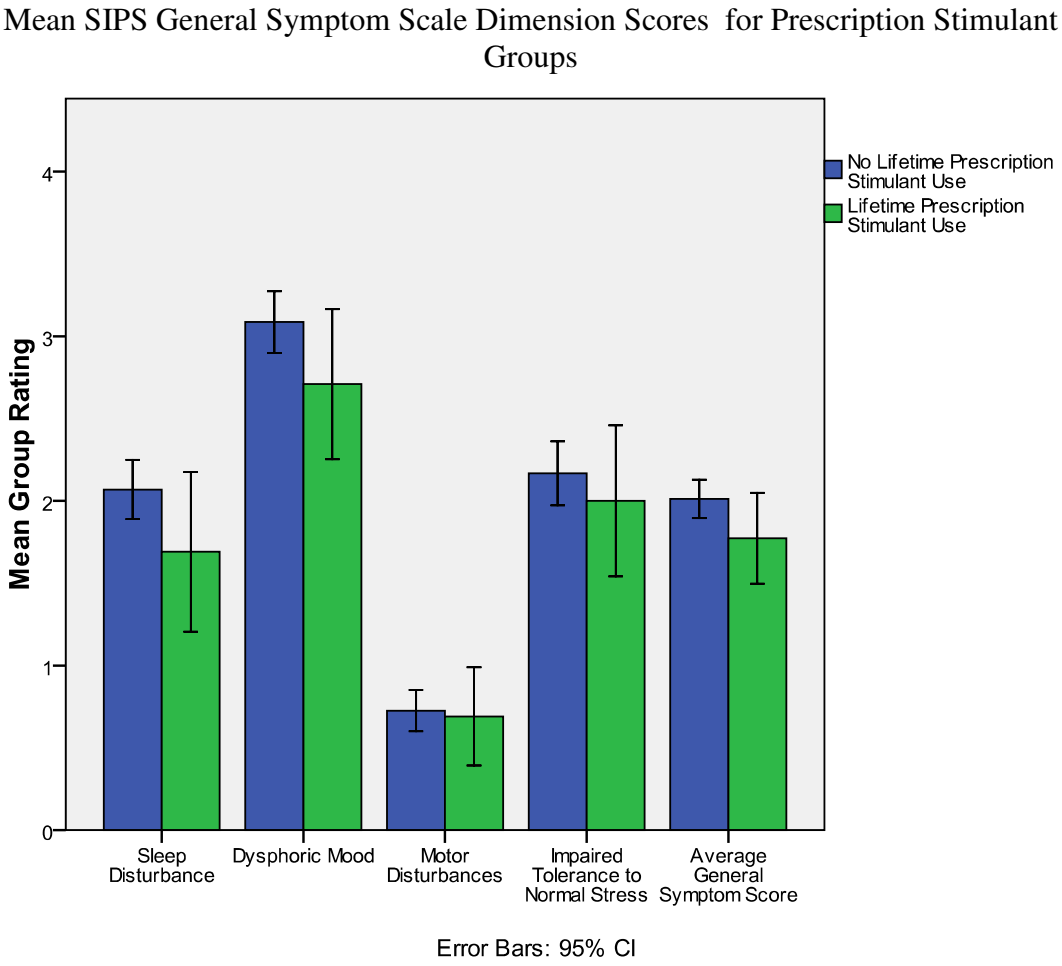

Figure 4: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the two groups.

Figure 5

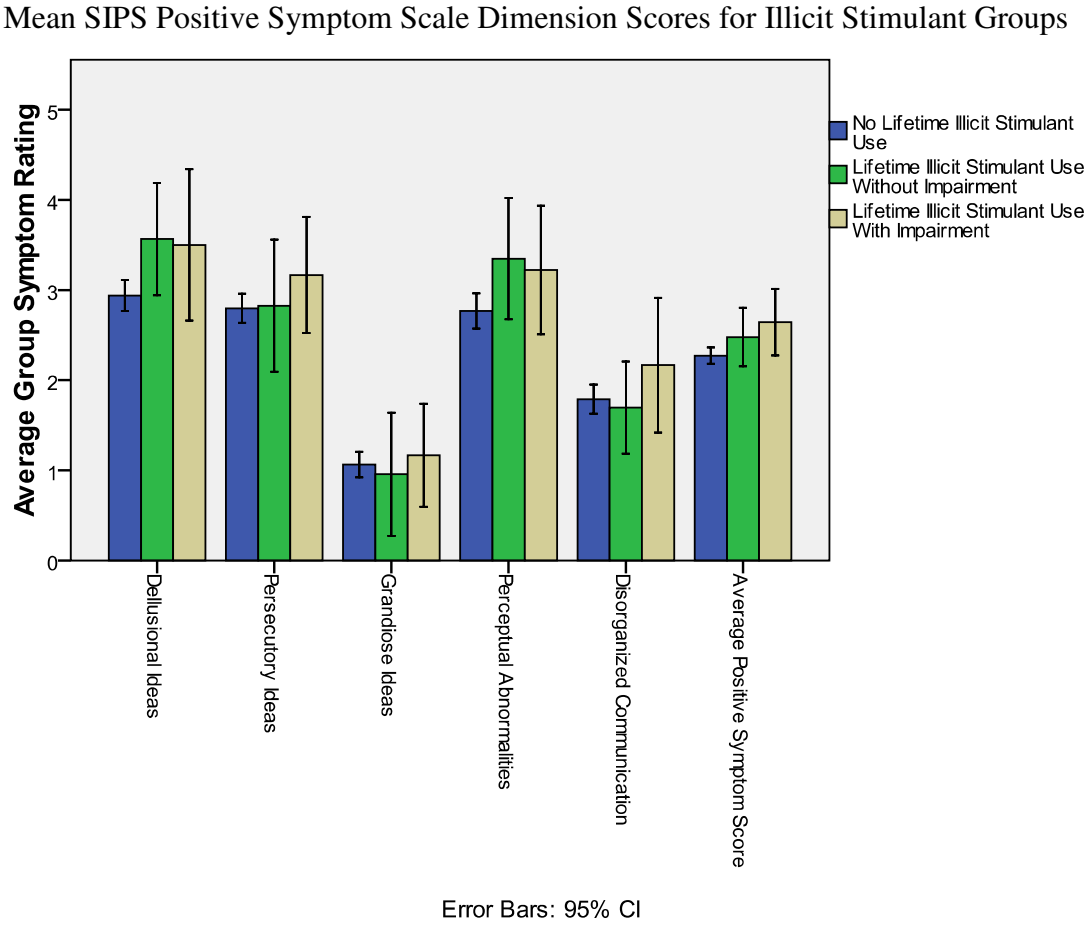

Figure 5: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the groups.

Figure 6

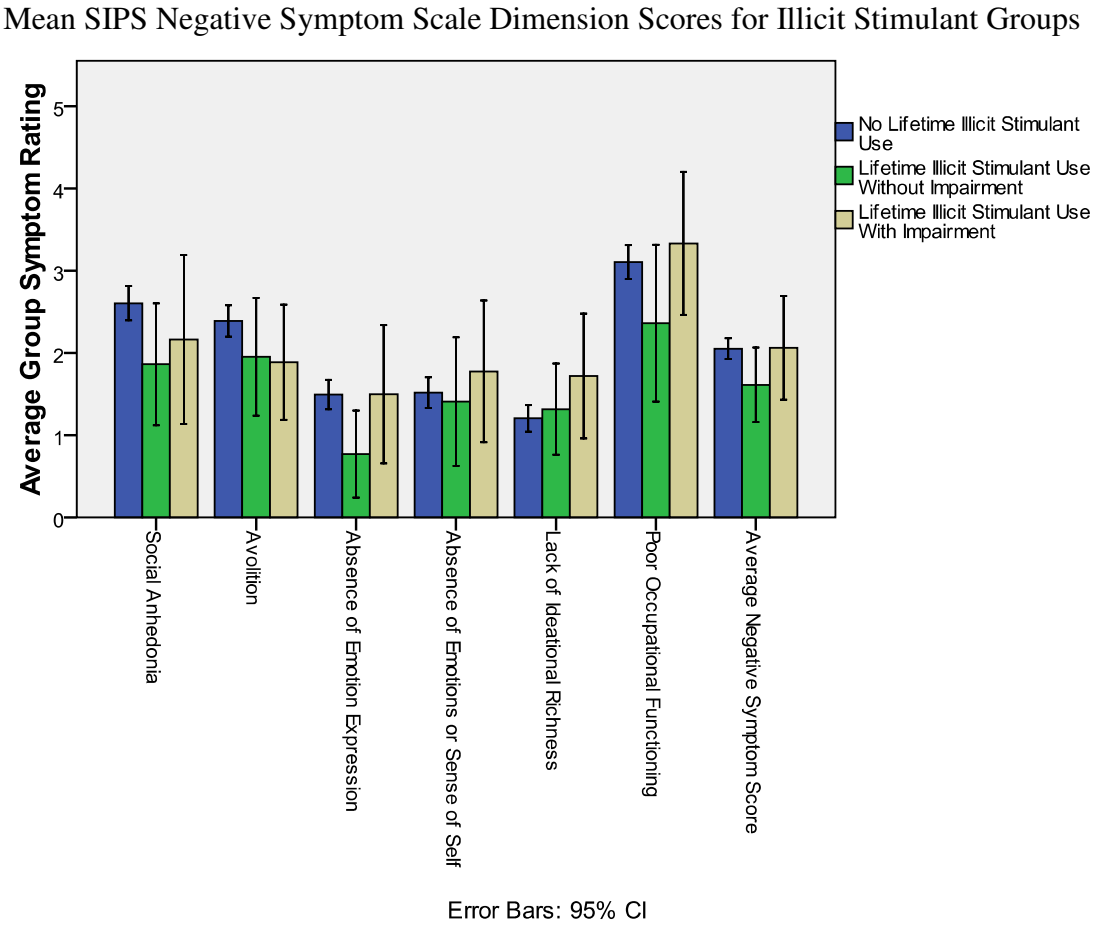

Figure 6: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the groups.

Figure 7

Mean SIPS Disorganized Symptom Scale Dimension Scores for Illicit Stimulant Groups

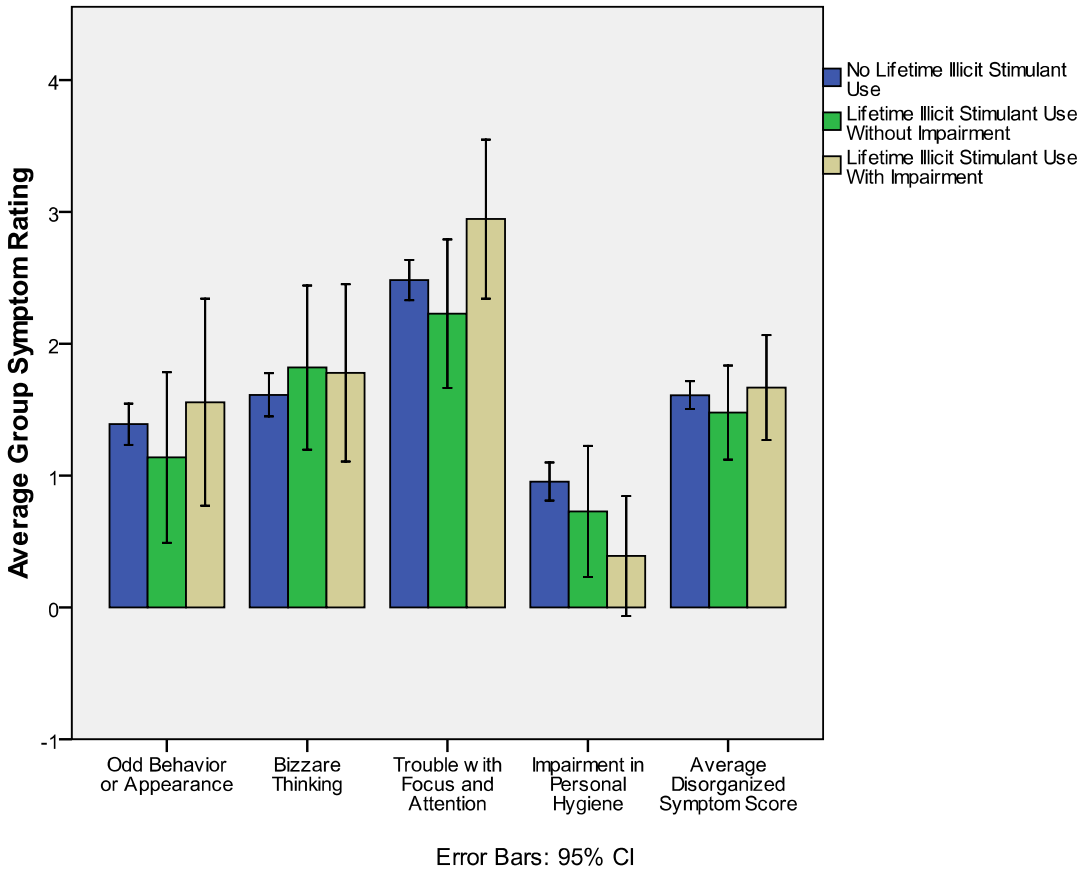

Figure 7: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the groups.

Figure 8

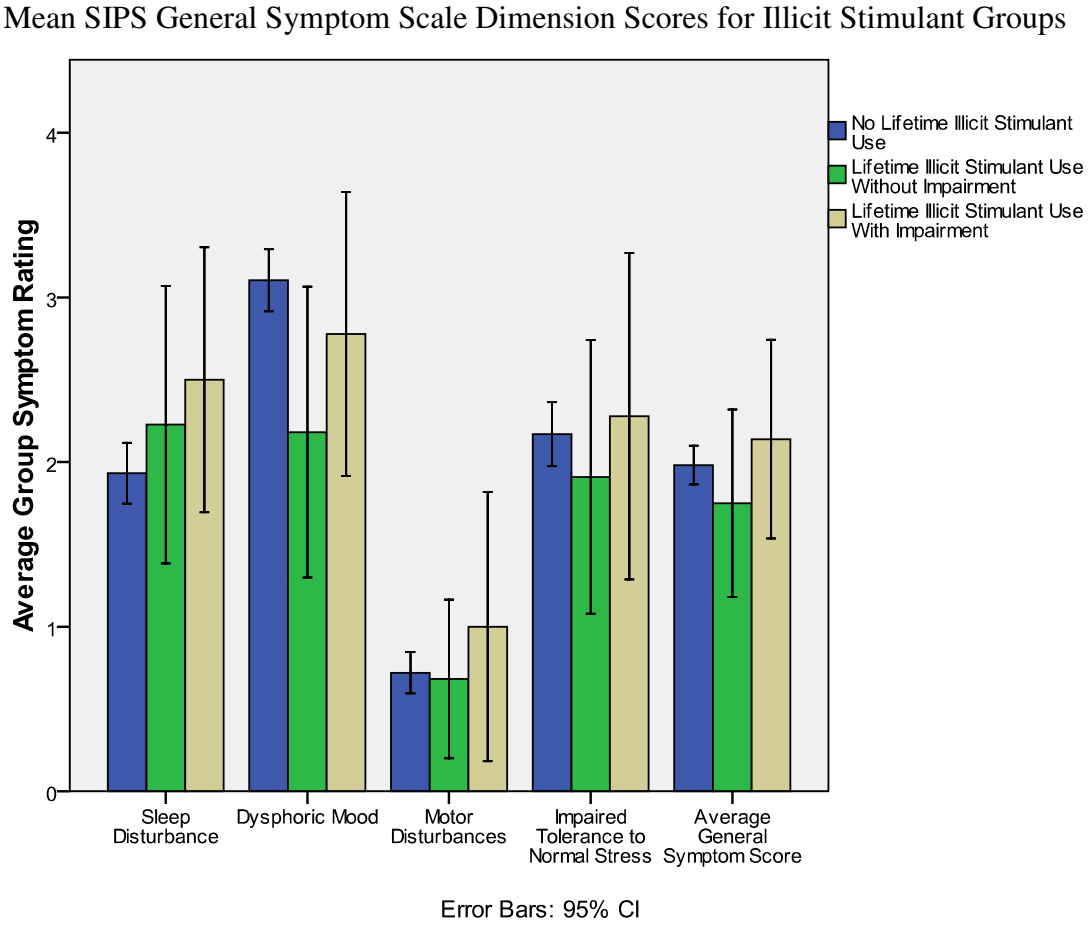

Figure 8: Error bars represent a 95% confidence interval around the mean. There was no significant omnibus difference between the groups.