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A ^{1}H-MRS and Neurocognitive Analysis of Psychotic Symptoms in Stimulant Dependence

by

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DEDICATION

This thesis is dedicated to my husband, Sean, for his patience, for always being understanding and for providing the voice of reason; and to my family, my parents Wendy and Evan and brother Stephen, for their never-ending support and encouragement, and for fostering a love of learning.

ABSTRACT

The association between stimulant drug use and the presence of a psychotic disorder raises questions about causation. Substance-induced psychosis may differ etiologically from schizophrenia despite similar phenotypic presentation. It is possible that stimulant drug users who develop symptoms of psychosis have a pre-existing vulnerability to schizophrenia. A recent theory building on the neurodevelopmental hypothesis of schizophrenia proposes that a second insult in conjunction with a pre-existing vulnerability may be necessary to trigger the onset of psychosis. Stimulant dependence may be one of these exogenous triggers for psychosis. This study investigated the possibility that stimulant dependence can trigger psychosis biologically by using proton magnetic resonance spectroscopy, and cognitively by using a battery of cognitive assessments. It was hypothesized the stimulant drug users who develop psychotic symptoms have a pre-existing vulnerability to psychosis that manifests when the substance use triggers abnormal neuropathological development. Evidence of this pathology should be found biologically in proton magnetic resonance spectroscopy measures of N-acetylaspartate, glutamate and choline, and cognitively in measures of processing speed and executive functioning. Abstinent stimulant-dependent users were recruited from the community and compared to a healthy control group and a group of non-substance-induced first episode psychosis patients. Results of this study provide support for the association between methamphetamine use and psychosis. The stimulant-dependent group had worse performance on measures of executive function and processing speed compared to healthy controls, but only processing speed was related to the presence of psychotic symptoms, providing

support for processing speed as a potential endophenotype for psychosis. The stimulant-dependent group also had abnormal neurochemical profiles as measured by N-acetylaspartate and glutamate. Finally, in comparison between stimulant-dependent users with symptoms of psychosis and a *de novo* schizophrenia, the factors predicting severity of psychotic symptoms differed substantially between groups. These results suggest that the cognitive and biological correlates of a substance-induced psychosis differ from a non-substance-induced psychosis, suggesting that a vulnerability to substance-induced psychosis may differ from the neurodevelopomental pathology associated with schizophrenia.

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List of Abbreviations

^{1}H-MRS – Proton Magnetic Resonance Spectroscopy

ACC – Anterior Cingulate Cortex

AMPA – 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid

ASDU – Abstinent Stimulant-Dependent User

ATS – Amphetamine-Type Stimulants

BAI – Beck Anxiety Inventory

BDI – Beck Depression Inventory

Cho – Choline

Cr – Creatine + Phosphocreatine

CSF – Cerebrospinal Fluid

DA – Dopamine

dlPFC – Dorsolateral Prefrontal Cortex

DSM-IV-TR – Diagnostic and Statistical Manual of Mental Disorders IV – Text Revision

EEPIC – Edmonton Early Psychosis Intervention Clinic

FEP – First Episode Psychosis

fMRI – Functional Magnetic Resonance Imaging

Gln – Glutamine

Glu – Glutamate

Glx – Glutamate + Glutamine

GM – Gray Matter

HC – Healthy Control

MA – Methamphetamine

MDMA – 3,4-Methylenedioxymethamphetamine

MIS – Magical Ideation Scale

mPFC – Medial Prefrontal Cortex

MRI – Magnetic Resonance Imaging

NAA – N-acetylaspartate

NAc – Nucleus Accumbens

NMDA – N-methyl-D-aspartic Acid

NSIP – Non-Substance-Induced Psychosis

OFC – Orbitofrontal Cortex

PANSS – Positive and Negative Syndrome Scale

PCP – Phencyclidine

PFC – Prefrontal Cortex

PRESS – Point Resolved Spectroscopy

RF – Radio Frequency

SAS – Social Anhedonia Scale

SCID – Structured Clinical Interview for DSM-IV Axis I Disorders

SF – Scaling Factor

SNR – Signal-to-Noise Ratio

STEAM – Stimulated Echo Acquisition Mode

TE – Echo Time

THC – Tetrahydrocannabinol

TMT – Trail Making Task

TR – Repetition Time

UNODC – United Nations Office of Drug and Crime

VTA – Ventral Tegmental Area

WCST – Wisconsin Card Sorting Test

WM – White Matter

Introduction

This research project focused on the potential for illicit stimulant users to develop psychotic symptoms that are similar in phenotypic presentation to paranoid schizophrenia. To date, factors influencing susceptibility to developing these symptoms are unknown. As a result, potential biological and cognitive differences between *de novo* schizophrenia and stimulant-induced psychosis are not fully understood. This research offers a unique perspective for investigating the etiology of schizophrenia by recruitment of abstinent stimulant-dependent users with and without symptoms of psychosis, and comparing them to a healthy control group and a non-substance-induced first episode schizophrenia group. No research to date has investigated neurotransmitter systems in conjunction with cognitive assessment in substance-induced psychosis.

There is an unquestionable association between drug dependence and mental health disorders. One possible explanation for this relationship is that drug dependence is able to trigger a mental illness in an already vulnerable brain. It is well established that methamphetamine use can lead to the development of psychotic symptoms that are nearly indistinguishable from paranoid schizophrenia (Griffith, Oates, & Cavanaugh, 1968). Amphetamine administration in rodents has been used as an animal model for schizophrenia (Borison & Diamond, 1978), and amphetamine can exacerbate psychotic symptoms in individuals with a pre-existing psychosis (Curran, Byrappa, & McBride, 2004). It may be that stimulant drug users who develop a persistent psychotic disorder share a core pathological vulnerability predisposing them to psychosis. To date, there is a lack of research investigating why some methamphetamine users develop psychosis and others do not.

One theory of the etiology of schizophrenia is the neurodevelopmental hypothesis, which proposes that an early life insult triggers abnormal neurodevelopment, resulting in neuropathology associated with schizophrenia. This study proposes that in addition to an early insult that may be genetic or related to birth complications, a second insult is necessary for the onset of psychosis, a so-called “two hit” theory. This project proposes that stimulant use

may act exogenously as a second trigger, stimulating pathological processes to manifest as psychosis.

The mechanism by which stimulants may exert abnormal neurodevelopment likely involves processes that mimic pathology in schizophrenia. As an example, stimulants, such as amphetamine and methamphetamine, affect dopamine transmission (Ellison, 1994). Given the proposed role of dopamine in schizophrenia (Willner, 1997), this is one possible mechanism underlying the disorder. These overlapping pathologies between stimulant-dependence and schizophrenia support the hypothesis that stimulant dependence may be a sufficient exogenous trigger for the onset of psychosis in an already vulnerable brain. Given this assumption, one would expect stimulant users with this pathological vulnerability to develop a persistent psychotic disorder that presents phenotypically, cognitively and biologically similar to a non-substance-induced psychosis comparison group.

This study used proton magnetic resonance spectroscopy to measure neurochemical profiles *in vivo*. Following the discovery that the glutamate receptor antagonist phencyclidine induces symptoms of psychosis, numerous studies have provided evidence implicating glutamate in the etiology of schizophrenia (Tsai & Coyle, 2002). Recent publications suggest that glutamate may play a progressive role in schizophrenia, with elevations in prodromal phases and reduced glutamate in a chronic course (Bernier & Tibbo, 2010). Another measureable metabolite, N-acetylaspartate reflects neural health, so that decrease may reflect neural damage (Moffett, Ross, Arun, Madhavarao, & Namboodiri, 2007) and may represent a marker of a vulnerable brain state for psychosis. Additionally, schizophrenia is accompanied by cognitive impairment. Specific domain impairment holds potential as an endophenotype for psychosis. An endophenotype is an intermediary measurable point between the genotype and the phenotype of a disorder; it must be heritable, state-independent, associated with illness in the population and must co-segregate within families (Joo, 2008). Processing speed has recently been proposed as a strong candidate because of evidence of impairment in high-risk samples, and the ability to differentiate high-

risk samples from healthy controls (Pukrop & Klosterkotter, 2010; Seidman et al., 2010). Conversely, executive function impairment is commonly reported in schizophrenia, but may be more related to the phenotype than the genotype (Purdon, Valiakalayil, Hanstock, Seres, & Tibbo, 2008). As such, executive functioning impairments may be related to the disease state, and less related to a specific neurodevelopmental pathology.

It is likely that the neuropathology associated with schizophrenia contributes to cognitive impairment and neurochemical profiles. For this study the Stroop Colour and Word Test colour reading measure was used as the primary measure of processing speed; the Wisconsin Card Sorting Test perseverative error measure was used as the primary measure of executive function. Proton magnetic resonance spectroscopy scanning took place in a 3 Tesla scanner with a region of interest in the medial prefrontal cortex. The negative symptoms of schizophrenia, as measured by the Positive and Negative Syndrome Scale, represent a marker of disease severity, as well as a marker of potential underlying vulnerability to psychosis given that they are more strongly related to the genotype of schizophrenia and to a history of obstetric complications (Rector, Beck, & Stolar, 2005). Negative symptoms have also been associated with structural and functional pathology (Makinen, Miettunen, Isohanni, & Koponen, 2008). As such negative symptoms were used as an indicator of vulnerability to psychosis.

The samples assessed in this study were a healthy control group (without any history of psychiatric illness or substance abuse or dependence), a first episode psychosis group (without a history of substance abuse or dependence), and an abstinent stimulant-dependent user group, comprised of both cocaine-dependent users and methamphetamine-dependent users.

Co-registration of biological and cognitive factors in the study of psychosis is an opportunity to add strength to the impact of known risk factors for schizophrenia. Further, the selected samples in this study, abstinent stimulant-dependent users with and without symptoms of psychosis, offer a unique method to examine potential etiological factors contributing to the onset of schizophrenia.

Chapter 1: Literature Review

Schizophrenia

Emil Kraepelin popularized the term *dementia precox* in 1893 to describe a disorder with cognitive (*dementia*) disabilities at an early age (*precox*). *Dementia precox* was described as a progressive disorder comprised of hallucinations and delusions. Later, in 1908, Eugene Bleuler coined the term schizophrenia to replace *dementia precox*. This term was derived from the schism of two minds (thought/emotion and behaviour). Bleuler described schizophrenia as having four fundamental symptoms: affect, autism, ambivalence, and associations (the four A's; Sadock & Sadock, 2003). This section briefly reviews schizophrenia before focusing on etiological theories.

Currently, schizophrenia is described in the Diagnostic and Statistical Manual-IV-Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) as a disorder requiring two or more symptoms for 1 month or longer, including delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behaviour, and negative symptoms (only one required if delusions are bizarre or hallucinations are a running commentary or involve two voices). Schizophrenia is comprised of symptom clusters (O'Donnell & Grace, 1998) that can be categorized as positive symptoms (thoughts, ideas, and behaviours that are in excess of normal patterns, often consisting of delusions, hallucinations, grandiosity, and paranoia); negative symptoms (thoughts, ideas, and behaviours that are absent from normal behaviours, often consisting of depression, anhedonia, lack of motivation, and a blunted affect); and cognitive symptoms, often characterized by executive function impairment but also including attention, planning, learning, and problem solving. The Positive and Negative Syndrome Scale (PANSS) is one tool currently used to quantify severity of these symptoms. It was developed in 1987 as a standardized measurement tool; validity assessment of this tool provided evidence that positive and negative symptoms are mutually exclusive constructs (Kay, Fiszbein, & Opler, 1987).

The current reported prevalence of schizophrenia is about 1%, with some variance in urban versus rural locations (Van Os, 2004). Schizophrenia affects

males and females at equal rates, though males have a younger age at onset and a worse clinical course (Stilo & Murray, 2010). The average age of onset for schizophrenia is in late adolescence or early adulthood (Sadock & Sadock, 2003). Persons with schizophrenia have a shorter than expected lifespan due to a higher rate of suicide and greater comorbidity with general medical disorders (e.g., heart disease) which is affected by higher rates of adverse lifestyle choices (e.g., tobacco use; Saha, Chant, & McGrath, 2007; Stahl, 2008; Stilo & Murray, 2010). The societal cost of schizophrenia is great, estimated to exceed the cost of all cancers combined (Sadock & Sadock, 2003), likely because schizophrenia is a non-curable disorder occurring over a lifetime.

A main focus of much research is determining risk factors for the development of schizophrenia. Recent reviews identify several risk factors including advanced parental age, winter or spring season of birth, obstetric complications, infection, nutritional deficiency, trauma *in utero*, early separation from parents, poor mothering, drug abuse or dependence, urban residence, migration, childhood adversity, chronic adult stress and social isolation (Maki et al., 2005; Stilo & Murray, 2010). Several etiologies for schizophrenia have been proposed including neurodevelopmental, neurodegenerative, immunological, inflammatory, infectious, and metabolic models (Oertel-Knochel, Bittner, Knochel, Prvulovic, & Hampel, 2011). The mechanisms for these risk factors, however, remain unclear.

Schizophrenia also has a genetic component, with a heritability of approximately 80% and a concordance between monozygotic twins of around 50% (Cardno & Gottesman, 2000). Several candidate genes have been identified that increase the risk of schizophrenia, including, but not limited to, COMT, NRG1, and DISC1 (Rapoport, Addington, & Frangou, 2005). The current consensus is that genes are neither specific nor necessary for schizophrenia, despite suggestion that they are the current greatest known risk factor for schizophrenia (Tiwari, Zai, Muller, & Kennedy, 2010). No single gene has been identified, or is expected to be identified, for schizophrenia. Instead, epigenetic

factors or gene-environment interactions may increase the vulnerability associated with any one gene alone.

Schizophrenia is a chronic mental illness, holding substantial stigma. The etiology of this disorder is not yet clearly defined and much research is dedicated to the search for a biological or endophenotype for this disorder.

Neurobiology of schizophrenia.

Historically, post-mortem investigation of schizophrenia suggested structural brain abnormalities were associated with the disorder. Both Bleuler and Kraeplin recognized that neuropathology was a primary feature of schizophrenia. The advent of *in vivo* imaging tools has enabled confirmation of many post-mortem findings, as well as new, more refined discoveries. To date, several neuroanatomical abnormalities have been associated with schizophrenia. The most robust is increased ventricle size, particularly in the lateral and third ventricles, sometimes associated with decreased brain volume (Shenton, Dickey, Frumin, & McCarley, 2001). Shenton and colleagues have written several reviews on structural magnetic resonance imaging (MRI) observations in schizophrenia. In 2001, their review suggested that the most robust structural abnormalities were reduced volume of temporal lobe structures, including the amygdala, hippocampus, and parahippocampal gyrus, and volume loss in the superior temporal gyrus, planum temporale, frontal lobes, corpus callosum, and cavum septi pellucidi. Abnormalities of structures making up the basal ganglia are less consistent, with most positive findings describing increased volumes that may be a result of neuroleptic treatment (Shenton et al., 2001). A recent update to the earlier review supported these results (Shenton, Whitford, & Kubicki, 2010). Longitudinal research in the last decade has begun to investigate abnormalities that may be progressive (i.e., vary through development and course of the schizophrenia), abnormalities that may be present before illness onset (and therefore potential markers for the disorder, and less confounded by the potential toxicity of psychosis or medication), and abnormalities that may be present in non-affected family members (i.e., genetic markers for the disorder). Current evidence points to schizophrenia as a neurodevelopmental disorder, rather than a

neurodegenerative one, with no evidence of neuronal loss or gliosis (Selemon & Goldman-Rakic, 1999). One may conclude from these studies that the neuropathology associated with schizophrenia occurs before acute symptom presentation and continues to progress through transition to psychosis, with less change after full disease onset (DeLisi, Szulc, Bertisch, Majcher, & Brown, 2006). This is supported by findings of accelerated gray matter (GM) reductions in high-risk individuals during a transition to psychosis period (Pantelis et al., 2005). It is likely that brain development in schizophrenia occurs over the lifetime and the location and nature of the abnormalities are a result of the brain's maturational state and the disease process (Pantelis et al., 2005). Much functional imaging research has focused on frontal lobe function in relation to cognitive and social dysfunction. Results suggest abnormal activation during executive function tasks in frontotemporal regions that may relate to disease severity (Purdon, Waldie, Woodward, Wilman, & Tibbo, 2011; Seidman et al., 1994; Wilmsmeier et al., 2010). Other studies have described an abnormal response to stimuli, suggesting a more global disconnectivity within the brain (Gur & Gur, 2010).

As neuroimaging technology continues to improve and enable more detailed and more precise examination of the human brain, research in the neuropathology of schizophrenia can only benefit. A better understanding of the pathology associated with schizophrenia allows for improved treatment opportunity and perhaps, via insight into etiology, may allow for prophylactic treatment as well.

Relevant neurochemistry.

There are several theories for the etiology and development of psychosis, and many complement each other, rather than being mutually exclusive. Coyle (1996) suggests that any theory to explain the pathophysiology of schizophrenia must account for the positive and negative symptoms, cognitive impairment, disease onset in early adulthood and deterioration of functioning.

Dopamine hypothesis. The dopamine (DA) hypothesis is based primarily on evidence that amphetamines (DA agonists) can induce the positive symptoms of schizophrenia and are able to exacerbate symptoms in schizophrenia (Griffith

at al., 1968; Young & Scoville, 1938). Because of this well-established relationship, most of the currently available and used antipsychotic medications are DA D2 receptor antagonists (Tsai & Coyle, 2002). This theory further posits that the positive symptoms of schizophrenia are associated with hyperdopaminergic activity in the mesolimbic pathways of the brain, while negative and cognitive symptoms are related to hypodopaminergic activity in the mesocortical pathways (Stahl, 2008). There have been several limitations to this theory, including the fact that some newer antipsychotic medications are far less potent DA D2 receptor blockers than previous medications while exerting more effective antipsychotic properties (Stahl, 2008). This theory also does not account for the latency from medication administration to symptom relief (often several weeks), nor does it account for some patients with schizophrenia who are "non-responders" to DA-based treatments (Bressan & Pilowsky, 2000; Konradi & Heckers, 2001). This evidence suggests that changes are occurring in other neurotransmitter systems that are necessary for the antipsychotic effect (Konradi & Heckers, 2001). Regarding Coyle's criteria for theories of schizophrenia, the DA theory does not address the cognitive deficits or deteriorating course in schizophrenia.

Glutamate hypothesis. More recently, glutamate (Glu) has been proposed as having a primary role in schizophrenia. In 1980, Kim and colleagues reported decreased levels of Glu in the cerebrospinal fluid (CSF) of schizophrenia patients (J. S. Kim, Kornhuber, Schmid-Burgk, & Holzmuller, 1980), sparking interest in this neurotransmitter. However, attempted replications of this finding were not successful (Perry, 1982). It was not until 1991 when Javitt and Zukin (1991) reported the effectiveness of phencyclidine (PCP), a non-competitive Glu N-methyl-D-aspartic acid (NMDA) receptor antagonist, as a model for schizophrenia that research into Glu's role in psychosis started to develop with intriguing implications for treatment. Currently, the Glu hypothesis of schizophrenia posits a hypofunctioning glutamatergic system, with most interest at the level of the NMDA ionotropic Glu receptor (Meador-Woodruff & Healy, 2000).

The application of PCP as a model of schizophrenia is based on research that PCP (along with other NMDA antagonists such as ketamine and MK-801) can induce a schizophrenia-like condition in healthy controls (HCs), and exacerbate symptoms in schizophrenia (Javitt & Zukin, 1991). The key advantage of the PCP model is that it is better able to mimic the spectrum of symptoms of schizophrenia, including the positive and negative symptoms and cognitive deficits, than previous amphetamine models. Another advantage to the PCP model is that a single administration of PCP is sufficient to produce animal models of these symptoms in rodents (i.e., stereotypy and behavioural sensitization), as opposed to necessary repeated systematic administration of amphetamine (Moghaddam, 2003; Moghaddam & Jackson, 2003). Further, in line with the time course of schizophrenia, children are resistant to the psychomimetic effects of PCP, which do not appear until early adulthood (Coyle, 2006a), suggesting that the mechanism by which PCP exerts its effects may be similar to the developmental pathology of schizophrenia. Finally, in humans PCP is able to induce neurophysiological abnormalities that are also present in schizophrenia (Coyle, Tsai, & Goff, 2003). The psychomimetic effects of PCP are not PCP-specific, but are rather related to blockade of the NMDA receptor, such that blocking the receptor by any means produces the same effects (Olney & Farber, 1995). Much research has been able to provide support for this theory. Animal studies manipulating the NMDA receptor also produce schizophrenia-like symptoms (Moghaddam, 2003). Neuregulin 1 is a candidate risk gene for schizophrenia that affects glutamatergic transmission (O'Tuathaigh et al., 2010); the hypomorphic neuregulin 1 mouse shows the behavioural phenotype of impaired prepulse inhibition and hyperlocomotion that may be associated with fewer NMDA receptors (Collier & Li, 2003). NMDA R1 knockout mice exhibit exaggerated spontaneous locomotion, stereotypy, and social and sexual deficits (Konradi & Heckers, 2003; Moghaddam & Jackson, 2003). In addition, genetic research in schizophrenia has identified a number of genes that express proteins that affect excitatory (i.e., glutamatergic) transmission (Moghaddam, 2004), while genes affecting serotonin and DA have not been as successfully linked to

schizophrenia (Collier & Li, 2003). Harrison (2003) suggests that all genes implicated in schizophrenia have direct or indirect effects on glutamatergic transmission.

Post-mortem studies have also supported a role for Glu in schizophrenia, with observations of increased binding of kainate and aspartate in the frontal cortex, decreased non-NMDA receptor messenger ribonucleic acid in the cortex, increased binding of MK-801 in the putamen and asymmetric loss of Glu terminals in the temporal lobe (Deakin & Simpson, 1997; Tsai & Coyle, 2002). Much of this post-mortem research has also been supported *in vivo.* Goff and Coyle (2001) report increased kainate receptors in the prefrontal cortex (PFC), decreased 2-amino-3-(5-methyl-3-oxo-1,2- oxazol-4-yl) propanoic acid (AMPA) and kainate receptor binding in the hippocampus, decreased AMPA receptors in the medial temporal lobe and increased binding to the glycine site of the NMDA receptor in the primary sensory cortex in schizophrenia. Abnormalities of Glu receptor density and subunit composition have also been documented in the thalamus, and abnormal NMDA receptor expression in the cortex and putamen has also been reported (Konradi & Heckers, 2003; Morris, Cochran, & Pratt, 2005; Ohrmann et al., 2005; Simpson, Slater, & Deakin, 1998). These studies all contribute to the evidence implicating a primary role for Glu in schizophrenia.

The Glu hypothesis of schizophrenia is better able to account for the positive and negative symptoms, cognitive disruptions and time course of schizophrenia than the DA theory alone. Olney and Farber (1995) also conclude that this hypothesis better accounts for structural brain abnormalities, response to neuroleptic treatment, and cognitive deterioration than the DA theory. The Glu theory of schizophrenia cannot, however, account for the uncommon, but still possible, childhood-onset schizophrenia because Glu's effects are proposed to emerge only after consolidation of brain maturation post-adolescence (Olney, Newcomer, & Farber, 1999). If Glu's involvement in schizophrenia is because of its role in early development that is expressed upon cerebral maturation, children under the age of maturation should not develop schizophrenia.

Neurodevelopmental hypothesis. A final theory, the neurodevelopmental hypothesis, is perhaps the strongest emerging theory for the etiology of schizophrenia because it incorporates the essential features of the DA and Glu hypotheses, while also accounting for disease latency and cognitive symptoms. The neurodevelopmental hypothesis proposes that aberrant events *in utero* or perinatally affect later life neurodevelopment, resulting in pathology associated with schizophrenia. There is some evidence that perinatal insults may have a more significant impact than prenatal disturbances (Kinney, Yurgelun-Todd, Waternaux, & Matthysse, 1994), and that only specific complications are related to later schizophrenia (broadly categorized into complications of pregnancy, abnormal fetal growth and complications of delivery; Cannon, Jones, & Murray, 2002). The human brain continues to develop and mature into early adulthood with synaptic and axonal pruning occurring into the second decade of life, and myelination continuing into the third decade of life (Keshavan & Hogarty, 1999). An early life insult may affect brain maturation at a much later time point. However, not all individuals who experience an early life insult develop schizophrenia; a trigger may be necessary. Cornblatt (2003) suggested that a vulnerability is necessary, but not sufficient, for the development of psychosis, and that full disease expression may require a trigger from an environmental or biological stressor. The interaction of these early life insults and a later life trigger may more directly affect the later life neurodevelopmental processes resulting in structural and functional neuropathologies that manifest as symptoms of psychosis. Support for the neurodevelopmental hypothesis includes research conducted with babies born under a range of obstetric complications, including complications of pregnancy (e.g., pre-eclampsia), complications of delivery (e.g., emergency Caesarian sections), and abnormal fetal growth who presented with a greater risk of developing psychosis (Rapoport et al., 2005). Further, some of the neurocognitive deficits associated with schizophrenia present early in the prodromal stages and remain fairly stable after conversion to psychosis and after pharmacotherapy (Cornblatt et al., 2003). Finally, physical abnormalities, such as eye folds and soft palate malformations, have been associated with increased rates

of schizophrenia (McGrath, Feron, Burne, Mackay-Sim, & Eyles, 2003; Rapoport et al., 2005; Rehn & Rees, 2005). As no single risk factor has been identified that is solely sufficient for psychosis, an amendment to the neurodevelopmental hypothesis is the so-called "two-hit" model. The "two-hit" model proposes that not only is an early risk to schizophrenia necessary that may be a genetic risk or an obstetric complication, but that a second "hit" later in life is also necessary to precipitate the onset of psychosis. The advantage of this model is that it explains why no single factor has proven sufficient for psychosis. It also has potential to explain the significant heterogeneity in clinical presentation in schizophrenia given that the "two hits" could be comprised of several combinations of risk factors, and with each distinct etiology, the clinical presentation may differ. The "two-hit" model is supported by Kinney and colleagues (1994) who suggest that there are at least two etiological factors for schizophrenia, and that one factor alone may manifest as a "milder" form of the disorder (e.g., schizotypal personality traits). Additionally, this "two-hit" model is an acceptable explanation for negative findings relating to birth complications when failing to assess other potential risk factors.

Genes are primary candidate factors that may interact with developmental processes to result in pathological mechanisms associated with schizophrenia. Individuals who have an endogenous (i.e., genetic) predisposition to schizophrenia and experience an *in utero* or perinatal event may be more likely to develop schizophrenia. Alternatively, experience or environmental (i.e., exogenous) triggers may also be sufficient for the onset of symptoms, given a genetic or early life insult vulnerability. Experiences during developmental life can contribute adversely to the risk for developing schizophrenia by affecting pruning of synapses or increasing functional efficiency (Keshavan & Hogarty, 1999). Potential exogenous triggers include viral exposure, exposure to pollutants associated with urban living, chronic stress, inadequate rearing environment, migration, or drug misuse (particularly misuse of cannabis or stimulants; Rutten & Mill, 2009; Van Os, 2004). It may be that early life events in conjunction with a genetic predisposition or exogenous triggers may work in concert with one

another to precipitate psychotic symptoms. If so, this could explain why the list of potential risk factors for psychosis continues to grow, but no single risk factor has proven sufficient for the disorder. Cannon and colleagues (2002) suggest that exposure to a risk factor that may have a small effect on the general population may have a large effect in someone with a pre-existing vulnerability to psychosis.

The neurodevelopmental hypothesis and the Glu hypothesis are not mutually exclusive, nor do they rule out involvement of DA. Neurotransmission is complex, and changes in any one neurotransmitter system affect transmission of another. As a relevant example, Glu may be able to modulate DA in schizophrenia (Carlsson, Carlsson, & Nilsson, 2004). Functional connections between frontal lobe regions and subcortical structures are modulated by Glu transmission; given that Glu and DA have reciprocal action, disruption in the functional glutamatergic connection between frontal and subcortical regions would likely affect dopaminergic function as well, resulting in the dissociation of hypo- and hyper-dopaminergic transmission cortically and subcortically (Meador-Woodruff & Healy, 2000). Glu and DA have substantial interaction, such athat excitation or blockade of DA receptors directly affects glutamatergic NMDA transmission (Laruelle, Kegeles, & Abi-Dargham, 2003). This obviously has direct implications for the efficacy of antipsychotic medications.

Another way that the neurodevelopmental hypothesis and Glu hypothesis may be complementary is that aberrant Glu transmission during a critical developmental time period may disrupt the neuroplasticity of the brain, affecting the ability of neurons to adapt to changes in the environment. Glu plays a primary role in synaptogenesis, such that abnormal glutamatergic transmission during a period of brain maturation may result in expression of symptoms at a time when a critical number of synaptic connections are lost, i.e., during early adulthood, the same time period as the onset of most cases of schizophrenia (Konradi & Heckers, 2003).

Schizophrenia can be a debilitating chronic disorder. The etiology of schizophrenia is not yet well defined and so the search for an endophenotype is on-going. Several theories exist and it may be that each theory contains just one

portion of the answer. Research into the development and etiology of schizophrenia is necessary so that treatment-based research can be optimized. The neurodevelopmental theory provides an etiology of schizophrenia that incorporates the DA and Glu hypotheses, while also offering an explanation for high heterogeneity in risk factors between individuals with schizophrenia. The "two hit" theory further offers explanation for why some individuals with risk factors develop schizophrenia and others do not. Given that second hits may involve substance dependence, inclusion of stimulant-dependent individuals in etiological investigation of schizophrenia offers unique insight into examining the neurodevelopmental hypothesis.

Substance Abuse and Dependence

Substance abuse and dependence are complex neurological and psychosocial disorders, defined by a compulsive drive to seek and administer drugs of abuse despite serious adverse consequences. The key point in this definition is that dependent users will seek and administer drugs despite conscious awareness of the unpleasant and negative effects of their behaviour. Substance dependence is a disorder that quickly progresses from impulsivity to compulsivity (Jentsch & Taylor, 1999; Koob et al., 2004). This section outlines the impact of substance dependence, before focusing on MA, and describing the neuropathology associated with substance use.

Drug use, like any other chronic illness, has wide-reaching societal impacts. The Canadian Centre on Substance Abuse estimated the costs of substance abuse in Canada in 2002 to be $39.8 billion, including productivity loss, health care costs, enforcement cost, and other direct costs (Rehm et al., 2006). Illicit substance use is associated with high morbidity and mortality (Dell & Garabedian, 2003). In particular, injection of illicit drugs is associated with increased health risks and contributes significantly to the spread of disease among users (United Nations Office on Drugs and Crime, 2009). Alcohol and tobacco are the most commonly used psychoactive substances in Canada, while cannabis is the most frequently abused illicit drug (Dell & Garabedian, 2003; Fischer, Rehm,

& Hall, 2009), followed by hallucinogens, cocaine, and amphetamines (Adlaf, Begin, & Sawka, 2005).

Population trends in stimulant misuse have shifted over time. For example, while cocaine is a commonly abused stimulant, reported use has been declining in North America since peaking in 2005 (United Nations Office on Drugs and Crime, 2009). Conversely, in the last decade illicit amphetamine use rates have increased significantly, particularly in Canada, with several reported indications that the problem with amphetamine-type stimulants (ATS; which include amphetamine, MA, methcathinone, and ecstasy (i.e., 3,4-methylenedioxymethamphetamine (MDMA))) is worsening, including increased seizures, laboratories in a growing number of countries, and increased production (United Nations Office on Drugs and Crime, 2009). The United Nations Office of Drug and Crime (UNODC) estimated that between 16 and 51 million people aged 15 to 64 used ATS (not including ecstasy) at least once in 2007 (United Nations Office on Drugs and Crime, 2009). The increased use of MA has caused concern about increased utilization of treatment centres, emergency rooms and mental health clinics.

Methamphetamine.

MA is a potent psychostimulant. The most common illicit form of MA, crystal MA, refers to the d-isomer. It is commonly referred to as a "bathtub drug" because it can be manufactured in homes (often literally in bath**t**ubs) using a range of accessible products, including, not but limited to, over-the-counter cold medication (ephedrine), iodine, battery acid (lithium), and matches or road flares (red phosphorus). The popularity and use of MA is not as dependent on drug trafficking and importing regulations as other drugs because of the ease with which MA can be manufactured. MA can be injected, snorted, smoked or swallowed. The most common form of administration is smoking (Winslow, Voorhees, & Pehl, 2007), which can lead to dental decay and oral skin lesions, "meth mouth" (Klasser & Epstein, 2005).

Amphetamines were first synthesized in 1887 in Germany. They were used medically in the early 1900's for nasal congestion and to increase attention.

Other clinical uses historically include depression and obesity (for a historical review see Yudko, Hall, & McPherson, 2003). Clinical use of amphetamines has waned and has been replaced by other stimulant medications because of the potency and addictive potential of amphetamines (Kelsey, Newport, & Nemeroff, 2006). Methylated amphetamine (MA) was first synthesized in 1919 in Japan and first used extensively by Japanese soldiers in WWII. Problems associated with MA use were recognized post-war when MA stores were made available to the public. In the United States, MA was first designated a controlled substance in the 1960's. In Canada, in 1995, the Royal Canadian Mounted Police established the National Chemical Precursor Diversion Program to encourage voluntary reporting of suspicious activity related to the manufacturing of MA by the chemical industry. Soon after, Canada passed the Controlled Drugs and Substances Act of 1997 that identified nine precursor chemicals. The Controlled Drug and Substances Act of 2003 established regulated control of chemicals by Health Canada supported by enforcement by the Royal Canadian Mounted Police; it prohibits the import, export, and possession for export of precursors sold in quantities above threshold levels except by licensed dealers (Hunt, Kuck, & Truitt, 2006). In Canada, the Controlled Drugs and Substances Act (1996), classified MA as a Schedule I drug, along with cocaine and heroin. Several amendments have been made to this act since 1996 with further control over manufacturing and possession of MA and MDMA, allowing for increased penalties, fines, and jail time.

In their most recent report the UNODC declared amphetamines the second most commonly abused illicit drug globally, behind cannabis (United Nations Office on Drugs and Crime, 2010). In 2008 approximately 1.5% of Canadians abused amphetamines, an increase from 2004 (United Nations Office on Drugs and Crime, 2010). According to the 2004 Canadian Addiction Survey, 6.1% of Albertans aged 15 or older reported having used amphetamines at some point in their lifetime (Adlaf et al., 2005). In the United States, MA-related emergency room visits rose by 88% from 1995 to 2002 (Meredith et al, 2005), while MA use increased 250% from 1996 to 2002 (Howell & Kimmel, 2008). The UNODC has

also reported an increase in the number of police contacts related to MA, the number of MA laboratories discovered and the number of presentations to the emergency room for MA-related concerns (United Nations Office on Drugs and Crime, 2009). In 2008, the country with the most dismantled MA laboratories was Canada (United Nations Office on Drugs and Crime, 2010). While enforcement has been gaining ground, Canadian-based organized crime groups' participation in MA manufacturing and distribution has grown significantly since 2003 (United Nations Office on Drugs and Crime, 2009). North America is the leader in the Western Hemisphere for ATS use. However, the UNODC acknowledges that estimated ATS use is difficult to measure because of the speed with which ATS can make it to market (because they are not imported), and the poor accuracy of assessing exactly how much of the drug users consume (United Nations Office on Drugs and Crime, 2009). These statistics highlight the remarkable growth of MA manufacturing and use in the last decade. This has put substantial stress on regional enforcement teams, and treatment centres.

A typical MA user is an 18 to 25 year old male, poly-substance user (Oetting et al., 2000; Winslow et al., 2007). High prevalence rates are also reported in transient street youth, aboriginal communities and gay communities (Barr et al., 2006). Because acute effects of MA include increased attention, use of MA has also surfaced in workplace settings and school settings. Reports also suggest use of MA as a method for extreme weight loss in youth (Gonzales, Mooney, & Rawson, 2010). MA is cheaper than cocaine and provides a longer high (Lineberry & Bostwick, 2006), which may partially explain its popularity with street people who use it to avoid sleeping on the streets and avoid feeling hunger.

MA is popular because of an intense and potent high and cheap cost. The effects of MA, as a stimulant, are much like cocaine, but are more immediate, last longer, and lead to dependence in a significantly quicker path (Gonzalez Castro, Barrington, Walton, & Rawson, 2000). Reasons for MA use include increased alertness, high energy, aphrodisiac effects, sociability, euphoria, increased sex drive, decreased need for sleep, and loss of inhibitions (Degenhardt & Topp,

2003; Winslow et al., 2007). These "positive" effects of MA are long-lasting, and can endure for 8 to 12 hours (Meredith, Jaffe, Ang-Lee, & Saxon, 2005). Short-term (i.e., not chronic) MA use can result in "tweaking", a term that refers to mania-like symptoms, including hyperactivity, obsessiveness, and extreme focus over brief periods of time. Negative effects over the short-term include paranoia, increased risk of a sexually transmitted disease, hepatitis C, and HIV, increased risk of being a burn victim, anxiety, death, seizures, aggression, insomnia, hallucinations, restlessness, increased heart rate, irritability, sweating, tremors, increased blood pressure, stroke, and cardiac failure, as well as cognitive and motor impairment (Maxwell, 2005; Meredith et al., 2005; Molitor et al., 1999; Simon et al., 2000; Spann et al., 2006; Winslow et al., 2007). Chronic MA use can lead to skin lesions, dental decay, cardiovascular disease, extreme weight loss, abscesses, memory loss, motor slowing, and comorbid psychiatric problems (Maxwell, 2005; Sommers, Baskin, & Baskin-Sommers, 2006; Winslow et al., 2007). Additionally, one third of stimulant users commit violent acts while under the influence of MA (Sommers et al., 2006). Stimulant users are also more likely to lose jobs, family, friends, homes, and income, and are at greater risk of psychological disorders, including suicide (Sommers et al., 2006; Zweben et al., 2004). A recent systematic review has identified several risk factors for MA use in youth, including a history of opiate use, family history of drug use, risky sexual behaviour and a psychiatric disorder (Russell et al., 2008). Withdrawal from chronic MA use can lead to irritability, musculoskeletal pain, depression, increased appetite, extreme fatigue, impaired social functioning, and cognitive impairment (Newton, Kalechstein, Duran, Vansluis, & Ling, 2004). MA use is also associated with significant health risks to the general population secondary to the discharge of the post-manufacturing toxins into the water supply and the risk of proximity to toxic and volatile residentially-based MA manufacturing laboratories (Meredith et al., 2005).

As a stimulant, MA differs from cocaine in several ways (for a review see Gonzalez Castro et al., 2000). MA is a chemical base, with acute effects lasting up to 24 hours. It is metabolized in the body in 24 to 48 hours. Compared to cocaine,

MA has no current medical use, is cheaper to purchase, and creates a more potent high. Cocaine is plant-based, with a short-lived high lasting for 30 minutes to 1 hour, and it is metabolized in the body in 1 hour. It cannot be made locally (i.e., in Canada), must be imported, has been used clinically as an anesthetic, and is more expensive than MA. MA has a higher rate of addiction and a faster route to addiction than cocaine (defined as a shorter latency period from first use to regular use, and a shorter period from first use to treatment seeking). Individuals who experiment with MA are more likely to become regular users and to do so in a shorter time frame than those who experiment with cocaine (Gonzalez Castro et al., 2000). Physiologically, MA is able to increase DA levels in the nucleus accumbens (NAc) up to 400% over baseline within 60 minutes, while cocaine increases DA levels in the NAc 75% over baseline in 30 minutes, with declining levels already occurring by 60 minutes (Y. Zhang, Loonam, Noailles, & Angulo, 2001). Currently there are no pharmacological treatments for stimulant dependence.

Neurobiology of substance dependence.

A description of the neurobiological processes of substance use follows, including implicated neural pathways and regions, neurochemical effects and the process of transition from acute to chronic use. Drugs are unnatural (in that they are not evolutionarily relevant like food and sex) rewards that artificially stimulate the brain. A reward serves as a positive reinforcer for behaviour by increasing the frequency in observable behaviour that results in that reward (Schultz, 2006). Of course, there are many types of drugs of abuse that act via different mechanisms in the brain, accounting for the varying effects and experiences from different drugs. Some substances (e.g., amphetamine) induce behavioural sensitization, where chronic use of the drug results in an increased sensitivity to that drug (Lapish, Seamans, & Chandler, 2006), whereas other drugs (e.g., alcohol) induce tolerance, where more of the substance is required to obtain the previous effects (Radlow, 1994). Despite these differences, the pathway to continued use and the associated neuropathology does not differ dramatically between drugs of abuse (Lingford-Hughes, 2005). The reward system in the

human brain is comprised of the mesocorticolimbic system. One subsection of this system, the mesolimbic tract, originates as dopaminergic cell bodies in the ventral tegmental area (VTA) and consists of projections from the VTA to the NAc, amygdala, and hippocampus (Adinoff, 2004). This system is responsible for the reinforcing effects of drugs, conditioned responses involved in craving, and determining incentive salience (Adinoff, 2004; Goldstein & Volkow, 2002; Jentsch & Taylor, 1999). During acute drug administration, elevated levels of DA in this tract activate memory networks that begin to establish learned associations with environmental stimuli and state representations that can prime the reward system to predict and anticipate rewards, thereby establishing reinforcing effects and conditioned responses (Kalivas & Volkow, 2005). Lesions of mesolimbic DA neurons or administration of DA receptor antagonists in the NAc attenuate the reinforcing effects of drugs (Jentsch & Taylor, 1999).

The other main component of the reward pathway, the mesocortical system, consists of projections from the VTA to cortical regions, specifically the PFC, orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). This tract plays a role in the conscious experience of intoxication, drug salience, and the compulsive drive to administer drugs. Functional magnetic resonance imaging (fMRI) studies describe frontal activation that correlates with perceived level of intoxication (Goldstein & Volkow, 2002) and cognitive impairment associated with frontal regions that develops after chronic drug use (Volkow, Fowler, & Wang, 2003).

The neuropathology that accompanies substance dependence is defined by neuroplastic changes that occur with increased salience attribution to drug-predicting stimuli (Kalivas & Volkow, 2005). Because the mesolimbic and mesocortical pathways run in parallel and have significant overlap, the behavioural outputs in substance dependence are determined jointly by activations in both circuits (Goldstein & Volkow, 2002). The NAc is a centre for innervations for the reward pathway (Jentsch & Taylor, 1999; Kalivas & Volkow, 2005). Neuroplastic changes with chronic administration at the NAc begin to affect the behavioural outputs by re-shaping reward systems to allow for the prediction of

reward. During withdrawal DA transmission within the NAc is attenuated (Jentsch & Taylor, 1999); drug craving is then experienced so that the user can exogenously elevate DA levels to normal states. It is this progression in which a user uses drugs to feel "normal". The amygdala also plays a primary role in the development of substance dependence. Studies have documented its involvement in making associations between neutral environmental stimuli and motivationally relevant events (Kalivas & Volkow, 2005). The increased salience attributed to these previously neutral stimuli poses a major problem to users in abstinence because these associations are long-lasting (Adinoff, 2004; Kalivas & Volkow, 2005).

Substance dependence is not just a disease of altered reward and pleasure pathways. Motivation and drive, memory and learning, and decision-making circuits all contribute to the behaviours and patterns evident in substance dependence (Volkow et al., 2003). Kalivas and Volkow (2005) point to a "final common pathway" for substance dependence involving primarily the PFC, NAc, and ventral pallidum. This final pathway, they suggest, is activated by regions from these other circuits including the hippocampus, thalamus, and amygdala. The implication of these other regions in substance dependence promotes the idea that substance dependence is not purely a disease of abnormal reward circuitry, but a complex disorder affecting several neurological processes.

Additionally, substance dependence can induce structural change in the brain. Substance dependence can lead to loss of GM in the PFC (Berman, O'Neill, Fears, Bartzokis, & London, 2008), ACC, limbic and paralimbic cortices (Baicy & London, 2007; Thompson et al., 2004), and hippocampus (Thompson et al., 2004), enlarged striatal volume (Berman et al., 2008; Chang, Alicata, Ernst, & Volkow, 2007), and altered cerebral vasculature including reduced blood flow, perfusion or metabolism (Lingford-Hughes et al., 2003). Many of these changes persist into abstinence and are part of the pathology that makes substance dependence a difficult disorder to treat.

The neurochemical effects of substance dependence allow it to be classified as an enduring form of neuroplasticity. As Glu is the primary

neurotransmitter involved in neuroplastic changes, it is likely that Glu also has a substantive role in the development of substance dependence. Several studies have demonstrated that both acute and chronic stimulant administration can increase Glu levels in the reward pathways that endure for weeks, particularly in the NAc and VTA (Cornish & Kalivas, 2000; Harris & Aston-Jones, 2003; Pierce, Bell, Duffy, & Kalivas, 1996; M. S. Reid & Berger, 1996; X. F. Zhang, Hu, White, & Wolf, 1997). This increase in Glu continues to rise beyond the duration of DA elevations and continues to rise even when DA returns to baseline; pre-treatment with Glu receptor agonists exacerbates this effect (Burrows & Meshul, 1997). Cessation of use results in reduced Glu levels in the NAc (D. A. Baker et al., 2003; Hotsenpiller, Giorgetti, & Wolf, 2001; Kalivas et al., 2003; Pierce et al., 1996). Animal models of behavioural sensitization, conditioned place preference, and drug reinstatement paradigms have also confirmed a role for Glu in substance dependence with specific roles in the NAc, VTA, amygdala and hippocampus (Backstrom & Hyytia, 2005; Cornish & Kalivas, 2000; Harris & Aston-Jones, 2003; Karler, Calder, Chaudhry, & Turkanis, 1989; Karler, Thai, & Calder, 2003; McFarland, Davidge, Lapish, & Kalivas, 2004; McFarland, Lapish, & Kalivas, 2003; McGeehan & Olive, 2003; Ohmori, Abekawa, Muraki, & Koyama, 1994; Park et al., 2002; Sutton et al., 2003; White & Kalivas, 1998; Xue, Ng, Li, & Wolf, 1996). Relapse to use may also be mediated by Glu transmission; administration of Glu receptor antagonists (e.g. MK-801) in rats on a previous schedule of cocaine self-administration prevented a drug-prime-induced relapse (Schenk et al., 1993).

The vulnerability of any one person to develop a substance dependence is ultimately a complex interaction between neurological predisposition and environmental factors, including drug availability (Volkow & Li, 2004). Imaging studies have revealed a number of factors that may contribute to the risk, including a pre-existing decreased sensitivity of reward circuits to natural rewards, disrupted control circuits, increased sensitivity to conditioned drug stimuli and increased responses of motivation and drive (Volkow, Fowler, & Wang, 2004). Once substance dependence is established, the cognitive effects of

chronic drug use contribute significantly to the difficulty in achieving abstinence. Regions associated with decision-making and inhibitory control, including the PFC and OFC, may be "hi-jacked" in chronic drug use (Volkow et al., 2003). Normal control is disrupted so that the user has less inhibitory control to abstain from drugs, despite the conscious knowledge of harmful consequences or the desire to stop. Drug dependence is a very difficult disease to treat given the associated cognitive impairment and neuropathology. The dangers of potent stimulants like MA and their increasing availability call for a need to better understand the pathology associated with substance dependence. Finally, the relationship of MA to mental health disorders is alarming (A. Baker & Dawe, 2005). MA use comorbid with a mental illness can have substantial deleterious effects. Therefore, understanding the pathology of comorbid disorders may offer insight to the etiology of how MA might trigger psychosis onset.

Comorbidity of Substance Dependence and Mental Illness

From the preceding evidence, it is clear that both substance dependence and schizophrenia have significant neurological impact, and further, that many of the neural substrates associated with substance dependence and schizophrenia overlap. It is therefore no surprise that comorbidity rates between mental illness and substance dependence are extremely high. The most common comorbidly used substance in those with a mental illness is tobacco. Up to 85% of individuals with a mental illness use tobacco and further, while tobacco use has dropped in the general population in recent years, there has been no change in the psychiatric population (Ziedonis, Williams, & Smelson, 2003). This suggests that the reasons for tobacco use in mental illness may differ from the reasons used in the normal population. In Canada, the 12-month prevalence of co-occurring disorders was 1.7%, and having one of substance use problems or a mental illness increased the risk of meeting criteria for the other by two to three times (Rush et al., 2008). One of the most researched illicit substances is cannabis, due to its more common prevalence and relationship with certain mental disorders. In particular, risk of psychosis in cannabis users increased by 40% in even mild users, while in heavy users the risk was 50 to 200% higher; it was suggested, therefore, that 14% of

young people who develop psychosis would not have if they had not used cannabis (M. Cohen, Solowij, & Carr, 2008). The mechanism of the relationship between cannabis and psychosis is unknown, but may involve premorbid genetic risk or the effects of cannabis on DA transmission (Linszen & van Amelsvoort, 2007; Luzi, Morrison, Powell, di Forti, & Murray, 2008).

These data illustrate the much higher rates of substance dependence in a psychiatric population than in the general population. Conversely, comorbid psychiatric disorders and symptoms are also very common in a substance-using population. In a study assessing psychiatric symptoms and previous psychiatric treatment in those seeking help for drug dependence, 20% had recently received psychiatric treatment and comorbid psychiatric symptom severity was greater than in the general population; the most severe psychiatric symptoms were in stimulant users (Marsden, Gossop, Stewart, Rolfe, & Farrell, 2000). Comorbidity specifically with stimulants will be expanded upon in a later subsection following a description of the effects of and theories for comorbid substance dependence and mental illness.

The effects of substance use concurrent with a mental illness are substantial. Individuals with comorbid substance use and mental illness are more likely to attempt suicide (Cardoso et al., 2008; Erfan, Hashim, Shaheen, & Sabry, 2010; Marshall & Werb, 2010), have lower medication compliance (Rehman & Farooq, 2007), have higher rates of relapse (Rehman & Farooq, 2007), present with worse functioning (Cardoso et al., 2008; Drewe, Drewe, & Riecher-Rossler, 2004; Erfan et al., 2010), have longer hospitalizations (Erfan et al., 2010; Schmidt, Hesse, & Lykke, 2011), be poly-substance users (Erfan et al., 2010), and report substance use as self-medication (Bizzarri et al., 2007). Aside from this significant impact on functioning and outcome, comorbid substance use can also affect the symptom presentation of a mental illness. As examples, alcohol abuse and dependence are associated with more depressive features and higher rates of psychosis in bipolar disorder (Cardoso et al., 2008), and cannabis use in psychosis is associated with higher positive symptom scores and fewer negative symptoms

(Dubertret, Bidard, Ades, & Gorwood, 2006; Machielsen, van der Sluis, & de Haan, 2010).

Comorbid substance use in a mental illness complicates the presentation of both disorders and makes treatment challenging. Several approaches to treatment of these comorbid disorders have been explored, including sequential treatment, parallel treatment and integrated treatment (for review see Mueser, Noordsy, Drake, & Fox, 2003). Pharmacotherapy for dual diagnosis is also a desired treatment strategy but no single medication to date has proven effective. In fact, in treatment of co-occurring substance use and schizophrenia it is possible that treatment with antipsychotics may actually worsen the substance use (Green, 2007). Investigations into possible effective pharmacotherapies are ongoing, with some evidence that Glu-targeted drugs may have a positive effect for substance use in psychosis (Coyle, 2006b).

Biological and pathological mechanisms underlying high rates of comorbid substance dependence in mental illness are not precisely known. Several studies observed that substance use during adolescence is particularly associated with mental illness, likely because adolescence is a period of continued brain growth and maturation (Bossong & Niesink, 2010) so that drug use during this time period has substantial and critical impacts on the structural and physiological development of the brain. There are at least two possibilities as to the relevance of the adolescent period of brain maturation in comorbid substance dependence and mental illness: one is that environmental or exogenous factors during this critical period act as a "second hit", in concordance with the two-hit model of schizophrenia described earlier, thereby disrupting a vulnerable brain state to trigger pathological change associated with mental illness; alternatively, adolescence may be comparable to any postnatal period for susceptibility to either exogenous factors or endogenous developmental factors to impact the developing brain in a deleterious way. Either way, this period of development is a common time for drug experimentation and is repeatedly associated with higher rates of mental illness (Squeglia, Jacobus, & Tapert, 2009). It is unknown if the age of

onset of substance dependence has any impact on later emergence of symptoms of mental illness.

To explain the high rates of comorbidity specifically in schizophrenia, Chambers, Krystal and Self (2001) described a primary addiction hypothesis, proposing that both schizophrenia and substance dependence are primary symptoms of the same disorder caused by common neuropathological mechanisms. Support for this model comes from evidence that the neurodevelopmental abnormalities present in schizophrenia overlay precisely on the neural substrates of substance dependence (i.e., the mesolimbic system). The mesolimbic system, as described above, is a primary mediator of substance dependence owing to excessive DA release in the NAc; this system is also the primary site of neuroleptic action in schizophrenia (Chambers et al., 2001). Chambers and colleagues (2001) report that in both schizophrenia and substance dependence abnormal hippocampal inputs lead to an increased sensitivity to DA and therefore an increased saliency of novel stimuli via both glutamatergic and dopaminergic signaling. Not only are the neural substrates of schizophrenia and substance use disorders common, but the mechanism may be one of glutamatergic transmission (Coyle, 2006a). There is growing evidence to support a common pathway and common pathological disturbances in both mental illness and substance use; however the ultimate goal of determining etiological mechanisms of these disturbances is not yet fully understood.

Theories of comorbidity between substance dependence and mental illness

There are several theories for the high rates of comorbid substance use and mental illness. The temporal relationship between drugs and mental illness is not always clear, and varies in individuals, making it difficult for any one theory to encompass the complete relationship.

Figure 1 shows several theoretical relationships for substance dependence and mental illness (adapted from Mueser et al., 2003).

Figure 1
Theories of Comorbidity

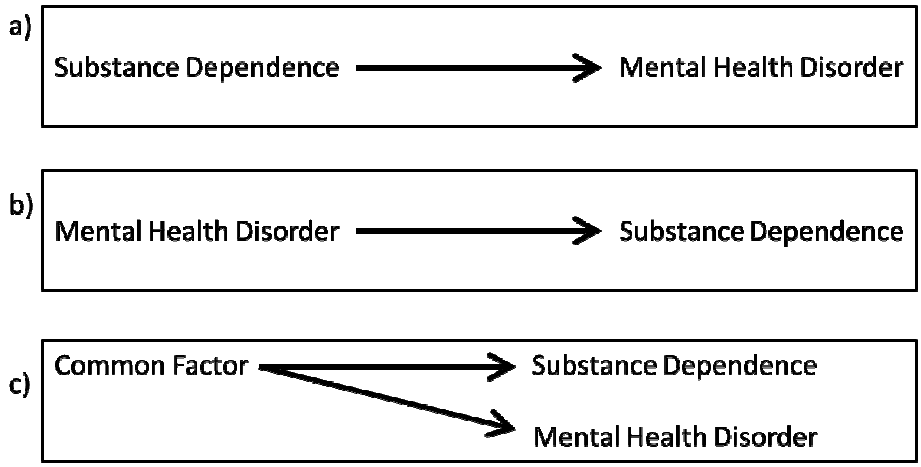


Figure 1 (a) Substance dependence causes a mental illness (b) Onset of a mental illness induces substance dependence as a form of self-medication (c) A common factor (e.g., genetics, environment, pathology, etc.) is common to both substance dependence and the mental illness

The first of these theories is that substances cause mental illness. For example, one who uses stimulants excessively may induce mania or psychosis that would not have emerged without the drug use. One of the largest debates surrounding this theory is the potential ability for cannabis use to cause psychosis (Hall & Degenhardt, 2000). Problems with this theory include the necessary predating of drug use to mental illness, which is not always the case. Additionally, determining whether a mental illness would have emerged without the drug use is difficult. Several studies have examined the potential for a causative relationship between substance dependence and mental illness, but little supporting evidence has been described. If substances of abuse could independently cause a mental illness, increased rates of use of particular drugs would initiate a proportional increase in mental illness, but this has not been observed (Bossong & Niesink, 2010). While some studies do support a causal role of cannabis in the onset of schizophrenia, this is still open for debate, and for other drugs of abuse there is far less evidence for a causal role in comorbidity (Gregg, Barrowclough, & Haddock, 2007).

The second of these theories proposes that a mental illness precedes a substance use disorder. Several explanations are possible, however the most commonly described is often referred to as the self-medication theory (Khantzian, 1985) where the symptoms of a mental illness are distressing so the individual turns to non-prescribed substances to ameliorate the symptoms in a self-regulated way. The first to publish on this theory, Khantzian, suggestsed that the self-medication theory is best able to account for the "emotional and psychological dimensions of the addictions that have been dismissed, neglected or inadequately considered in other investigations" (Khantzian, 1997, p. 232). However, several points argue against this theory: firstly, the temporal pattern necessary for this theory (the emergence of distressing symptoms followed by initiation of drug use) is rarely as clear; secondly, there is no repeatedly demonstrated association between choice of drug and symptom experience (Mueser, Drake, & Wallach, 1998). For this theory to hold true, certain drugs of choice (e.g., stimulants) would be better suited than others (e.g., opiates) to ameliorate specific symptoms (e.g., depression). Thirdly, patients with more severe symptoms of a mental illness would be more likely to abuse substances than those with milder symptoms, but this is not a common observation (Gregg et al., 2007). Finally, this theory does not explain why successful treatment of a mental illness often does not result in cessation of drug use. However, there is some support for this theory; in a longitudinal study individuals who transitioned from normal alcohol use to an alcohol use disorder had higher rates of premorbid mental health disorders (Behrendt et al., 2011). The self-medication theory may be able to account for a portion of the comorbidity between substance use and mental illness but cannot explain the high rates of poly-substance use and a comorbid relationship in which the drug use predates the illness.

Finally, the last theory suggests that a common vulnerability leads to both drug use and mental illness. This would include both biological and exogenous factors, as well as the interactions between the two. Because both drug use and mental illness are neuropathological disorders, it may be that an underlying pathological vulnerability may render an individual more susceptible to both

substance dependence and mental health problems. Supporting this, the neural substrates and neurotransmitters involved in both disorders have considerable overlap, and drug use often exacerbates symptoms of mental disorders, particularly schizophrenia (Chambers et al., 2001). It is also possible that a genetic vulnerability may be related to both mental illness and substance dependence. This has been supported by several twin studies (Degenhardt, Hall, & Lynskey, 2004) but to date no single gene has been implicated in both disorders (Gregg et al., 2007). A variation of this theory is the neural diathesis-stress model that suggests a neurobiological vulnerability interacts with environmental stressors (e.g., substance use) to precipitate a mental disorder. Support for this theory comes from substance misuse being associated with earlier onset schizophrenia (Tucker, 2009) and the recent finding that cannabis use by adolescents who have the Val/Val polymorphism of the COMT gene are at a higher risk of developing psychosis in young adulthood (Estrada et al., 2011). Current literature most often supports the common vulnerability and interaction model because of the problems with the self-medication theory, and a lack of support for a direct causal relationship between substances and mental illness.

Temporal patterns are currently the best way to delineate which theory may best be able to explain a comorbid substance use and mental illness. However temporal patterns are often more difficult to determine than it would seem; both substance dependence and some mental illnesses develop gradually overtime, often originating in adolescence (Gregg et al., 2007). For the case of a substance-induced disorder, the patient would have had no psychiatric symptoms prior to drug use, or in the very least would not meet diagnostic criteria for a mental illness; the symptoms would have initiated after persistent and chronic use of a substance and would attenuate in abstinence from the substance. Persistent psychiatric symptoms present after a substantial period of absence from substance use are one common way of ruling out a substance-induced disorder, and would indicate a different etiological pathway.

Comorbidity of substance use, abuse, and dependence with mental illness is a significant problem, with impacts on the etiology, prevention, and treatment

of these disorders. Some argue for better definitions and measurement tools for more consistency in investigating psychiatric comorbidity (Sinclair, Nausheen, Garner, & Baldwin, 2010). It is likely that no single theory will account for all cases of comorbid substance use and mental illness, and that subgroups may exist that would be representative of each of the described theories. Gregg and colleagues (2007) conclude that "the challenge now is to identify which models apply to which people and if we are able to develop more effective treatments" (p. 505).

Stimulant dependence and schizophrenia.

Rates of comorbid substance use in schizophrenia are particularly alarming, with up to 80% of individuals with schizophrenia also presenting with a comorbid substance dependence disorder (Westermeyer, 2006), and patients with schizophrenia are up to 5.3 times more likely to have substance use disorders than persons without mental illness (Cantor-Graae, Nordstrom, & McNeil, 2001). While there is an established relationship between many substances of abuse and psychosis (Thirthalli & Benegal, 2006), up to 31% of individuals with schizophrenia have a history of stimulant abuse (Mueser, Yarnold, & Bellack, 1992). The relationship between stimulants and psychosis has been well-established. As described earlier, amphetamine has been used as an animal model of psychosis, contributing to the DA theory of schizophrenia. Some have argued against this model for psychosis because of the inability of amphetamines to induce the negative symptoms of psychosis (Javitt & Zukin, 1991). Others have suggested that amphetamine is an appropriate model for psychosis but that the schedule of amphetamine administration is critical to representativeness of the model; induced stereotypy in rodents after a single large dose of amphetamine is a different, less representative model of psychosis than chronic low dose amphetamine-induced behavioural sensitization (Machiyama, 1992).

With the emergence of crystal MA as a popular, cheap drug of abuse, this potent stimulant has raised concern about the possibility of increased rates of psychosis. The search is ongoing to determine if the symptoms of psychosis that emerge during and persist after MA use are etiologically, phenotypically,

cognitively, and biologically similar to *de novo* schizophrenia, or whether this MA-induced psychotic disorder is a different disorder, warranting different treatment and with different complications. In a sample of 189 MA-dependent users, 28% were described as having a primary psychotic disorder, 24% of which were labeled as substance-induced (Salo et al., 2011). While this study made an effort to differentiate substance-induced symptoms from non-substance-induced symptoms, often this is a difficult task, and many reports fail to make this distinction. The most commonly reported comorbid symptoms in amphetamine users are depression, anxiety, paranoia, hallucinations, and violent behavior (Hall, Hando, Darke, & Ross, 1996). MA can increase the probability of two more psychotic symptoms by 9 to 21% (McKetin, Hickey, Devlin, & Lawrence, 2010).

Several researchers have attempted to determine if there are measureable differences between MA users who develop psychosis and those who do not. MA users with psychosis were more likely to attempt suicide (Akiyama, Saito, & Shimoda, 2011), were younger at first MA use, had more premorbid schizoid and/or schizotypal personality traits, and had higher rates of major depressive disorder, comorbid alcohol dependence, and antisocial personality disorder (Chen et al., 2003). Genetic risk may also be involved as MA users who had a spontaneous relapse to psychosis had higher rates of the met allele of the COMT gene as compared to HCs (Suzuki et al., 2006), and only MA users who developed psychosis had abnormal alleles of the hDAT1 gene (Ujike et al., 2003). Genetic risk is also supported by evidence that a family history of schizophrenia increases risk of developing psychosis in MA users (Chen et al., 2005). It has been repeatedly reported that MA users with psychosis have elevated levels of norepinephrine as compared to HCs (Yui, Goto, Ikemoto, & Ishiguro, 1995, 1997a, 1997b; Yui et al., 2001; Yui et al., 2002), decreased DA transporter levels (Ujike et al., 2003), abnormal cerebral blood flow (Iyo, Sekine, & Mori, 2004), and abnormal metabolite concentrations in the basal ganglia (Iyo et al., 2004). Together these factors tend to implicate a genotype resulting in a biological predisposition to the development of MA-induced psychosis that may not be entirely dependent on MA use patterns, as some have suggested (Hall et al.,

1996). However, in MA users who develop psychosis, the emergence of symptoms has also been related to education, poly-drug use, frequency of MA use, dose of MA use, injection use, and prior psychiatric symptoms (Hall et al., 1996; Ujike & Sato, 2004). Further, reports have suggested that the longer the MA use, the worse the prognosis for the emergent psychosis (Ujike & Sato, 2004), while other studies have shown no relationship between MA use and symptoms of psychosis (Nakama et al., 2008). The current status of risk relating to emergence of psychosis in MA users requires replication. No theory has been proposed offering a mechanism for this association.

Some research has attempted to demonstrate clinical differences between MA-induced psychosis and non-substance-induced psychosis (NSIP; i.e., *de novo* psychosis). The most commonly reported difference is a higher positive to negative symptom ratio in MA-induced psychosis (Sato, 1992; Srisurapanont et al., 2003; Zorick, Rad, Rim, & Tsuang, 2008), though conversely, several reports describe MA-induced psychosis as indistinguishable from paranoid schizophrenia (e.g. Griffith et al., 1968; Srisurapanont et al., 2011; Tomiyama, 1990). In a recent factor analysis, Srisurapanont and colleagues (2011) observed that in both MA-induced psychosis and NSIP, symptoms presented in a three factor model: positive symptoms, negative symptoms and anxious/depressive symptoms. Not only were similar symptoms present in both groups, but they were rated in the same way. One currently used definition of MA-induced psychosis is as a paranoid hallucinatory state that develops gradually with repeated MA abuse and continues after MA withdrawal (Sweeting & Farrell, 2005). This definition differs substantially from DSM-IV-TR criteria for substance-induced psychosis, and illustrates how definition of terms is an important consideration in this research. Varying definitions have also affected the reported rates of MA-induced psychosis. Some suggest that as many as 10% of chronic MA users develop a persistent psychotic disorder, while at least 23% develop clinically significant psychotic symptoms (McKetin, McLaren, Lubman, & Hides, 2006), although depending on the definition some report rates of MA-induced psychosis as high as 92% (Ujike & Sato, 2004).

In MA-induced psychosis the most commonly described symptoms are positive symptoms, specifically persecutory delusions, auditory hallucinations, strange beliefs and thought reading (Chen et al., 2003; Srisurapanont et al., 2003), though in the smaller proportion of stimulant users that experience negative symptoms, poverty of speech, psychomotor retardation, and flattened affect are also common (Srisurapanont et al., 2003). It may be that acute use of MA accounts for the more commonly observed positive symptoms, but that over a gradual progression the psychotomimetic effects progress into full symptoms of psychosis, with a progression from psychotomimetic, to pre-psychosis to full psychosis (Ujike & Sato, 2004).

In a study dividing MA-induced psychosis into three types: transient, prolonged, and persistent, the persistent type presented with moderate to severe disturbances in social functioning and had similar eye tracking deficits as compared to NSIP (Mikami et al., 2003). In a similar breakdown, a genetic difference was reported between transient and prolonged MA-induced psychosis; the ala/val polymorphism of the SOD2 gene was related to greater risk of developing persistent MA-induced psychosis (Nakamura et al., 2006). Some of the pathological findings in MA-induced psychosis have also related to symptom presentation. In a multimodal imaging study, reduced creatine:choline was negatively correlated with positive symptoms (Sekine et al., 2002), as was reduced DA transporter levels in NAc, caudate/putamen, OFC, and dorsolateralPFC (dlPFC; Iyo et al., 2004; Sekine et al., 2003). There have been so few studies comparing MA-induced psychosis to NSIP that no clear consensus can be drawn regarding comparison of the two types of psychosis. It is therefore unclear if a substance-induced psychosis requires the same treatment needs as a NSIP. Further, understanding the cognitive and biological correlates of symptoms of psychosis offers insight to potential risk factors and may aid in identifying high-risk groups.

Some studies have explored drug specificity with relation to the emergence of psychosis because cocaine is also a stimulant with a similar mechanism of action. MA-dependent users were more likely to report psychotic

symptoms than cocaine-dependent users (Mahoney, Kalechstein, De La Garza, & Newton, 2008). This may be due to the more potent effect MA has on DA transmission as compared to cocaine (Y. Zhang et al., 2001). Alternatively, it may be due to different mechanisms of action on DA; cocaine inhibits the DA transporter, while MA reverses the action of the DA transporter (Volkow, Fowler, Wang, & Swanson, 2004). The reason for higher rates of MA-induced psychosis as compared to cocaine-induced psychosis remains conjecture.

In summary, comorbid substance use and mental health disorders are a relative commonly occurrence, yet the etiology is not well understood, and likely differs by subgroups. In 2008 a review was written assessing studies explicitly examining substance-induced psychosis. The study examined only 49 articles, almost half of which were case reports. The authors concluded that there was a lack of research examining DSM criteria across substances and a lack of research in treatment and best practices (Mathias, Lubman, & Hides, 2008). Investigating comorbidity is important for its impact on etiology, prevention, and treatment. Given that stimulant dependence may be an independent risk factor for psychosis, the cognitive and biological correlates of these comorbid disorders may offer insight to the neurodevelopmental trajectories associated with psychosis.

Proton Magnetic Resonance Spectroscopy

Proton magnetic resonance spectroscopy (^{1}H-MRS), is an invaluable tool for measures of *in vivo* neurochemicals. This section reviews this imaging technique along with descriptions of commonly measured metabolites. For a review on the physics and methods of MRS, see Salibi and Brown (1998). A detailed description of reports of use of ^{1}H-MRS in schizophrenia and in substance dependence follows.

^{1}H-MRS, like other forms of MRI, uses the magnetic properties of the proton to derive *in vivo* information about otherwise inaccessible parts of the human (or other living creature) anatomy. The process for nuclear magnetic resonance was developed over 60 years ago, but continued improvements in instrumentation and technique have enabled ^{1}H-MRS to become a valuable tool for *in vivo* chemical identification. ^{1}H-MRS provides a unique opportunity to

investigate *in vivo* pathological processes in neurological disorders. Given that both schizophrenia and substance dependence disorders involve neuropathology, metabolite data may offer insight into the nature of the change and potential mechanisms.

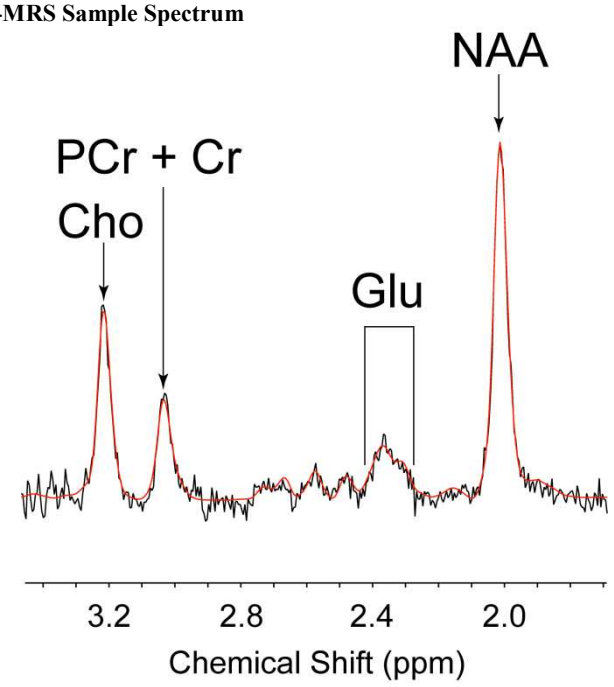
The proton is the most abundant atom within biological systems, making it an ideal candidate for spectroscopy (though spectroscopy is also possible with other nuclei, e.g., carbon and phosphorus). Magnetic resonance can occur with any atom with a nuclear spin (i.e., has an odd atomic weight and odd atomic number or odd number of protons and neutrons). It is the nuclear spin of an atom that is associated with a magnetic field, thus, the interaction between this spinning atom and an external, applied magnetic field (radio frequency (RF) pulse) makes ^{1}H-MRS possible. In a magnetic field, the protons align parallel or anti-parallel to the field, while precessing about the magnetic direction. How fast these protons precess is determined by the strength of the field, given by the Larmor equation: $\omega_o = \gamma B_o$, where ω_o is the precession frequency (in Hz), γ is the gyro magnetic ratio, and B_o is the strength of the external magnetic field (in Tesla). This equation determines the frequency of the RF pulse, which must be the same frequency as the rate of precession. When an external RF pulse is applied, the spins of the protons excite and precess in phase, in a transverse orientation. When the RF pulse is stopped, the protons emit energy when relaxing back to their natural state, in line with the external magnetic field. This emitted energy is released into the lattice, increasing longitudinal magnetization. When the RF pulse is shut off the protons also de-phase, reducing transverse magnetization. The emitted energy in this process is transferred between protons instead of into the surrounds (i.e., lattice). The energy emitted during these two processes can be transmitted to a receiver coil. The time between RF pulses allows for tissue differentiation because of the inherent properties of different tissues. The delay between RF pulses is TR (repetition time). The time between the excitation pulse and the signal maximum is TE (echo time). There are many types of pulse sequences that optimize different features and produce different types of images. In STEAM (stimulated echo acquisition mode) there are three RF pulses of 90 degrees. This

sequence is optimized for voxel selection. In PRESS (point resolved spectroscopy) there is one RF pulse of 90 degrees and two of 180 degrees. This sequence allows for better quantification of metabolites with less susceptibility to motion and with better signal-to-noise ratio (SNR).

The instrumentation required for ^{1}H-MRS includes a magnet, a gradient system, an RF system, a computer, and a data acquisition system. The strength of the magnet is measured in Tesla, where 1 Tesla is 10,000 Gauss. Higher strength magnets improve spectral separation and increase the SNR. The primary magnet quality is a homogeneous magnetic field, which is further improved through the use of shim coils. Variations in the magnetic field are produced using gradients. These are used for spatial localization, as they are able to encode in three dimensions. In ^{1}H-MRS, the voxel selection must be large (>1 cm^3) in order to detect molecules that are 1000 to 100,000 times less concentrated than water (Salibi & Brown, 1998). A receiver coil detects the voltage from the spins. Water is the primary signal detected in ^{1}H-MRS. Because of this strong signal, it is more difficult to observe weaker signals from less concentrated metabolites and it becomes necessary to suppress the water signal.

The Fourier transformation is used to convert the digital signal into a function of time and frequency. The resulting spectrum output presents peaks that are proportional to the number of spins for the given metabolite and the position of the peak is related to the type of spin. The scale of this spectrum is in ppm, which defines frequency relative to a reference frequency. Figure 2 shows a sample output spectrum with the relative peak height and placement of each neurochemical.

Figure 2
^{1}H-MRS Sample Spectrum



Neurochemicals measured by ^{1}H-MRS.

The metabolites most commonly measured by ^{1}H-MRS include N-acetylaspartate (NAA) at 2.02 ppm on the spectrum. NAA is the dominant peak (referenced to water) in the human brain. The NAA peak also contains signal from N-acetylaspartylglutamate. The role of NAA in the human brain is not yet clearly defined, and it is likely that NAA is involved in many processes including myelin synthesis, osmoregulation, and axon-glial signaling (Moffett et al., 2007). NAA also has a role in brain development (van der Knaap et al., 1990), with increasing NAA throughout development until as late as the third decade of life, and decreases of NAA throughout later-life aging. NAA is most commonly reported as a marker of neuronal integrity because decreases of NAA are associated with regions of neuronal loss, as in stroke, epilepsy, or tumors.

Creatine and phosphocreatine (Cr) are represented by the peak at 3.02 ppm. It was previously thought that Cr was a stable compound throughout the brain and throughout development and aging (Maton & Kuzniecky, 2000). For this reason, Cr was often used a reference metabolite to enable comparison of other metabolites. It is now believed that Cr is not an ideal internal reference for ^{1}H-MRS because of abnormalities reported in several disease states (e.g., Ongur,

Prescot, Jensen, Cohen, & Renshaw, 2009; Theberge et al., 2007a; Wood et al., 2003). Cr may be related to cellular energy production and, though normally stable, may be affected by energy requirements (Ongur et al., 2009).

Choline and choline-containing compounds (Cho) are represented on the spectrum by the peak at 3.2 ppm. Cho is regarded as a product of myelin breakdown (Salibi & Brown, 1998) and increased signals in Cho may reflect gliosis (i.e., proliferation of astrocytes at the site of neuronal damage). Cho is found in higher concentrations in tumors and sites of inflammation (Gillard, Waldman, & Barker, 2004).

Glu is represented at the peak at approximately 2.1 ppm. Glu is the primary excitatory neurotransmitter in the mammalian brain. It is synthesized from glucose and glutamine (Gln) and is present in high concentrations throughout the central nervous system (Sadock & Sadock, 2003). Glu has many roles, but approximately 30% of the Glu in the central nervous system acts as a neurotransmitter. Glu as a neurotransmitter has a role in brain maturation and development by stimulating neurite growth, synaptogenesis, and maturation of synapses (Konradi & Heckers, 2003). Excess extracellular Glu is neurotoxic and can lead to cell degeneration (Snider & Choi, 2003). Glu is a difficult metabolite to accurately quantify because it resonates in close proximity to Gln between 2.1 and 2.4 ppm (Gillard et al., 2004). Therefore, Glu is best measured in higher strength magnets, and with sequences optimized for its quantification. One method for optimizing Glu is to use a long TE. Long TEs result in less overlap in the spectrum by suppressing signal from macromolecules (e.g., lipids) that can conceal the Glu peak.

The concentration (i.e., area under the peak in the spectrum) of these metabolites is dependent on many factors, including subject age, voxel placement (regional differences), and voxel composition (GM vs. white matter (WM)). As expected effect sizes in metabolite concentrations are low, large sample sizes and proper study design are important factors in any ^{1}H-MRS study.

There are several limitations to ^{1}H-MRS (e.g., patient movement can result in the widening of peaks in the spectrum, incorrect localization, or loss of

signal). Each parameter has a direct and significant impact on the spectrum. Therefore, the optimization of parameters is critical to obtaining valuable data, including TE, TR, number of acquisitions, voxel size, and voxel position. Magnetic resonance techniques are slower than other imaging techniques, which results in a longer acquisition time, increasing the likelihood of negative impact from patient movement. The SNR in ^{1}H-MRS is relatively poor; large voxels are needed for adequate SNR because the signals from the neurochemicals of interest are so much smaller compared to the signal from water. Additionally, there are several contra-indications for receiving an MRI (e.g., some surgical implants, recent surgery, severe claustrophobia), that exclude subsets of the population.

There are also several advantages to magnetic resonance techniques over other imaging modalities. MRI does not involve radiation, making it more suitable for longitudinal studies. MRI allows for soft tissue contrast and can isolate slices in any orientation. ^{1}H-MRS, specifically, is unique in its ability to provide functional *in vivo* metabolic information.

^{1}H-MRS studies of schizophrenia.

The use of ^{1}H-MRS in studies of psychiatric disorders began to grow in the early 1990's. Since then, techniques have improved and several reviews and meta-analyses have been written describing findings in several psychiatric disorders, but particularly in schizophrenia. Researchers have also begun to design longitudinal studies using ^{1}H-MRS to investigate neurochemical presentation with respect to illness stage. Additionally, several researchers have begun to focus on those considered at clinical or genetic high-risk for developing schizophrenia to investigate potential biomarkers for the disorder.

As described above, the mostly commonly measured metabolites are NAA, Cr, Cho and Glu (or some other variation of Glu, like Glx (Glu + Gln)). NAA is considered the most robust finding in ^{1}H-MRS studies of schizophrenia, and several studies have demonstrated a reduction in NAA in schizophrenia as compared to HCs. Across disease subtypes and stages (i.e., childhood onset schizophrenia, medication-naïve first episode psychosis (FEP), and chronic, medicated schizophrenia) reductions of NAA have been described in the

hippocampus (Bertolino, Callicott, Elman et al., 1998; Bertolino, Kumra et al., 1998; Bertolino et al., 2003; Blasi et al., 2004; Deicken, Zhou, Schuff, Fein, & Weiner, 1998; Klar et al., 2010), dlPFC (Bertolino, Callicott, Elman et al., 1998; Bertolino, Kumra et al., 1998; Bertolino et al., 2003; Ohrmann et al., 2008; Stanley et al., 2007), ACC (Bustillo et al., 2010; Deicken, Zhou, Schuff, & Weiner, 1997; Ende et al., 2000; Ohrmann et al., 2008; Premkumar et al., 2010; Wood et al., 2007; Yamasue et al., 2002), generally in the frontal lobe (Cecil, Lenkinski, Gur, & Gur, 1999; Delamillieure et al., 2002; Hagino et al., 2002; Ohrmann et al., 2006; Premkumar et al., 2010; Tanaka et al., 2006), basal ganglia and occipital lobes (Goto et al., 2011), temporal lobes (Cecil et al., 1999; Tanaka et al., 2006), and globally (Bustillo et al., 2008). Some of these findings have been reproduced successfully over a 90 day period with no change (Bertolino, Callicott, Nawroz et al., 1998; Mullins et al., 2003).

Despite these fairly consistent and replicated findings, some studies have described no change in NAA levels in schizophrenia, including in both FEP and chronic schizophrenia in the frontal lobe (Bartha et al., 1997; Galinska et al., 2009; Goto et al., 2011; Sigmundsson et al., 2003; Stanley et al., 1996), temporal lobes (Bartha et al., 1999; Galinska et al., 2009; Wood et al., 2008), and thalamus (Delamillieure, Constans, Fernandez, Brazo, & Dollfus, 2000; Galinska et al., 2009). Negative findings may be the result of subtypes of psychosis, as demonstrated by the observation of reduced NAA only in those with the deficit syndrome (Delamillieure et al., 2000), which was supported by a finding showing a correlation between symptom severity and NAA in the dlPFC of deficit syndrome schizophrenia only (Sigmundsson et al., 2003). Negative findings may also be due to disease onset type, as demonstrated by those with early-onset psychosis presenting with lower NAA than adult-onset psychosis (Stanley et al., 2007). Contradictory findings may also be due to unmeasured confounds, such as lateralized deficits (Zabala et al., 2007) or differences in voxel composition (Lim et al., 1998).

Despite some negative findings, most studies support a reduction of NAA in schizophrenia. Some have suggested that reduced NAA is apparent early in the

illness (Maier & Ron, 1996) and does not seem to normalize with medication, even up to 12 months (Bertolino, Callicott, Elman et al., 1998; Bustillo et al., 2002; Bustillo et al., 2008; Bustillo et al., 2010). Others have described differences between FEP and chronic schizophrenia with reduced NAA/Cr in the left hemisphere (Molina et al., 2005) and dlPFC (Ohrmann et al., 2005) of chronic schizophrenia only, not in FEP, suggesting that progressive change of NAA may occur, however recent reports do not support this theory.

Measuring NAA is further complicated by its relationship to a normal aging brain. Some investigations of schizophrenia have described negative NAA/Cr correlations with age in the frontal lobe (Block et al., 2000; Delamillieure et al., 2002) and thalamus (Delamillieure, Constans et al., 2000) and reduced NAA may not withstand covariance with age (Block et al., 2000). As with any study of chronic schizophrenia, it may be that medications play a role in normalizing NAA. Several studies have examined the effect of typical and atypical antipsychotics with respect to NAA and demonstrated that individuals on typical antipsychotics had lower levels of NAA than those on atypical antipsychotics (Bustillo et al., 2001; Ende et al., 2000). Others have observed NAA increases over time in region-specific areas with treatment, (i.e., in the dlPFC and thalamus but not in the hippocampus or temporal lobes; Bertolino et al., 2001; Szulc et al., 2005). However, these findings are in question given that others reported no difference in NAA in the frontal and temporal lobes and thalamus between patients treated with atypical antipsychotics and those treated with typical antipsychotics (Szulc et al., 2007).

An early review suggested that NAA is, in fact, consistently reduced in schizophrenia in the temporal lobes (Kegeles, Humaran, & Mann, 1998). A subsequent review concluded that reduced NAA is, at best, an inconsistent finding, but that methodological errors might account for the inconsistencies (Sanches, Crippa, Hallak, Araujo, & Zuardi, 2004). In 2005, a systematic review and meta-analysis was conducted by Steen and colleagues (Steen, Hamer, & Lieberman, 2005), reviewing 64 English-language papers of ^{1}H-MRS in schizophrenia and focusing exclusively on measurement of NAA. They described

evidence that NAA is reduced in several regions of the brain in schizophrenia patients. Most of the included studies (88%) were performed on a 1.5 Tesla scanner, and most (77%) reported on chronic patients, with the remaining focused on FEP, childhood onset, drug-free, and drug-naïve patients. In a follow-up to this meta-analysis, Abbott and Bustillo (2006) concluded that NAA in the medial temporal and PFC regions is reduced in schizophrenia. Very recently, a review and meta-analysis was written using 97 ^{1}H-MRS articles and separating them by illness stage (at-risk, FEP, or chronic schizophrenia; Brugger, Davis, Leucht, & Stone, 2011). They demonstrated that NAA is consistently reduced in the frontal lobe, temporal lobes and thalamus in both FEP and chronic schizophrenia. At-risk individuals presented with reduced NAA in the thalamus, with a trend in the temporal lobe and no reduction in the frontal lobe. It seems that most meta-analyses and reviews support the finding of reduced NAA in schizophrenia. NAA reductions have been observed in affective psychosis as well (Blasi et al., 2004). Given the association between NAA and psychosis, NAA may be reduced in other subtypes of psychosis as well, including postpartum psychosis or substance-induced psychosis. Few studies have investigated this possibility.

Glu (and/or Gln or Glx) has also been commonly reported in ^{1}H-MRS studies of schizophrenia because of the glutamatergic theories of schizophrenia. Observations with Glu have been far less consistent than with NAA, given the difficulty in differentiating the peak on the spectrum. Early on, Bartha and colleagues (1997) observed an increase of Gln in the medial PFC (mPFC) of never-treated FEP patients, though most studies failed to replicate this finding. After a review describing inconsistencies in measuring Glu (Kegeles et al., 1998), one of the first studies attempting to differentiate Glu and Gln used a 4T magnet and observed higher Gln in the left ACC, with no change in the left thalamus (Williamson et al., 1999).

In the first of a series of sequential studies examining Glu in schizophrenia, Theberge and colleagues (2002) first selected the ACC and thalamus in FEP and observed elevated Gln. Replicating the methodology but examining chronic schizophrenia, Theberge and colleagues (2003) observed

lower Gln and Glu in left ACC and higher Gln in the thalamus, partially replicating the previous finding. In a longitudinal study, Theberge described elevated Gln in ACC and thalamus of medication-naïve FEP that was then reduced after 30 month follow-up (Theberge et al., 2007b). These studies were among the first to suggest that there may be progressive change in Glu and/or Gln in schizophrenia, with elevations during initial phases, and reductions in later, chronic schizophrenia. This has been supported by studies reporting reduced Glx in the dlPFC in chronic schizophrenia as compared to FEP (Ohrmann et al., 2006; Ohrmann et al., 2005), elevations of Glu in the dlPFC and hippocampus of FEP (Olbrich et al., 2008), and reduced Glu in the basal ganglia of chronic schizophrenia (Tayoshi et al., 2009). In an attempt to confirm Glu findings, Hashimoto and colleagues examined Glu in the CSF of never-medicated FEP patients and observed elevations of Gln/Glu, supporting the findings from ^{1}H-MRS (Hashimoto et al., 2005).

There have been contradictory findings as well. Elevated Glu was observed in the dlPFC and hippocampus in chronic schizophrenia (Tebartz van Elst et al., 2005), and the initial elevations of Gln/Glu demonstrated before treatment, showed no change at 12-month follow-up (Bustillo et al., 2010). Further, several studies have failed to show any difference in Glu, including in the ACC (M. A. Reid et al., 2010; Wood et al., 2007), frontal lobe, temporal lobes, or thalamus (Galinska et al., 2009; Wood et al., 2008). More so with Glu than with the other neurochemicals, these inconsistent findings are likely a result of methodology. As Glu is a more difficult signal to differentiate, study design plays a critical role in findings. A review suggested that studies with stronger magnets may be more consistent in reporting abnormalities of Glu and Gln (Abbott & Bustillo, 2006). One study has also reported the potential for gender effects in the measurement of Glu (Tayoshi et al., 2009). There is a need to replicate many of these study designs, and for more studies to employ use of higher strength magnets capable of measuring Glu independent from Gln. Generally these studies support a role of Glu in schizophrenia, however the timing and direction of these changes is unclear.

Most studies do not focus on measures of Cr because it was previously considered a stable neurochemical. Therefore, many studies have used Cr as a reference measure, in ratio with other neurochemicals. However, recent reports have questioned the stability of Cr (Ongur et al., 2009). In schizophrenia research the most consistent finding is no change in Cr levels, including in the ACC (Deicken et al., 1997; Ende et al., 2000), thalamus (Galinska et al., 2009), hippocampus (Delamillieure et al., 2002), dlPFC (Sigmundsson et al., 2003; Zabala et al., 2007), medial temporal lobes (Galinska et al., 2009; Wood et al., 2008), and generally in the frontal lobes (Delamillieure et al., 2002; Galinska et al., 2009; Tanaka et al., 2006). Rarely, differences in Cr are found, including reduced Cr in the PFC in FEP and chronic schizophrenia as compared to HCs (Ohrmann et al., 2006).

There is less direct evidence for an involvement of Cho in schizophrenia, and most studies fail to report any change in Cho as compared to HCs, including in the ACC (Deicken et al., 1997; Ende et al., 2000), frontal lobes (Galinska et al., 2009; Sigmundsson et al., 2003; Tanaka et al., 2006; Zabala et al., 2007), thalamus, and temporal lobes (Galinska et al., 2009). Still, some studies have observed Cho/Cr elevations in the frontal lobe (Cecil et al., 1999) and ACC (Yamasue et al., 2002) and reductions in the PFC in chronic schizophrenia as compared to FEP (Ohrmann et al., 2006). No mechanism of pathology relating to changes in Cho have been described.

^{1}H-MRS studies of high-risk samples. An important avenue to explore using ^{1}H-MRS is to examine neurochemical profiles in individuals considered at clinical or genetic high-risk for developing schizophrenia. In this way, one might be able to determine if the neurochemical changes present at later points in the disorder are potential endophenotypes or biomarkers, or if they are related to the disease state. In early studies, first-degree relatives and off-spring of schizophrenia patients presented with a trend for decreased NAA/Cho in the ACC (Keshavan et al., 1997) and reduced hippocampal NAA/Cr (Callicott et al., 1998). In more recent years there has been mounting evidence for reduced NAA in high-risk groups as compared to HCs in the corpus callosum (Aydin, Ucok, & Guler,

2008), left frontal lobe, ACC, left superior temporal lobe (Jessen et al., 2006), caudate (Keshavan et al., 2009), and left thalamus (Yoo et al., 2009). In addition, children with symptoms of schizophrenia spectrum disorders (and therefore considered at-risk of developing psychosis) presented with lower NAA/Cr in the left frontal lobe as compared to HCs (Brooks et al., 1998). These reports of reduced NAA in at-risk groups have been supported by a lack of difference in NAA between FEP groups and high-risk groups (Aydin et al., 2008).

Other neurochemicals have also been measured in at-risk groups, including increased Glx in the mPFC of a genetic high-risk group (Tibbo, Hanstock, Valiakalayil, & Allen, 2004). This same research group has also reported that the variability in Glu was much greater in a genetic high-risk sample than in controls, and that higher levels of Glu were related to worse cognitive performance (Purdon et al., 2008). Glu was also elevated in a high-risk sample in the dorsal caudate (de la Fuente-Sandoval et al., 2011). Reduced Cr and Cho have also been described in the caudate (Keshavan et al., 2009) and left thalamus (Yoo et al., 2009) of high-risk groups. In a longitudinal study it was reported that those at high-risk who converted to psychosis had elevated Cho/Cr and lower NAA/Cho in the ACC as compared to non-converters; this group concludes that NAA may be a vulnerability marker for schizophrenia and that Cho may be able to predict conversion to psychosis in high-risk samples (Jessen et al., 2006). Replication of these studies is needed.

More recently researchers have begun to investigate those considered in an at-risk-mental-state. These individuals present with prodromal symptoms of schizophrenia without meeting full criteria for psychosis or schizophreniform disorders. Some of the first at-risk-mental-state studies described lower Glu in the thalamus (Fusar-Poli et al., 2011; Stone et al., 2009) and medial temporal lobe (Valli et al., 2011) and higher Gln in the ACC (Fusar-Poli et al., 2011; Stone et al., 2009). Another at-risk-mental-state study reported a negative relationship between Glu and DA in the hippocampus (Stone, Bramon, Pauls, Sumich, & McGuire, 2010). All of these findings support a role for Glu prior to full disease

onset, suggesting that Glu may be involved in early pathological processes in schizophrenia.

Several contradictory findings have also been published (Byun et al., 2009; Lutkenhoff et al., 2010; Uhl et al., 2011; Wood et al., 2003; Wood et al., 2010; Yoo et al., 2009). A very recent review investigating ^{1}H-MRS findings by illness stage showed that the only significant difference between stages of illness was reduced NAA in the frontal lobes in FEP but not in the high-risk group. The review reported that the biggest differences between at-risk groups and HCs was reduced NAA in the thalamus, concluding that reduced thalamic NAA may be a trait marker for schizophrenia risk (Brugger et al., 2011). As there are contradictory reports, future studies need to focus on ^{1}H-MRS methodology and region-specific findings.

^{1}H-MRS co-registered with cognitive performance. Another important avenue to explore using ^{1}H-MRS is the possible co-registration of spectroscopic observations and cognitive assessment. NAA has been of particular interest, given that NAA is regarded as a marker of neuronal integrity. A loss of neurons in the frontal regions of the brain may partially explain some of the cognitive impairment in schizophrenia. Several studies have described a relationship between NAA and cognitive performance, including a positive correlation between NAA/Cr and verbal memory (Hagino et al., 2002) and working memory (Bertolino et al., 2000; Bertolino et al., 2003; Ohrmann et al., 2006). NAA/Cr also positively correlated with Stroop Colour and Word Test scores in deficit schizophrenia in the mPFC (Delamillieure, Constans, Fernandez, Brazo, & Dollfus, 2004). NAA has consistently correlated with performance on the Wisconsin Card Sorting Test (WCST; Galinska et al., 2007; Ohrmann et al., 2008; Tanaka et al., 2006). While most of these studies investigated frontal lobe NAA, global NAA also correlated with global measures of cognitive performance in schizophrenia (Bustillo et al., 2008).

One other metabolite provides consistent findings with relation to cognitive performance. Gln/Glu and Gln have positively correlated with performance on the WCST (Ohrmann et al., 2008; Shirayama et al., 2010) and the

digit span test (Shirayama et al., 2010). In a recent study taking advantage of a potential role for Glu in the development and pathology of schizophrenia, elevated Glu in a group of genetic high-risk subjects was associated with poor performance on a task of sustained attention (Purdon et al., 2008). Some contradictory findings have also been published, including no relationship between any measured metabolite and cognitive performance (Premkumar et al., 2010) and elevated Glu in the hippocampus correlated with poor WCST performance, with no correlation in the dlPFC (Rusch et al., 2008). Again, this is a relatively new focus of ^{1}H-MRS research, and replication is required. However, given the evidence for a relationship between neurochemical profile and cognitive function, the right combination of these two factors holds potential to represent a more specific endophenotype for schizophrenia than either factor alone.

^{1}H-MRS and relationship to symptom presentation. Many researchers have also examined the relationship between neurochemical measures and symptom presentation. No clear consensus has been drawn, but several studies have described a potential relationship. Again, NAA is the metabolite with the strongest potential for a relationship to symptom presentation, with mostly negative correlations. The strongest support is for a negative correlation between NAA and negative symptoms (Aydin et al., 2008; Callicott et al., 2000; Sigmundsson et al., 2003; Tanaka et al., 2006; Yamasue et al., 2002). However, several studies have also reported negative correlations with positive symptoms (Callicott et al., 2000; Martinez-Granados et al., 2008; Premkumar et al., 2010; Sigmundsson et al., 2003; Theberge et al., 2004). In a sample of medication-naïve patients, NAA correlated with positive symptoms (Szulc et al., 2005), and as symptom scores improved (based on the PANSS) in those treated with clozapine, NAA also increased (Ertugrul et al., 2009). NAA has also correlated negatively with the duration of prodromal symptoms (Theberge et al., 2004), and social functioning level (Sigmundsson et al., 2003). NAA was also the best predictor of outcome in an 18-month longitudinal study, with up to 30% of the variance in outcome explained by NAA/Cr in the PFC (Wood et al., 2006). Still, there are

findings of no relationship between NAA and scores on the PANSS, and depression and mania rating scales (Blasi et al., 2004).

Reports with other metabolites are less consistent, but a negative correlation between Glx and negative symptoms in a medication-naïve sample has been described (M. A. Reid et al., 2010; Szulc et al., 2005). This is supported by the finding of increased Glx/Cr as negative symptoms improved with treatment (Goff et al., 2002). Other observations include a correlation between Cr and positive and general symptoms, and a correlation between Cho and positive symptoms (Premkumar et al., 2010). Replication of these studies is required. The relationship between metabolite profiles, symptom presentation and cognitive performance may provide an opportunity for a better understanding of disease severity, or may provide more insight into groups considered at-risk for developing psychosis.

Summary of ^{1}H-MRS and schizophrenia. Inherent in ^{1}H-MRS research are limitations to the technology, in the reproducibility of findings, and in the methodology (e.g., Bertolino & Weinberger, 1999; Keshavan, Stanley, & Pettegrew, 2000; Stanley, Pettegrew, & Keshavan, 2000). In a review of NAA with inconsistent findings, it was suggested that small sample size, variation in clinical and demographic characteristics and lack of standardized ^{1}H-MRS parameters are candidate causes for the inconsistencies (Sanches et al., 2004). An early summary of ^{1}H-MRS studies suggested that discrepancies in observations may be a result of several factors each with substantial impact, including statistical power (due to small sample sizes and small anticipated effect sizes), localization (targeting smaller, more specific regions is better than whole lobe analysis), GM and WM differences, methodology (reference to Cr or water), medication effects, and severity of the disorder (Bertolino & Weinberger, 1999). Further, most spectroscopy studies to date are under-powered, with a mean number of patients per study of 18.9 (Steen et al., 2005).

One research team wrote a two-part publication that outlined the difficulties in conducting ^{1}H-MRS studies. They highlighted the difficulty in understanding the neurochemistry and interpreting the meaning of findings, the

difficulty in optimizing parameters for data collection, the difficulty in spectrum interpretation with overlapping peaks, factors that affect SNR, varying types of voxel localization, post-processing methods and quantification of results (Stanley et al., 2000). In the second part, they describe the problem of ^{1}H-MRS findings with specificity to disease and state-trait issues, the abundance of cross-sectional studies, and the difficulty in comparing across studies due to methodological differences (Keshavan et al., 2000). For these reasons, it is easy to understand the inconsistent findings in much ^{1}H-MRS schizophrenia research. There is a need for more longitudinal studies in schizophrenia research, using higher strength magnets to examine the changes in metabolites through the progression of the disorder and to relate these findings to functioning and outcome.

^{1}H-MRS studies of substance abuse and dependence.

Using ^{1}H-MRS in the study of substance misuse started in the late 1990's. Most studies have focused on stimulant dependence, but have included nicotine, alcohol, and opiates. As with the use of ^{1}H-MRS in studies of schizophrenia, advances in technology and methodology have made recent studies more robust, as previous studies more often used a lower strength magnet, used ratio comparisons and/or did not account for tissue segmentation.

^{1}H-MRS has occasionally been used to investigate the effects of licit drugs, including nicotine, alcohol, and inhalants (specifically toluene). Most commonly, ^{1}H-MRS studies of nicotine dependence examine nicotine as a comorbid factor with other substance dependence in an attempt to determine the additive or potential protective effects of nicotine. As an example, alcoholic smokers had less normalization of metabolite levels than alcoholic non-smokers during early sobriety (Durazzo, Gazdzinski, Rothlind, Banys, & Meyerhoff, 2006). Durazzo suggests that the effects of nicotine may mediate other effects described in the literature, as rarely are smokers differentiated from non-smokers (Durazzo, Gazdzinski, Banys, & Meyerhoff, 2004).

Several studies of alcoholism have reported reduced NAA and Cho levels (Durazzo et al., 2004; Ende et al., 2006; Jagannathan, Desai, & Raghunathan, 1996; E. Lee et al., 2007; B. C. Schweinsburg et al., 2003). These reductions may

normalize with abstinence (Durazzo et al., 2006; Ende et al., 2005; Martin et al., 1995; Parks et al., 2002) accompanied by increasing brain volume and improvements in cognitive function (Bartsch et al., 2007; Bendszus et al., 2001). Durazzo has reported metabolite differences in alcohol-dependence of NAA and Cho between those who relapse to alcohol use and those who abstain, suggesting that these neurochemicals may play a role in a vulnerability to alcohol dependence (Durazzo, Gazdzinski, Yeh, & Meyerhoff, 2008; Durazzo, Pathak, Gazdzinski, Mon, & Meyerhoff, 2010).

Studies of cannabis are limited, but also describe reductions of NAA (Hermann et al., 2007). One study (Chang, Cloak, Yakupov, & Ernst, 2006) reported a normalization of Glu levels in HIV positive subjects when concordant for cannabis use, whereas a quite different effect was shown for HIV positive subjects concordant for MA use: in this study, an additive effect was shown, where MA users showed further reductions of NAA and Cr (Chang, Ernst, Speck, & Grob, 2005). Stimulants are far more frequently investigated using ^{1}H-MRS. Studies of MDMA have reported inconsistent reductions of NAA in frontal regions. No changes in NAA have been reported in the mPFC, hippocampal and parietal regions (Chang, Ernst, Grob, & Poland, 1999; Cowan et al., 2007; Daumann et al., 2004; de Win et al., 2007), whereas NAA may be lower generally in the frontal cortex (Reneman, Majoie, Flick, & den Heeten, 2002) and this reduction may correlate with degree of memory impairment (Reneman, Majoie, Schmand, van den Brink, & den Heeten, 2001). Investigations of MDMA are difficult to interpret because MDMA users are most commonly poly-drug users (Gouzoulis-Mayfrank & Daumann, 2006) and because of the lack of ability to determine purity of MDMA pills.

^{1}H-MRS studies of cocaine have described consistent reductions of NAA (Chang, Ernst, Strickland, & Mehringer, 1999; Li, Wang, Pankiewicz, & Stein, 1999) and increases in Cr (Chang, Ernst, Strickland et al., 1999; Chang et al., 1997) that may correlate with frequency of use (Chang et al., 1997). One study reported gender differences in frontal levels of Cho with higher levels of Cho in males (Chang, Ernst, Strickland et al., 1999). This finding has not been examined

in other substances. Other studies report reduced Glu/Cr that correlated with years of cocaine use (Yang et al., 2009). Most ^{1}H-MRS research in substance dependence varies considerably by sample, voxel location and methodology. As such, consensus on observations is not clear and replication is required.

MA has been the most commonly investigated drug using ^{1}H-MRS, likely because of the strong evidence showing that MA is neurotoxic to dopaminergic and serotonergic systems. The first study, by Ernst and colleagues (2000) reported reduced NAA and Cr in the basal ganglia and elevations of Cho in frontal GM. Several studies have corroborated these findings (Chang et al., 2007; Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007; Sekine et al., 2002). Reductions of NAA may correlate with lifetime use (Ernst et al., 2000), cumulative dose of MA (Sung et al., 2007), performance on an attention task (Salo et al., 2007), and the presence of psychiatric symptoms (Sekine et al., 2002), whereas reduced Cr/Cho may correlate with duration of use and severity of psychotic symptoms (Iyo et al., 2004). There are inconsistent reports of potential normalization of NAA with abstinence (Nordahl et al., 2005). While NAA may be reduced in early abstinence (0 to 4 months; Ernst et al., 2000; Nordahl et al., 2002; Salo et al., 2007), no difference was reported after 2 years of abstinence relative to HCs (Sung et al., 2007), though this is not a consistent finding (Nordahl et al., 2005). Fewer studies have measured Glu (or Glx), though there is some evidence that Glx may normalize with longer duration of time abstinent in MA users (Ernst & Chang, 2008).

In summary, it seems that non-specific drug use is associated with reductions of NAA, which may normalize with duration of time abstinent. These reports suggest that substance use has direct effects on neuronal integrity. Use of ^{1}H-MRS in studies of substance dependence is complicated by many factors. Firstly, as with many studies of substance dependence, data are collected in a self-report manner, making it difficult, if not impossible, to verify or corroborate usage patterns. For many street drugs, it is also difficult to determine the purity of the drug, which creates confounds not only in poly-substance use, but also in users with a primary substance dependence given that purities, potencies and

contaminants by drug may differ. Further, as with research in schizophrenia, ^{1}H-MRS is affected by sample size, inconsistent clinical and demographic variables, and lack of standardized parameters (Keshavan et al., 2000; Sanches et al., 2004; Stanley et al., 2000). Again, similar to schizophrenia research, methodologies are constantly changing and improving; study designs are addressing factors like medication effects and clinical variables, and more longitudinal studies are being designed.

Cognition

Cognition, generally, is the ability to interact with one's environment and to execute behaviours that allow for functioning in everyday life. Impairment of cognition can affect many aspects of living, including relationships, ability to be employed and quality of life. Impairments are associated with many neurodegenerative and psychiatric illnesses, including, but not limited to, Alzheimer's disease, Parkinson's disease, depression, bipolar disorder and schizophrenia. This section describes distinct cognitive domains relevant to the current project, and describes cognitive impairment in schizophrenia, substance dependence and comorbid disorders.

Cognition covers so many processes that it is almost always referred to in domains that describe more specific aspects of cognition. These domains include attention, memory, language ability, learning, speed of information processing and executive functioning. While there is general consensus on the definition of key domains, comparison of findings between studies is often confounded by the use of different assessments to measure the same described domain.

Cognitive impairment is evident in both schizophrenia and substance dependence disorders. The emergence of cognitive impairment is likely modulated by neuropathological change and may provide insight into the etiology of the disorders. Particularly in schizophrenia, different cognitive domains may provide insight into varying time points in disorders, such that some cognitive impairment may precede the disorder, while others may emerge as symptoms of the disorder. Two relevant domains include processing speed and executive functioning.

Processing speed.

Processing speed refers to "the speed with which different cognitive operations can be executed" (Reichenberg, 2010, p. 386). Some studies lump attention processes and processing speed into similar categories (Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009), though in the simplest form, processing speed involves timed tasks with low cognitive load. Several measures of processing speed exist. Any test that involves performing a task in a timed environment may be considered a test of processing speed. As such, the complexity or difficulty of these tests can vary substantially (Denny & Lynch, 2009; Jensen, 1965). Some of the more basic tests include the Stroop Colour and Word Test colour reading and colour naming measures (Golden, 1975; Stroop, 1935), which was identified as a measure of processing speed in a factor analysis (Denny & Lynch, 2009; Jensen, 1965); the Trail Making Test-A (TMT-A; Halstead, 1947; Reitan, 1979; War Department & Adjutant General's Office, 1944), which is a simple measure of processing with a motor speed component (Goudsmit et al., 2004); and the Digit Symbol Substitution Test (Wechsler, 1981), which measures processing speed that is unaffected by intellectual prowess, memory or learning (Erber, Botwinick, & Storandt, 1981).

Processing speed has not been examined comprehensively for neural correlates (Dickinson, Ramsey, & Gold, 2007). From the few studies using fMRI and assessing processing speed, evidence supports activation in the fronto-parietal-cortical network. Usui and colleagues (2009) suggest that these areas represent the visual search process and working memory process. In another study examining two tasks sensitive to processing speed (The Paced Auditory Serial Addition Task and the Digit Symbol Substitution Test), fMRI data revealed different activations depending on the cognitive load of the task. The task with greater cognitive load (the Paced Auditory Serial Addition Task) activated more frontal regions than the Digit Symbol Substitution Test, which activated primarily parietal regions (Forn et al., 2010).

Executive functioning.

Executive functioning refers to a complex set of higher order cognitive processes. Several operational definitions exist, with one example describing executive functioning as the ability "to plan a behaviour strategy, to implement the plan, to sustain the plan, and to show mental flexibility in shifting the plan" (Purdon, Labelle, & Boulay, 2001, p. 58). Other definitions of executive functioning include the ability to search, self-monitor, plan, problem-solve, have abstract thinking, mental flexibility, inhibition, reasoning and abstraction (Reichenberg, 2010). Executive functioning is one of the latest cognitive processes to fully develop in humans (Freedman & Brown, 2011; Pantelis, Yucel, Wood, McGorry, & Velakoulis, 2003) making it more susceptible to pathological disruption throughout development.

Because executive functioning, by definition, encompasses many different processes, high heterogeneity in assessments is often reported. One of the most commonly used measures is the WCST perseverative error score, which was identified as a measure of executive function in factor analysis (Koren et al., 1998). Other assessments include the Stroop Colour and Word Test (interference score), which assesses the ability to shift sets and suppress habituated responses (Johnson-Selfridge & Zalewski, 2001), and the TMT-B, which measures, among other things, mental flexibility, which is a component of executive functioning (Spreen & Strauss, 1991).

Executive functioning is related to the frontal regions of the brain, in many cases, specifically the dlPFC and ACC (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). The WCST, in particular, is widely used as a marker of frontal function because of studies in the 1960's (Milner, 1963) reporting that patients with frontal lobe lesions performed poorly on this task as compared to HCs. Several studies have since replicated this finding, observing that in normal performance on the WCST blood flow in the region of the dlPFC is increased, while failure on this task is associated with a lack of increased blood flow (Weinberger, Berman, & Zec, 1986). Some recent studies have reported that the WCST is neither sufficiently sensitive nor specific to the frontal lobes (S. W.

Anderson, Damasio, Jones, & Tranel, 1991). Neural correlates of other tasks of executive function, like the TMT-B, also implicate frontal regions, but only in addition to involvement of the superior temporal cortices (Shirayama et al., 2010; Zakzanis, Mraz, & Graham, 2005). In summary, tests of executive function may have relatively high sensitivity to frontal lobe function, but low specificity.

In diseases with cognitive impairment, like schizophrenia, assessment of these impairments, along with neural correlates or functional associations offer opportunities to investigate the pathology associated with the disease.

Cognitive impairment in psychosis.

Cognitive impairment is both common and clinically relevant in schizophrenia. There are arguments for and against the inclusion of cognitive – specific criteria in the DSM-V (Keefe & Fenton, 2007). This demonstrates a recognized importance of the cognitive impairment in schizophrenia, but a hesitation in the placement of that importance. Knowledge of the etiology of cognitive impairment in schizophrenia is still in its infancy, and it is unclear if cognitive impairments are a direct risk factor for schizophrenia, are associated with other risk factors, are symptoms of the disease, are a consequence of other clinical symptoms (e.g., positive symptoms), or if they may be secondary to medication effects, social or occupational status (Maccabe, 2008). It is possible, and likely, that because of the heterogeneity of cognitive impairment in schizophrenia several of these possible relationships may be true and different cognitive processes may be associated with different aspects of the disease state.

Several reviews and meta-analyses have been published describing broad deficits of cognitive function in schizophrenia. These include deficits in verbal fluency (Allott, Liu, Proffitt, & Killackey, 2011; Bokat & Goldberg, 2003; Bowie & Harvey, 2005; Henry & Crawford, 2005), declarative memory (Cirillo & Seidman, 2003; Doughty & Done, 2009; Leavitt & Goldberg, 2009), working memory (Allott et al., 2011; Bowie & Harvey, 2005; Forbes, Carrick, McIntosh, & Lawrie, 2009; J. Lee & Park, 2005; Piskulic, Olver, Norman, & Maruff, 2007; Reichenberg, 2010; Tamminga, 2006), visual and spatial perception (Allott et al., 2011; Hardoy et al., 2004), processing speed (Allott et al., 2011; Dickinson et al.,

2007; Nuechterlein et al., 2004; Palmer, Dawes, & Heaton, 2009; Reichenberg, 2010; Tamminga, 2006), reasoning and problem solving (Allott et al., 2011; Nuechterlein et al., 2004; Tamminga, 2006), learning (Allott et al., 2011; Bowie & Harvey, 2005; Nuechterlein et al., 2004; Reichenberg, 2010; Tamminga, 2006), verbal comprehension (Nuechterlein et al., 2004), intelligence (Bowie & Harvey, 2005; Woodberry, Giuliano, & Seidman, 2008), attention/vigilance (Allott et al., 2011; Reichenberg, 2010; Tamminga, 2006), and executive functioning (Bowie & Harvey, 2005; Prentice, Gold, & Buchanan, 2007; Reichenberg, 2010). In a recent review, it was reported that schizophrenia patients performed at the lowest 5 to 10% of the general population on cognitive assessments (Keefe, 2007). Conversely, some studies have attempted to show preserved cognitive functions in schizophrenia, which may include attention, procedural memory, language abilities, perception, non-declarative memory and emotion processing (Gold, Hahn, Strauss, & Waltz, 2009; Reichenberg, 2010). Because of the broad range of impairment, the varying time points of illness that are studied, and potential effects of treatment, it has been proposed that subtypes of schizophrenia may exist that present with varying degrees of and domain-specific cognitive impairment, thereby accounting for some contradictory findings (A. S. Cohen et al., 2007; Mahurin, Velligan, & Miller, 1998).

Impairments in schizophrenia are frequently associated with the clinical phenotype, including correlations with positive symptoms (Bowie & Harvey, 2005; Sharma & Antonova, 2003), negative symptoms (Dibben, Rice, Laws, & McKenna, 2009; Donohoe & Robertson, 2003; Henry & Crawford, 2005; Liddle, 1987; Mahurin et al., 1998; Moritz et al., 2002; Sharma & Antonova, 2003; Ventura, Hellemann, Thames, Koellner, & Nuechterlein, 2009) and insight (Donohoe, Corvin, & Robertson, 2005; Shad, Tamminga, Cullum, Haas, & Keshavan, 2006). Notably, far more studies report association to negative symptoms than positive symptoms.

An important area of research is the potential ability for cognitive performance to predict outcome variables. Some have been able to describe relationships between cognition and the ability to obtain and maintain

employment (Bowie & Harvey, 2005; Kurtz, 2011; Meltzer, Thompson, Lee, & Ranjan, 1996), efficacy of cognitive-behavioural therapy (Kurtz, 2011), and functional outcome (Bowie & Harvey, 2005; Sharma & Antonova, 2003). The ability to predict the course of illness by a simple measurable process provides substantial advantage in the ability to appropriately treat the disorder.

Arguably, a defining feature of cognitive impairment in schizophrenia is the stability of these deficits throughout disease chronicity, from FEP to a chronic course (Bozikas & Andreou, 2011; Censits, Ragland, Gur, & Gur, 1997; Kurtz, 2005; Meltzer et al., 1996; Moritz et al., 2002; Sharma & Antonova, 2003; Weinberger & Berman, 1996). However, there are some contradictory findings. In a recent longitudinal study cognitive function improved in a schizophrenia sample at the same rate of improvement as in a HC sample (Szoke et al., 2008), while conversely, some have suggested that cognitive decline occurs from early- and late-high-risk states, through to FEP and a chronic course, with little stability (Pukrop & Klosterkotter, 2010). Treatment of cognitive symptoms has been challenging, as they have proven somewhat resilient to antipsychotic treatment (Weinberger & Berman, 1996). However, some investigations of atypical antipsychotics have provided evidence for mild improvement in cognitive deficits (Woodward, Purdon, Meltzer, & Zald, 2005). The general consensus is that not only is the course of cognitive impairment relatively stable, but many of the impairments are detectable in the prodrome prior to illness onset (Bowie & Harvey, 2005; Lencz et al., 2006; Lewandowski, Cohen, & Ongur, 2011; Sharma & Antonova, 2003). The cognitive performance of prodromal patients, individuals at high-risk for developing psychosis and first- and second-degree relatives of schizophrenia patients is currently being reviewed by many researchers. The interest primarily surrounds the potential ability for cognitive impairment to predict later development of frank psychotic symptoms. While there is substantial support for impairment in both genetic and clinical high-risk individuals (Lencz et al., 2006; O'Connor et al., 2009), others report that cognitive ability is intact in high-risk groups, and that cognitive impairment is a state, not trait, factor (Brewer et al., 2006; Pukrop & Klosterkotter, 2010). It is possible that these contradictory

findings are at least partially due to differences of definition, including definitions of cognitive domains, as well as definition of "high-risk". Not only do high-risk samples differ in specific risk (i.e., clinical or genetic), but the degree of risk also varies. As an example, "genetic high-risk" has been defined as offspring of parents with schizophrenia, a sibling of an affected individual, or even second-degree relatives. Clinical high-risk samples range from those with social or functional decline to those that are seeking treatment for psychotic episodes. It is also possible that different cognitive processes are implicated at different stages of the disease, with some more likely to precede illness onset (and therefore with more potential to predict conversion to psychosis), while others present after disease onset and may be more related to the phenotype.

Cognitive deficits are often cited as evidence in support of the neurodevelopmental model of schizophrenia, as little evidence of neurodegeneration accompanies the impairment, as seen in a disease like Alzheimer's disease (Tamminga, 2006). Some studies have begun to describe a relationship between specific cognitive dysfunction and neurochemical presentation. For example, elevated Glu has correlated with poor sustained attention, with the authors proposing that Glu might represent a potential endophenotype for schizophrenia (Purdon et al., 2008). This is supported by the strong association of cognitive impairment and activity in the dlPFC that is mediated partially by glutamatergic transmission (Lewis & Moghaddam, 2006). Further, while cognitive impairment used to be regarded as disruption of frontal lobe function, recent evidence is pointing to more globalized neural regions (Fioravanti, Carlone, Vitale, Cinti, & Clare, 2005), especially including the temporal lobe structures and networks of connectivity cortically and subcortically. Some correlation between cognitive performance and ventricle size, whole brain volume and temporal lobe structure sizes has been described, and may be specific to schizophrenia (Antonova, Sharma, Morris, & Kumari, 2004; Crespo-Facorro, Barbadillo, Pelayo-Teran, & Rodriguez-Sanchez, 2007). These reports of a relationship between cognitive impairment and neural structure and function

support the theory that cognitive impairment, at least in some domains, represents neural pathology and a potential underlying vulnerability to psychosis.

Some have argued that cognitive deficits in schizophrenia may have aspects that are unique and specific to schizophrenia, allowing for better differential diagnoses. Compared to affective disorders, cognitive impairments in schizophrenia are earlier, more severe and more independent from clinical presentation (Keefe & Fenton, 2007). Effect sizes of cognitive impairment in schizophrenia are also larger than in bipolar disorder (Bora, Yucel, & Pantelis, 2010). Similarly, schizophrenia patients present with worse cognitive functioning than those with schizoaffective disorder, especially true on tests of mental speed, working memory, and executive function (Bora, Yucel, & Pantelis, 2009), suggesting the cognitive impairment in schizophrenia might differentiate it from other mental disorders, and even from other psychotic disorders. Bora and colleagues (2010) suggest that early cognitive impairment in schizophrenia might also be a defining feature of schizophrenia. In a recent study, five measures were found to model the genetic liability to schizophrenia; each of these five measures was sensitive to schizophrenia, and not schizoaffective disorder or bipolar disorder with psychosis (Glahn et al., 2007). However, significant heterogeneity exists even within discrete schizophrenia populations (Fioravanti et al., 2005), and it may be that specific subtypes of schizophrenia will emerge with respect to cognitive impairments. Several studies identify a "deficit syndrome" thought to represent a unique pathophysiology marked by persistent negative symptoms. These patients have been described as having more global impairment on neuropsychological assessments than non-deficit syndrome patients (A. S. Cohen et al., 2007). Others have identified the "cognitive dysmetria" concept as disruptions of thought and action, central to cognitive functioning that may present with more severe cognitive impairment (O'Leary et al., 2000).

Processing speed. Processing speed is an often over-looked aspect of impairment in schizophrenia, but has been garnering more attention in the last several years as the hunt for a suitable endophenotype continues. Several lines of evidence support processing speed deficits in schizophrenia. One recent meta-

analysis reported that the single largest impairment in schizophrenia was on the digit-symbol task, a measure of processing speed (effect size = -1.57; Dickinson et al., 2007). This was supported by a meta-analysis exclusively in FEP patients describing maximal deficits in processing speed and verbal memory, with two of the largest effect sizes for the Digit Symbol Substitution Test, and Stroop Colour and Word Test colour naming task (Mesholam-Gately et al., 2009). This finding has been replicated several times (Bora et al., 2010; Knowles, David, & Reichenberg, 2010; Palmer et al., 2009). In a meta-analysis only including studies with adequate statistical power, processing speed was the most predictive domain of later functional outcome (Allott et al., 2011). Processing speed was also the only cognitive domain that was able to differentiate children of schizophrenic parents from children of non-schizophrenic parents (Sharma & Antonova, 2003), and first- and second-degree relatives of schizophrenic patients from HCs (Glahn et al., 2007; Hilti et al., 2010; Laurent et al., 2000; Pukrop & Klosterkotter, 2010). In a similar vein, processing speed is the strongest cognitive domain at differentiating a high-risk group from HCs (Keefe et al., 2006; Ma et al., 2007; Niendam et al., 2006; O'Connor et al., 2009), at identifying a high-risk group that later converted to full psychosis (Keefe et al., 2006; Pukrop & Klosterkotter, 2010), and was the most sensitive measure to model genetic liability to schizophrenia (Glahn et al., 2007). In a recent meta-analysis, all 11 reviewed papers described slower processing speed in FEP and chronic schizophrenia, with no reported change over time (Townsend & Norman, 2004). Further, this impairment may be resilient to medication effects (Dickinson, 2008; Keshavan et al., 2010).

In schizophrenia, processing speed has been related to global functioning, autonomy, self-care, vocational outcome, social functioning and quality of life (Keshavan et al., 2010; Sanchez et al., 2009). For the impressive and substantial evidence that processing speed deficits exist prior to disease onset and its presence in first- and second-degree relatives, many have begun to single out processing speed as a strong potential endophenotype for schizophrenia. As such,

processing speed may also be able to identify individuals with an underlying pathology associated with risk for psychosis.

Executive function. Executive function in schizophrenia is one of the most often cited impairments. Some have reported that executive functioning impairments are the most enduring and difficult to treat symptom in schizophrenia (Eisenberg & Berman, 2010). In a meta-analysis, executive function impairment in schizophrenia was approximately 1.5 standard deviations below HCs, and worse than other psychiatric control groups (Johnson-Selfridge & Zalewski, 2001). While impairments of executive function are consistently reported in FEP and chronic patients, dysfunction in the prodrome is inconsistently reported, at best (Breton et al., 2011; Chkonia et al., 2010; Giakoumaki, Roussos, Pallis, & Bitsios, 2011). At least one study described impairments in relatives of schizophrenia patients on the WCST, and suggested that executive function is a potential endophenotype (Birkett et al., 2008), though supporting evidence is lacking.

Executive function is associated with hypofrontality (Minzenberg et al., 2009), often with specific reference to the dlPFC (Eisenberg & Berman, 2010). Several studies support a role for the PFC in executive functioning, and in some cases more specific tasks are localized to specific regions, such as decision-making and organizing behaviour to the OFC (Antonova et al., 2004; Schoenbaum, Roesch, & Stalnaker, 2006), guessing in the ventromedial PFC (Elliott, Rees, & Dolan, 1999), learning and inhibition in the ACC (Antonova et al., 2004; Ohrmann et al., 2008) and abstraction and flexibility in the dlPFC (Antonova et al., 2004), as examples. Determining the neural correlates of executive functioning is difficult given the diverse processes encompassed within this single domain. Successful executive functioning may not be specific to the frontal lobes (S. W. Anderson et al., 1991), but may involve subcortical structures as well. Supporting this, the basal ganglia has been associated with goal-directed behaviour, the temporal lobe and hippocampus have correlated with executive function (Antonova et al., 2004), and amygdala volume is also associated with executive function (Rusch et al., 2008). In a study examining HCs, executive

functioning activated the dlPFC, ventrolateralPFC, ACC and thalamus; a similar network was activated in schizophrenia patients but with less activation in the dlPFC and ACC (Minzenberg et al., 2009). Executive functioning has also correlated with some neurochemical findings. Ohrmann and colleagues (2008) observed a correlation between NAA and WCST performance in the dlPFC in HCs, but failed to find a similar pattern in schizophrenia patients. Poor WCST performance was also associated with increased Glu in the hippocampus of schizophrenia patients, but not in HCs, with no correlations apparent in the dlPFC (Rusch et al., 2008).

Executive functioning is so multidimensional that it is difficult to determine if more specific factors are individually contributing to the global deficit (Donohoe & Robertson, 2003; Kosmidis, Bozikas, Zafiri, & Karavatos, 2006). Freedman and Brown (2011) suggested that by better understanding executive function in schizophrenia, one has the opportunity to better understand factors that could modify the course of the illness, but that this requires better instruments and techniques at capturing the specific components of the domain.

Cognitive impairment in substance abuse and dependence.

As substance misuse encompasses many different types of substances and each substance has a unique mechanism of action, it is likely that cognitive domains are affected in a unique way for each substance. Further, because substance dependence itself is characterized by a loss of control over behaviour, several domains are more strongly implicated than others, including inhibitory mechanisms, decision-making, memory, attention, and learning (Weinstein & Cox, 2006). Some have even defined substance dependence as usurpation of learning and memory (Hyman, 2005).

Cannabis abuse and dependence has been associated with impairment of learning, executive functioning, working memory, attention, processing speed, verbal memory, response inhibition, decision-making and motor coordination (Lundqvist, 2005; Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2002; A. D. Schweinsburg, Brown, & Tapert, 2008; Solowij & Battisti, 2008; van Holst & Schilt, 2011; Vik, Cellucci, Jarchow, & Hedt, 2004; Yucel, Lubman, Solowij, &

Brewer, 2007). Some studies have reported that cognitive impairments are only present in current cannabis users, not former users (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011), though contradictory findings exist (e.g., Hanson et al., 2010). MDMA abuse and dependence has also been associated with deficits in executive functioning, verbal learning and memory, distraction, focusing, reaction time, flexibility, attention, processing speed, episodic memory, self-control, semantic recognition, verbal reasoning, and impulsivity (Kalechstein, De La Garza, Mahoney, Fantegrossi, & Newton, 2007; Lundqvist, 2005; van Holst & Schilt, 2011; Vik et al., 2004; Yucel et al., 2007). Meta-analyses on MDMA research, however, have reported only small to medium effect sizes (Kalechstein et al., 2007). Cocaine abusers have presented with impairments on executive functioning, flexibility, verbal memory, attention, learning, reaction time, verbal fluency, visual memory, working memory, language, sensory perception, visuospatial ability and abstraction (Jovanovski, Erb, & Zakzanis, 2005; Lundqvist, 2005; van Holst & Schilt, 2011; Vik et al., 2004; Yucel et al., 2007). Some have reported that the single largest effect size, and therefore the largest impairment, is in the domain of attention, implicating involvement of the ACC (Jovanovski et al., 2005). Reported spared domains in cocaine misuse include construction ability, verbal fluency and long term memory (Vik et al., 2004).

The class of amphetamines is particularly interesting because acute small doses of amphetamines are known to improve some cognitive functioning, including attention and focus (Cruickshank & Dyer, 2009; Nordahl, Salo, & Leamon, 2003). Therefore, stimulants are used as clinical treatment for problems of attention, like attention deficit hyperactivity disorder (Advokat, 2010). Of course, the acute effects of amphetamines differ from effects of chronic use (Simon et al., 2002). MA dependence is associated with several impairments of cognitive function. MA abusers have deficits of executive functioning, verbal memory, planning, learning, delayed recall, processing speed, working memory, visual memory, visuospatial skills, attention, reaction times, decision-making, spatial working memory, recognition memory, verbal fluency, motor skills, recall,

abstract reasoning, shifting strategy, episodic memory, language ability, visuoconstruction and delay discounting (Barr et al., 2006; Chang et al., 2002; Chung et al., 2007; Ersche & Sahakian, 2007; Gonzalez, Bechara, & Martin, 2007; Kalechstein, Newton, & Green, 2003; S. J. Kim et al., 2006; London et al., 2005; Lundqvist, 2005; Maxwell, 2005; Monterosso et al., 2006; Monterosso, Aron, Cordova, Xu, & London, 2005; Moon, Do, Park, & Kim, 2007; Nordahl et al., 2003; Ornstein et al., 2000; Paulus et al., 2002; Paulus, Hozack, Frank, Brown, & Schuckit, 2003; Rogers et al., 1999; Salo et al., 2005; Salo et al., 2007; Salo et al., 2002; Scott et al., 2007; Thompson et al., 2004; van Holst & Schilt, 2011; Vik et al., 2004). MA has been associated generally with a 40% prevalence of global neuropsychological impairment (Barr et al., 2006). Observations of executive functioning impairment are the most inconsistent, likely because executive function measures cover an array of cognitive abilities. For example, MA users showed no impairment on the WCST as compared to HCs (S. Grant, Contoreggi, & London, 2000), as well as no impairments of reaction time (Scott et al., 2007) or implicit attention (Salo et al., 2008). In a meta-analysis of neurocognitive performance of MA users, the largest effect sizes were for learning and memory, with medium effect sizes for processing speed and motor skills, and small effect sizes for attention, working memory, visuoconstruction and language. In this study, duration of time abstinent correlated with effect size, suggesting some recovery in protracted abstinence (Scott et al., 2007). MA users also had larger effect sizes than cocaine or cannabis users (Scott et al., 2007; Simon et al., 2002). Interestingly, a few studies have described potential for protective factors of cannabis use in poly-drug use. MA users who concurrently used cannabis had better cognitive performance than those who did not concurrently use cannabis; both groups though, performed worse than HCs (Gonzalez et al., 2004).

Cognitive impairments associated with substance abuse and dependence are inconsistently related to drug use patterns. Some studies have been able to define relationships between severity of cognitive deficit and frequency of use, dose, or age at first use (Monterosso et al., 2005; Solowij & Battisti, 2008). Some

have reported that cognitive impairment is a predictor to relapse to drug use (Garavan & Hester, 2007), as intact executive functioning, particularly inhibitory control, memory and attention, is critical to maintaining abstinence (Weinstein & Cox, 2006). In MA users, cognitive impairment may relate to duration of time abstinent (Scott et al., 2007), frequency of use (Simon et al., 2000), or amount of use (Monterosso et al., 2005), but conversely many fail to observe a relationship with substance use patterns (Chang et al., 2002; Hoffman et al., 2006).

Several neuroimaging studies, particularly fMRI, have attempted to locate the neural correlates of the cognitive deficits in substance dependence. Reward processing, in general, is associated with the striatum and frontal connectivity, primarily through dopaminergic transmission. In substance dependence, decreased DA release in the striatum and projections to the OFC are involved in the reinforcing effects of drug use and implicated in the cognitive disruptions mediated by the PFC (Chang & Haning, 2006). Dissociation between the PFC and limbic regions of the brain is anticipated in substance dependence because of the apparent impulse control impairments (Fishbein et al., 2005). Impairments of executive functioning implicate the PFC, as well as reciprocal connections between frontal and subcortical regions including the hippocampus, amygdala, limbic system and striatal areas (Crews & Boettiger, 2009; Yucel et al., 2007). Volume loss in regions associated with executive function has also been reported in substance use; a dose-dependent relationship may exist in frontotemporal and frontoparietal regions (Yucel et al., 2007). Abnormal blood flow in the PFC and NAA levels in the PFC and ACC have also been associated with cognitive performance in substance abusers (Salo et al., 2007; Yucel et al., 2007). Changes in cognitive function may be due to long lasting changes of dendritic branching in the NAc, parietal cortex and PFC (Ornstein et al., 2000). In MA abusers specifically, performance on an executive function task correlated with WM integrity in the PFC (Chung et al., 2007), GM density in the mPFC (S. J. Kim et al., 2006), and less activation of the OFC, dlPFC and ACC as compared to HCs (Paulus et al., 2002; Paulus et al., 2003). A vigilance task correlated negatively with ACC activation in MA users, whereas a positive relationship was reported in

HCs (London et al., 2005). Generally, cognitive impairment in substance-dependent disorders likely involves cortical-subcortical connections that align with reward processing pathways, mediated by dopaminergic and glutamatergic changes, in some cases exacerbated by toxicity of the specific substance.

One obstacle in the study of cognition in substance dependence is the difficulty in determining which deficits may have predated the substance use (rendering an individual more vulnerable to use substances), which deficits may accompany acute use or acute withdrawal, and which deficits may emerge during use and persist into prolonged abstinence. Many studies have demonstrated a recovery of cognitive performance in abstinence (Barker, Greenwood, Jackson, & Crowe, 2004; Fernandez-Serrano et al., 2011; Stewart, 2005; van Holst & Schilt, 2011), while some studies failed to demonstrate recovery (Pope et al., 2002; A. D. Schweinsburg et al., 2008). Likely, some domains recover in abstinence, while others do not (Verdejo-Garcia, Bechara, Recknor, & Perez-Garcia, 2006), as in the meta-analysis in cannabis users describing cognitive performance of long-term abstinent cannabis users as normal in every domain except learning and forgetting (I. Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). In MA users, there are inconsistent findings about recovery in abstinence. A meta-analysis reported that duration of time abstinent correlated with cognitive performance, but there were also some indications that cognitive performance actually worsens in initial stages of abstinence (Scott et al., 2007). In a study examining varying time points in abstinence from MA abstinence there was some evidence of cognitive improvement at 3 months, particularly in inhibitory control, but word recall remained impaired at 6 month follow-up (Simon, Dacey, Glynn, Rawson, & Ling, 2004). This same study reported that the best neuropsychological performance was by the currently using group, followed by a group that had achieved abstinence but relapsed, and finally, followed by the group maintaining abstinence (Simon et al., 2004). It may be that as dopaminergic transmission recovers to normal in abstinence, that this recovery process is also related to recovery of cognitive function (Ersche & Sahakian, 2007).

Cognitive impairment in comorbid disorders.

Very few studies have thoroughly investigated cognitive performance of comorbid disorders. In fact, individuals with a dual diagnosis of a psychiatric illness and a substance abuse or dependence disorder are most frequently excluded from research on either schizophrenia or substance dependence separately, with researchers commonly citing the need to control for confounding factors as a rationale for such exclusion. It is theorized by many (e.g., Nixon, Hallford, & Tivis, 1996), however, that substance use concurrent with a psychosis-spectrum illness would have a deleterious effect on cognitive performance, due to the neurotoxic effects of substances in the brain, and the relationship of substance abuse or dependence and cognitive impairment in the absence of a psychiatric disorder. Contrary to this hypothesis, however, the few studies investigating this claim have most consistently failed to support an additive effect of substance use on cognition, and in some cases comorbid substance dependence in schizophrenia may actually improve performance in some cognitive domains (Addington & Addington, 1997; Benaiges, Prat, & Adan, 2010; Carey, Carey, & Simons, 2003; Copersino et al., 2004; Herman, 2004; Nixon et al., 1996; Pencer & Addington, 2003; Potvin, Joyal, Pelletier, & Stip, 2008; Smelson et al., 2002; Thoma, Wiebel, & Daum, 2007; Wobrock et al., 2007). Specific cognitive domains that may be improved by comorbid substance dependence include processing speed, memory, and motor skills. Additionally, some studies have reported no difference in individuals with schizophrenia who are current users of cocaine as compared to those who are remitted users of cocaine, suggesting that any cognitive effects are not due to the acute use of the substance (Peer, Bennett, & Bellack, 2009). It may be that individuals with schizophrenia who misuse illicit drugs have intact executive functioning skills and social cognitive skills that are necessary to seek out and obtain the drugs, accounting for the unexpected finding (Thoma et al., 2007). Other theories are that cognitive impairment in schizophrenia is so substantial and diversified that the addition of substance use offers no further impairment (Peer et al., 2009). Alternatively, methodological differences could account for the discrepancy

(Nixon et al., 1996). Subtypes of schizophrenia may offer varying patterns of cognitive impairment (Benaiges et al., 2010). Sample size effects, gender effects and instruments used could also account for these unexpected findings. Still, some studies do describe additional impairment in dually diagnosed individuals with schizophrenia and substance dependence, including in the ability to learn and recall verbal information (Bowie & Harvey, 2005; Serper et al., 2000; Serper, Copersino, Richarme, Vadhan, & Cancro, 2000; Sevy, Kay, Opler, & van Praag, 1990), motor skills (Smelson et al., 2003), working memory (Potvin et al., 2008) and impulsivity (Duva, Silverstein, & Spiga, 2011). Only one group reported worse cognitive impairment in schizophrenia with comorbid alcohol dependence in several domains, suggestive of an additive effect (Manning et al., 2009; Manning et al., 2007). In a recent meta-analysis investigating the neuropsychological impairment of MA-induced psychosis compared to paranoid schizophrenia, no single cognitive difference existed between the two groups (Jacobs, Fujii, Schiffman, & Bello, 2008).

Most studies that investigate cognitive performance of comorbid samples primarily focus on a schizophrenia sample with and without comorbid substance use. The other, less examined perspective involves a sample of substance-dependent individuals with and without symptoms or diagnoses of psychosis. This alternative perspective may offer new insight into cognitive deficits specific to the effects of psychotic symptoms. Given that cognitive impairment in stimulant dependence is to a lesser degree than in schizophrenia, stimulant-dependent users with symptoms of psychosis may present with cognitive impairment related to that psychosis and therefore more comparable to a NSIP sample than to their non-psychotic stimulant-dependent counterparts.

Chapter 2: Project Model and Hypotheses

Model

There is an irrefutable association between drug dependence and mental illness, though the direction of the association is challenging to clarify. The ambiguity in causation is particularly problematic in regard to stimulant use and psychosis because many stimulants can induce relatively persistent psychotic states that appear to mimic the symptoms of paranoid schizophrenia. Alternatively, substance use may be a trigger for the onset of psychosis in an individual with a pre-existing vulnerability.

MA use can lead to the development of psychotic symptoms that are nearly indistinguishable from paranoid schizophrenia (Dore & Sweeting, 2006). MA-induced psychosis presents with varying clinical courses; in most cases, the symptoms dissipate with abstinence, typically within the first 10 days (Sato, Numachi, & Hamamura, 1992; Ujike & Sato, 2004; Zorick et al., 2008) without the need for treatment or intervention. These transient symptoms are most likely related to the acute and withdrawal effects of MA. However, up to 30% of MA users develop a persistent psychotic disorder (Hall, Teesson, Lynskey, & Degenhardt, 1999; McKetin et al., 2006). In a smaller proportion of cases psychotic symptoms that develop during use persist beyond 1 month of abstinence and persist indefinitely (Sato et al., 1992; Ujike & Sato, 2004). These individuals are often treatment-seeking, and are treated according to the same guidelines as NSIP. The DSM-IV-TR states that psychotic symptoms are not, in fact, substance-induced if symptoms persist "for a substantial period of time (i.e., a month or more) after the end of Substance Intoxication or acute Substance Withdrawal" or if "the development of symptoms are substantially in excess of what would be expected given the type or amount of the substance used or the duration of use" (American Psychiatric Association, 2000, p. 339). Clarification of these terms is not provided.

It may be that stimulant drug users who develop a persistent psychotic disorder share a core pathological vulnerability predisposing them to psychosis. To date, there is a lack of research investigating why some MA users develop

psychosis and others do not. Several recent studies have offered preliminary data suggesting a number of potentially relevant demographic, psychological, familial and biological factors that may contribute to the risk of persistent symptoms of psychosis among MA users. Risk of psychosis appears to be greater among individuals with a younger age at first use (Chen et al., 2003), increased quantity of use (Chen et al., 2003), preference for injection as a method of administration (Hall et al., 1996), premorbid schizoid or schizotypal traits (Chen et al., 2003), a high familial morbid risk of mental health disorders (Chen et al., 2005), decreased DA-transporter levels (Ujike et al., 2003), abnormal cerebral blood flow (Iyo et al., 2004), abnormal metabolite concentrations in the basal ganglia (Iyo et al., 2004), and genetic polymorphisms (Iyo et al., 2004; Ujike et al., 2003). Further, severity of psychotic symptoms may be related to earlier and longer exposure to stimulants (Lichlyter, Purdon, & Tibbo, 2010). Some of these factors suggest a critical developmental period that is most susceptible to the deleterious effects of stimulant exposure, however the specific developmental processes encompassed in this period are unknown.

In many substance-dependent individuals, experimental substance use begins in early adolescence and progresses to a dependent nature. Adolescence is a critical period of neural, cognitive, and social development, such that potent exogenous stimulation of developing brain regions has the potential to disrupt normal maturation. For this reason, the age of onset of substance use may be a critical factor in the functional outcome of a user (Squeglia et al., 2009; Yucel & Lubman, 2007; Yucel et al., 2007). Neurodevelopment in adolescence and early adulthood involves synaptic refinement and myelination that serve to improve WM integrity, improving connectivity in the brain, and improving the efficiency of that connectivity, allowing for better top-down control (Squeglia et al., 2009). In normal development these neural changes correlate with improved cognitive functioning (Crews & Boettiger, 2009). Disruption of this development is likely to affect cognitive performance. With the frontal lobes the last to develop, use of potent substances during this critical time period may disrupt natural development affecting the PFC (Squeglia et al., 2009), preventing the immature brain from

developing. The immature brain is less efficient at frontal activation (Crews & Boettiger, 2009), likely to manifest as impairment of executive planning and decision-making. In addition, some previous reports suggested that increased quantity of MA use may be related to emergence of psychotic symptoms (Chen et al., 2003). It may be that MA use can only trigger psychosis if a minimum threshold of use is achieved. Given that the precise self-report post-hoc assessment of quantity of MA used is difficult to accurately quantify (Chang et al., 2005), duration of time as a regular user and frequency of use may better represent a continuum of use severity that could encompass a critical threshold of use. Along this line, injection use (as opposed to other methods of drug administration) has been related to presentation of psychotic symptoms (Hall et al., 1996), however the authors propose no mechanism for this association. It may be that injection of stimulants allows the neuroactive substances to cross the blood brain barrier so rapidly that it allows for more potent neural stimulant than can be achieved through other means of administration.

Currently, the biological differences between *de novo* schizophrenia and MA-induced psychosis are not fully understood. Biological and cognitive investigation of psychotic symptoms among stimulant abusers offers an opportunity to investigate etiological differences in the development of psychosis, and an opportunity to contribute to the understanding of known risk factors for the disorder.

One theory for the development of psychosis, described earlier, is the neurodevelopmental hypothesis that posits that aberrant events *in utero* or perinatally may contribute to later life onset of psychosis. During a critical developmental period, possibly in adolescence or young adulthood, abnormalities in normal maturational events, like neuron pruning and myelination may contribute to the development of psychosis by affecting neurotransmitter function and neural structure development. These abnormalities may be precipitated by exogenous triggers. Some variations on the neurodevelopmental hypothesis suggests that after abnormal early-life events, like obstetric complications, a "second hit" may be necessary to trigger psychosis. A "two-hit" model of

psychosis has been presented, which posits that a "first hit" disrupts the trajectory of normal neural development, rendering the brain vulnerable to a "second hit" that precipitates the onset of psychosis. This theory is supported by the high degree of heterogeneity in schizophrenia with varying symptom presentation, functioning level, cognitive disruption and course of illness (J. E. Anderson, O'Donnell, McCarley, & Shenton, 1998; Bayer, Falkai, & Maier, 1999; Maynard, Sikich, Lieberman, & LaMantia, 2001). One group identifies four distinct factors (i.e., genes, early insult, drug use and social factors) and proposes that each represents a piece of the development of schizophrenia, and any combination of the four could comprise these two "hits" (Broome et al., 2005). The premise of this theory is that each "hit" on its own is insufficient to induce schizophrenia, but the combination of more than one risk factor, or "hit", is enough for the onset of schizophrenia. Cornblatt (2003) suggests that an underlying neuropathological vulnerability is necessary but not sufficient for the development of psychosis, and that full disease expression may require a trigger, such as an environmental or biological stressor. Heavy and/or chronic stimulant use may represent a "second hit" and thereby, an exogenous trigger for psychosis.

Stimulants affect neurotransmitter function (particularly DA), and there is some evidence that stimulants may have an effect on neuronal integrity, as measured by ^{1}H-MRS NAA values (Licata & Renshaw, 2009). Both DA and NAA changes are possible mechanisms for the disruption of neural development. Support for stimulants as potential exogenous triggers includes evidence of a dose-response relationship between severity of substance use and prevalence of psychotic symptoms (Smith, Thirthalli, Abdallah, Murray, & Cottler, 2009), a relationship between the quantitative amount of MA measured in the body after use and severity of presenting psychosis (Batki & Harris, 2004), and a relationship between severity of psychotic symptoms in stimulant users and earlier and longer exposure to stimulants (Lichlyter et al., 2010). Drugs of abuse may be sufficient to induce neuropathological change associated with schizophrenia, or may work in concert with other endogenous or exogenous events. It may be that stimulant users who develop a persistent psychotic disorder

exhibit neuropathology similar to individuals who develop NSIP (Sato et al., 1992). Dopaminergic disturbance in the NAc, for example, has been reported in both schizophrenia and stimulant dependence (Zorick et al., 2008). Stimulants are known to alter dopaminergic transmission in the mesocorticolimbic pathways, with increases up to 35-fold over baseline levels, which stimulate DA release-inhibiting autoreceptors resulting in a hypodopaminergic state (Grace, 2000). In schizophrenia DA also has a well-established role (for review see Stahl, 2008). These overlapping pathologies between stimulant dependence and schizophrenia support the hypothesis that stimulant dependence may be a sufficient exogenous trigger for the onset of psychosis in an already vulnerable brain, where stimulants are able to mimic aberrant neurochemical function that relate to the presentation of symptoms in schizophrenia. Given this assumption, one would expect stimulant users with this vulnerability to develop persistent psychotic symptoms that present phenotypically, cognitively and biologically similarly to a NSIP comparison group.

Neurochemistry.

In this study ^{1}H-MRS was used as a measure of *in vivo* neurochemicals. The Glu hypothesis of schizophrenia is described earlier (for review see Coyle, 2006a). Abnormal Glu levels in the human brain are concerning because excess Glu is neurotoxic and can lead to neurodegeneration (Goff & Wine, 1997) that may be associated with emergence of various symptoms, including cognitive decline. Evidence of Glu in schizophrenia suggests progressive change throughout development of the disorder (Bernier & Tibbo, 2010). Glu may be elevated in individuals at high-risk for developing psychosis, which leads to excitotoxic damage, ultimately rendering a hypofunctioning glutamatergic state in a chronic course of schizophrenia and affecting dopaminergic function (D. A. Baker, Cornish, & Kalivas, 2003) that may relate to the presentation of positive symptoms. To date, evidence in FEP has been mixed. Many of these studies vary in methodology and voxel location so that full acceptance of the theory of a progressive change in Glu in schizophrenia is not possible without further support.

Glu is also a major contributor to the neuroplastic changes in substance dependence. Given that substance dependence itself involves neuroplastic alterations within the brain, it is plausible that Glu is implicated in dependence pathology as a regulator of learning and plasticity (Harris & Aston-Jones, 2003). Several studies have demonstrated that both acute and chronic stimulant administration can increase Glu in the reward pathways, particularly in the NAc (Cornish & Kalivas, 2000; Harris & Aston-Jones, 2003; Pierce et al., 1996; M. S. Reid & Berger, 1996). It is with chronic stimulant use that the reward pathways rely less on DA-based signaling and Glu takes on a more primary role (D. A. Baker, McFarland et al., 2003; Pierce et al., 1996). ^{1}H-MRS-specific studies of Glu in substance dependence are generally lacking in number, but one study suggested that Glx levels are reduced in early abstinence and relate to MA craving (Ernst & Chang, 2008). Glu clearly plays a role in both schizophrenia and stimulant dependence, but the potential involvement of Glu in the emergence of psychosis in stimulant users has not been investigated.

Another relevant neurochemical measured by ^{1}H-MRS is NAA. NAA is often regarded as a marker for neuronal integrity where increases suggest increased size or density of neurons (Bracken et al., 2011). It is possible that due to early life events affecting brain development, NAA may be a marker of a vulnerable brain state. Several studies support reductions of NAA in the PFC in chronic schizophrenia (e.g., Ohrmann et al., 2005). Results in FEP are less consistent but global reductions of NAA have been described (Bustillo et al., 2008). In substance dependence, reductions of NAA have been observed in the PFC (Licata & Renshaw, 2009), with varying reports of normalization during abstinence. Several studies have reported no difference in NAA in stimulant users with prolonged abstinence as compared to HCs (Nordahl et al., 2005; Sung et al., 2007). Some have suggested that NAA has potential as a biomarker for schizophrenia; it has not yet been examined if this finding is also present in stimulant-induced psychosis.

Another neurochemical measured by ^{1}H-MRS in this study is Cr. ^{1}H-MRS studies focussing on Cr are fewer because it was often used a reference value for

other neurochemicals, given that it was assumed to be a stable compound. Most findings of Cr in both chronic and FEP report negative results (Bernier & Tibbo, 2010); similar negative findings are reported in studies of stimulant use (Licata & Renshaw, 2009). Though not yet described in current published literature, there is no reason to suspect that Cr would be affected in stimulant-induced psychosis.

Yet another quantified metabolite, Cho, is involved in the synthesis of phospholipids, and is regarded as a marker of cell membranes. Increases of Cho have been reported in abstinent MA users (Ernst et al., 2000; Nordahl et al., 2005; Salo et al., 2007) that may normalize with prolonged abstinence (Nordahl et al., 2005). Nordahl and colleagues (2005) propose that elevations of Cho in early abstinence may be due to gliosis, membrane synthesis or release of Cho associated with acute damage to the membrane. They propose that this process slows in sustained abstinence, thus normalizing levels of Cho. The described pathology associated with schizophrenia does not indicate a change in cell membrane synthesis, thus reports of Cho are usually negative in both chronic and FEP populations (Bernier & Tibbo, 2010). Elevations of Cho are a unique aspect of substance dependence that is unlikely to play a role in the development of psychotic symptoms.

Cognition.

Schizophrenia is associated with a wide range of cognitive impairment. A search is on-going for a cognitive endophenotype that may be able to predict conversion to psychosis, or differentiate high-risk individuals from HCs. A recent meta-analysis reported that in FEP cognitive impairments are broad, and approach or match those of chronic schizophrenia with the greatest impairments in immediate verbal memory and processing speed (Mesholam-Gately et al., 2009). Processing speed has been identified as one of the most sensitive measures able to differentiate a group at clinical high-risk for developing psychosis from HCs (Pukrop & Klosterkotter, 2010; Seidman et al., 2010). Pukrop and Klosterkotter (2010) have provided evidence for a continuous decline in processing speed performance with best performance in HCs, followed by individuals in an early high-risk state, individuals in a late high-risk state, FEP, and finally chronic

schizophrenia. This progressive change may demonstrate that processing speed impairments are present early in the illness, as a potential endophenotype, but worsen at illness onset. Processing speed is consistently one of the top three largest effect size deficits in schizophrenia (Dickinson et al., 2007) and with this disproportionate deficit compared to other domains, processing speed may show some specificity to schizophrenia (Dickinson, Ragland, Gold, & Gur, 2008). Processing speed was one of the first factors proposed with strong potential as a cognitive endophenotype (Nuechterlein, 1986) and may be a potential endophenotype directly related to a vulnerable brain state, supporting the neurodevelopmental hypothesis. Abstinent MA users also have moderate impairment in processing speed (Scott et al., 2007), but to a lesser magnitude than in schizophrenia(Goldstein et al., 2004). Processing speed may be a cognitive domain that could differentiate substance users at risk of developing psychosis.

Executive function is another domain commonly described as impaired in schizophrenia, most frequently measured with the WCST. The same meta-analysis described earlier reported a large impairment in executive function in FEP (Mesholam-Gately et al., 2009), but there are several negative findings of executive function impairment in individuals at-risk for psychosis (Brewer et al., 2005), and executive functioning has not been identified as having power in predicting conversion to psychosis (Pukrop & Klosterkotter, 2010; Seidman et al., 2010). Impairment of executive functioning may be one of the core symptoms of schizophrenia, with little value in predictive validity (Battaglia et al., 1994). As such, executive functioning may be related to the disease state, and less related to a specific neurodevelopmental pathology contributing to disease onset. Abstinent MA users have also presented with moderate impairment on the WCST (Scott et al., 2007). Executive function is likely related to the phenotype of schizophrenia and due to the impairments of executive function present in stimulant dependence, likely has less power in identifying stimulant users at risk for psychosis.

It is possible that abnormal neurodevelopment associated with early-life brain insults or specific genotypes causes pathological alterations in specific brain regions associated with specific cognitive processes. These specific impairments

are then measurable and may differentiate an at-risk group from HCs. These abnormal developmental trajectories and cognitive phenotypes are likely to affect neurochemical presentation as well, particularly NAA and Glu. Support for this theory comes from studies describing a relationship between NAA and cognitive performance (Ohrmann et al., 2008; Ohrmann et al., 2006; Ross & Sachdev, 2004; Tanaka et al., 2006), and studies describing a relationship between Glu and cognitive performance (Purdon et al., 2008).

Conversely, some research has suggested that some cognitive deficits are related to the emergence of symptoms in psychosis and not the developing psychopathology (Goldberg et al., 1993), so that cognitive impairment develops as a symptom of schizophrenia with a similar trajectory as the positive symptoms. It is likely that both of these theories are true, that cognitive impairment can differentially represent both an endophenotype for psychosis, as well as a symptom of psychosis, dependent on the specific domain. Supporting this, NAA has also been negatively associated with symptom presentation (Premkumar et al., 2010; Sigmundsson et al., 2003), with most consistent evidence for an association with negative symptoms in high-risk subjects, FEP and chronic schizophrenia (Aydin, Ucok, & Cakir, 2007; Aydin et al., 2008; Callicott et al., 2000).

For this study the standardized score of the Stroop Colour and Word Test colour reading measure was used as the primary measure of processing speed, with support from the TMT-A and Digit Symbol Substitution Test. The age-standardized WCST perseverative error measure was used as the primary measure of executive function, with support from the Stroop Colour and Word Test interference measure and TMT-B.

Negative symptoms.

The negative symptoms of schizophrenia are an ideal measurable phenotype to investigate potential underlying vulnerability to psychosis. Negative symptoms may be more related to the risk of developing schizophrenia than the positive symptoms. This risk may be the genotype associated with the disease, or an alternative risk trajectory, like obstetric complications. Negative symptoms are more related to obstetric complications and later development of schizophrenia

than positive symptoms (Rector et al., 2005). Negative symptoms have also been related to left-handedness and left-eye-dominance, providing support that negative symptoms may be associated with schizophrenia neuropathology, in support of a neurodevelopmental model (Gureje, 1989). Supporting this theory, high-risk subjects who later converted to psychosis had greater premorbid negative symptoms than those at high-risk who did not convert (Brewer et al., 2005). Further, negative attitudes toward social affiliation were the only self-report measure able to differentiate relatives of schizophrenia patients from relatives of other psychiatric groups (Rector et al., 2005), suggesting that negative symptoms might also be unique to psychosis-spectrum disorders.

Negative symptoms have consistently correlated positively with cognitive impairment. Relevant to the current study, the effect of processing speed on functional outcome in schizophrenia was mediated by negative symptoms (McDowd, Tang, Tsai, Wang, & Su, 2011). As well, processing speed impairment correlated positively with negative symptoms and predicted residual negative symptoms in a 1 year follow-up of schizophrenia patients (Leeson et al., 2010). There is much stronger evidence supporting a relationship between negative symptoms and general cognitive function than positive symptoms (de Gracia Dominguez, Viechtbauer, Simons, & Van Os, 2009; Leeson et al., 2010; Niendam et al., 2006; O'Leary et al., 2000; Pantelis, Stuart, Nelson, Robbins, & Barnes, 2001; Townsend & Norman, 2004; Ventura et al., 2009). Negative symptoms are less frequently associated with executive function impairment (de Gracia Dominguez et al., 2009; O'Leary et al., 2000; Pantelis et al., 2001). Of direct relevance, in stimulant users with psychotic symptoms, negative symptoms related to severity of cognitive impairment (Lysaker, Bell, Bioty, & Zito, 1997). Given that cognitive impairment, which is postulated to arise from region-specific pathology, is associated with negative symptoms suggests that negative symptoms may represent a measure of underlying neuropathology, or vulnerability. For these reasons, negative symptoms are the most suitable measurable clinical phenotype to best represent a potential pre-existing neuropathology and underlying

vulnerability to psychosis, and were used as the primary dependent variable in analysis.

Comorbid symptoms as measured by self-report assessment of anxiety and depression were assessed as covariates because a portion of negative symptoms as measured by the PANSS may also represent an affective disorder. Further, by definition in the two-hit model, stimulant users should be psychosis prone. Therefore, two psychosis proneness scales were used to assess trait vulnerability.

Medial prefrontal cortex.

The mPFC was selected in this study as the region, or voxel, of interest in the ^{1}H-MRS imaging. The mPFC is used extensively in ^{1}H-MRS Glu research allowing for comparison to previously published data. The mPFC receives glutamatergic afferents from the thalamus as well as other cortical regions with structural imaging abnormalities in schizophrenia research (Tibbo et al., 2004) making it an ideal selection for the measurement of Glu in schizophrenia. The mPFC also provides a region of interest that yields high GM composition, which was a target for the current study because of the high density of Glu within GM. Several imaging modalities (fMRI, diffusion tensor imaging and voxel based morphometry) have provided evidence for abnormalities in the mPFC in schizophrenia (Pomarol-Clotet et al., 2010), including reduced GM and volume (Sigmundsson et al., 2001).

The frontal cortex is one of the last regions of the brain to fully develop, making it susceptible to pathological change during development (Keshavan & Hogarty, 1999; Knable & Weinberger, 1995). As an example, perinatal stress can affect development of the PFC, inducing long-lasting changes of dopaminergic transmission (Brake, Sullivan, & Gratton, 2000). In animal models, induced obstetric complications also affect dopaminergic transmission in the NAc that modulates activity and function of the PFC (Brake et al., 2000). Not only can *in utero* and perinatal events affect development and function of the mPFC, but chronic stress postnatally and throughout development can continue to affect this region. Chronic stress has led to dendritic remodeling of the mPFC, affecting inhibitory behaviour (Shansky & Morrison, 2009). There is strong evidence to

support a role for the mPFC in cognitive processes. In particular, decision-making abilities recruit the mPFC, where inhibitory responses are regulated (Paulus et al., 2002).

In addition, the mPFC has long been implicated in other mental health disorders like post-traumatic stress disorder and major depression. In these disorders the mPFC has a role in mood and emotion regulation (particularly negative affect), attention and concentration, perseveration and decision-making (Pomarol-Clotet et al., 2010; Shansky & Morrison, 2009). Logically then, the frontal regions are strongly associated with the negative symptoms of schizophrenia. Several studies have described reduced GM and WM volumes in various prefrontal regions that correlate with negative symptom severity (Gur et al., 2000; Martino, Bucay, Butman, & Allegri, 2007; Wible et al., 2001). Also, mPFC abnormalities may be responsible for some of the negative features of schizophrenia, as evidenced by a disruption of cingulate striatal connectivity producing a behavioural syndrome with negative features (Sigmundsson et al., 2001).

The mPFC is also implicated in stimulant abuse and dependence. The mPFC receives glutamatergic afferents from the dopaminergic cell bodies of the VTA, and is crucial for behavioural sensitization (such that lesions to the mPFC prevent its development). The implication is that subcortical activity is mediated by glutamatergic neurons in the mPFC (Cador, Bjijou, Cailhol, & Stinus, 1999).

The glutamatergic inputs, developmental trajectory, association with cognitive impairment and negative symptoms make the mPFC an ideal candidate region to investigate neurodevelopmental abnormalities associated with symptoms of psychosis, particularly through means of ^{1}H-MRS. It is also an ideal region to examine the potential interaction between cognitive function and neurochemical presentation.

Rationale for samples.

The samples assessed in this study were a HC group (without any history of psychiatric illness or substance abuse or dependence), a non-substance-induced FEP group (without a history of substance abuse or dependence), and an abstinent

stimulant-dependent user group. Within the abstinent stimulant-dependent user group, a separate group existed. Because MA was the primary stimulant of interest with relation to the development of psychotic symptoms, two groups were assessed: an abstinent MA-dependent group, and an abstinent cocaine-dependent group (without a history of MA use). This cocaine sample allowed for the examination of specificity of findings. Although cocaine has been related to psychosis in some cases, the prevalence is much less than in MA misuse (Thirthalli & Benegal, 2006). Similarly, the physiological mechanism of MA and cocaine differs, such that MA is a more potent stimulant with much more powerful effects on dopaminergic systems than cocaine; MA has a shorter latency from first use to chronic use and from first use to treatment seeking (Gonzalez Castro et al., 2000). It is proposed that MA would be a more powerful exogenous trigger on the neurodevelopmental pathology for the onset of psychosis than cocaine.

Summary.

The developing understanding of the etiology of schizophrenia is that it is not a singular, defined event, but rather the accumulation of several events. The neurodevelopmental hypothesis suggests that early life disruptions of normal development are related to later life psychosis. These early life disruptions to development may arise via pre-, peri-, or post-natal complications; they may also be a genetic make-up that affects development abnormally. These events, while necessary, are not sufficient for development of later life psychosis. Rather, a "second hit" or event may be a necessary trigger for psychosis onset. This second hit may be deficient rearing, environmental factors or any number of events or exposures that are yet identified. This "second hit" could also be exposure to potent stimulant drugs, like MA.

The advantage of this model is that is explains why the odds ratios or effect sizes are so small for any one etiological risk factor alone. For example the odds ratios for obstetric complications range from 1.6 to 2.4 (Geddes & Lawrie, 1995; Isohanni et al., 2004). Likewise, odds ratios reported from the Genome Wide Approach to Schizophrenia have been around 1.1 to 1.2 (Duan, Sanders, &

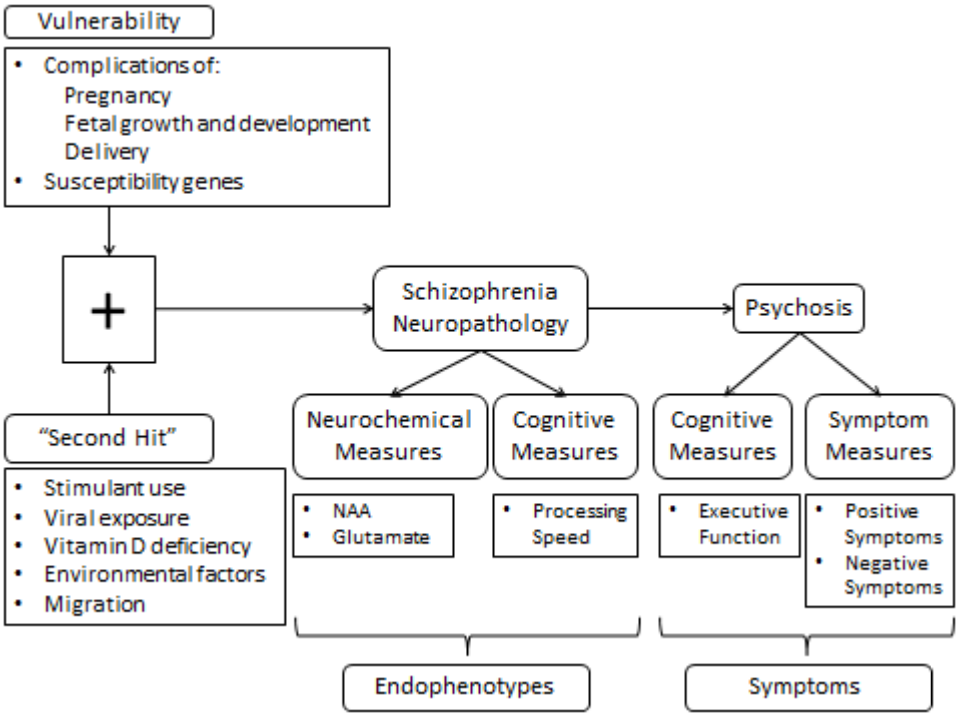
Gejman, 2010). While genes are associated with schizophrenia, no single gene has been identified that is solely sufficient for schizophrenia, and therefore, genes alone cannot account for the full phenotype of schizophrenia in a Mendelian way (Glahn et al., 2007). Although it has been reported that the single best predictor of schizophrenia is a family history, the fact is that most (~60%) of those who develop the disorder do not have a positive family history (Allen, Griss, Folley, Hawkins, & Pearlson, 2009), and replication of genetic risk factors has not been promising (Isohanni et al., 2004). It is the epigenetic events or experiences subsequent to an early developmental disruption that compound the effects of this abnormal development resulting in psychosis (Isohanni et al., 2004).

To test this model, MA use was proposed as a "second hit" that can trigger the onset of psychosis in an already vulnerable brain. Given that only a proportion of stimulant users will have a pre-existing vulnerability, this model also purports to explain why only some stimulant-dependent users develop symptoms of psychosis, while others do not. It is proposed that in those stimulant users where symptoms of psychosis develop the consequences of developing psychosis should mimic those present in psychosis that is not triggered by stimulant use. Further, endophenotypes for psychosis, given their relationship to genes, should be present in stimulant users who develop symptoms of psychosis, and not present in those who do not. In addition, drug use patterns may be a critical factor in the ability of MA to act as a second-hit trigger, therefore drug use thresholds were examined with respect to experienced symptoms of psychosis. Further, if MA use is a trigger for psychosis, cessation of use after the emergence of symptoms of psychosis should not result in attenuation of symptoms without treatment.

Figure 3 presents the overall proposed model for the project. For the development of psychosis an individual must have a pre-existing vulnerability. This vulnerability may be a genetic risk to schizophrenia, or a complication experienced *in utero*, peri- or post-natally whereby the development of the brain is affected. Second, an individual must experience a "second hit" causing that vulnerable brain to develop the pathology associated with schizophrenia. The second hit may be any of the individual risk factors that have been identified. This

list is extensive and only a few examples are shown in the figure, including migration, viral exposure, urban rearing, and chronic stress. In this study, it is proposed that MA use is one of the triggers that may cause a vulnerable brain state to develop psychosis. This study employed use of measures that are purported to be associated with the pathology of schizophrenia, including spectroscopy measures of NAA and Glu. It is also proposed that the cognitive impairment apparent in schizophrenia is likely derived from cognitive processes that both pre-date the onset of illness (potential endophenotypes) and that emerge post illness onset and are associated with the clinical phenotype. It is proposed that processing speed, due to substantial evidence in genetic and clinical high-risk studies, pre-dates the onset of illness and may be a marker for schizophrenia. Conversely, executive function has far more inconsistent evidence for pre-dating the illness and may more likely be a symptom, or consequence of developing symptoms of psychosis. These items, as well as the clinical symptoms of schizophrenia (i.e., positive and negative symptoms) were measured in this study.

Figure 3
Proposed Model



Research Objectives and Hypotheses

So few studies have compared the biological and cognitive correlates of MA-induced psychosis to NSIP that there is no agreement if these two psychosis subtypes may share a similar underlying pathological vulnerability that predates illness onset or if these two subtypes are different disorders altogether despite similar clinical presentation.

Research Objective 1: Drug use and severity of psychotic symptoms

Several reports have suggested that patterns of drug use are associated with the development of psychotic symptoms in stimulant users. Potential factors include a younger age at first use (Chen et al., 2003), increased frequency of use (Chen et al., 2003) and injection use (Hall et al., 1996). These findings have not been replicated and negative findings exist (e.g., McKetin et al., 2008). The lack of reproduction may be because drug use patterns, *per se,* are not directly related to severity of psychotic symptoms, but that any drug use is sufficient. Alternatively, the frequency, quantity, potency and timing of use may be critical to trigger the onset of psychotic symptoms in a vulnerable individual. Additionally, given the association between cannabis abuse or dependence and psychosis, a history of comorbid cannabis dependence may contribute to the presentation and/or severity of psychotic symptoms. Finally, given the proposed two-hit theory, if MA use is able to trigger psychosis in some users, duration of time abstinent in those users should have no bearing on the symptom presentation. In order to clarify these mixed findings regarding patterns of use, the **first objective** of the research was to determine whether selected drug use patterns were associated with severity of psychotic symptoms. **Hypothesis 1** was that duration of time as a regular stimulant user, MA use (as compared to cocaine use), age at first use, injection use, history of cannabis dependence and frequency of use would all significantly predict severity of psychotic symptoms, whereas duration of time abstinent would not predict severity of psychotic symptoms.

Research Objective 2: Neurochemical correlates of psychotic symptoms in stimulant-dependent users: N-acetylaspartate

NAA is often regarded as a marker for neuronal integrity, where increases suggest increased size or density of neurons (Bracken et al., 2011). It is possible that in psychosis, due to early life events affecting brain development, NAA may be a correlate of the underlying neuropathology associated with schizophrenia. In substance-dependence, reductions of NAA likely normalize in prolonged abstinence as compared to HCs (Nordahl et al., 2005; Sung et al., 2007). NAA has not been conclusively investigated in a stimulant-dependent sample in relation to the presence of psychotic symptoms, but given that a portion of the user sample may have a pre-existing vulnerability to psychosis, stimulant users may present with reduced NAA. To address this gap in knowledge, the **second objective** of the study was to compare NAA in abstinent stimulant-dependent users to HCs[1]. **Hypothesis 2** was that NAA would be reduced in abstinent stimulant-dependent users relative to HCs.

Research Objective 3: Neurochemical correlates of psychotic symptoms in stimulant-dependent users: Glutamate

Glu's involvement in schizophrenia is consistent with the neurodevelopmental hypothesis. It is plausible that Glu may be elevated in high-risk individuals leading to excitotoxic damage so that Glu is reduced in chronic schizophrenia. However, findings in FEP have been mixed, and replication is needed. Further, many of these studies vary in methodology and voxel location, making it difficult to conclusively understand the role of Glu in the course of illness. For these reasons it is unclear what role Glu may have in a stimulant-induced psychosis sample. To contribute to findings of an association between Glu and psychosis, the **third objective** of the study was to compare Glu in abstinent stimulant-dependent users to HCs[2]. **Hypothesis 3** was that stimulant-

[1] Due to a procedural error, explained in the methodology, the NSIP group could not be included in this analysis.
[2] Again, due to an error in ^{1}H-MRS methodology, described later, the NSIP sample could not be included in this analysis.

dependent users would present with abnormalities of Glu relative to HCs, without an *a priori* prediction of direction of change.

Research Objective 4: Cognitive correlates of psychotic symptoms in stimulant-dependent users: Processing Speed

Processing speed may be a cognitive correlate of the neuropathology underlying schizophrenia. Processing speed deficits have not been investigated in stimulant users experiencing psychotic symptoms. Given the possibility that processing speed deficits may exist prior to full disease expression, processing speed impairment should be present in at-risk samples and should relate to the vulnerability as measured by negative symptoms. As such, the **fourth objective** of the study was to compare the cognitive processing speed of abstinent stimulant-dependent users to NSIP and HCs, and to assess the effects of PANSS Negative symptom severity on processing speed performance. Given that some stimulant-dependent users will have a vulnerability to psychosis that may be related to processing speed deficits **Hypothesis 4** was that abstinent stimulant-dependent users would present with cognitive processing speed that is intermediary to HCs and NSIP, and that PANSS Negative symptom severity would impact performance.

Research Objective 5: Cognitive correlates of psychotic symptoms in stimulant-dependent users: Executive Functioning

Executive function is one of the most commonly described cognitive impairments in schizophrenia research. Inconsistent reports of a relationship between executive function and vulnerable populations suggest that impairment of executive function in schizophrenia is a symptom of the disorder and not a marker for the disorder. Abstinent MA users have also presented with moderate impairment in executive function, however, executive functioning deficits have not been investigated in stimulant users with respect to presence of psychotic symptoms. In order to address this gap in knowledge, the **fifth objective** of the study was to compare executive functioning of abstinent stimulant-dependent users to NSIP and HCs. Given that some stimulant-dependent users with psychotic symptoms exhibit the same executive functioning deficits that are

observed in psychosis while some stimulant-dependent users without psychotic symptoms do not, **Hypothesis 5** was that abstinent stimulant-dependent users would present with executive function that is intermediary to HCs and subjects with a NSIP. It was further hypothesized that performance on a task of executive function would not be related to negative symptoms of psychosis.

Research Objective 6: Predicting severity of psychotic symptoms by co-registration of cognitive and neurochemical measures

To the extent that the pathology underlying schizophrenia is related to region-specific cognitive impairment, it is logical to believe that cognitive impairment and neurochemical profiles should manifest as more severe symptoms of psychosis. Thus, changes in Glu and NAA levels in psychosis as compared to HCs are likely to correlate with the severity of symptom presentation. There is evidence for both Glu and NAA abnormalities in samples of subjects at high-risk for developing psychosis, providing support for the idea that these neurochemicals may be related to an underlying pathology. Given the evidence reviewed earlier that negative symptoms best correlate with pathological change, these neurochemicals may be predictive of disease severity as measured by negative symptoms of psychosis. Similarly, processing speed is consistently abnormal in groups at high-risk for psychosis, and shows progressive change through development of psychotic disorder. Thus, to the extent that cognitive processing speed is a potential endophenotype for psychosis, it should also predict severity of psychotic symptoms, as measured by negative symptoms. Conversely, executive functioning is less consistently impaired in high-risk groups and family members and is more likely a consequence, or symptom, of developing positive symptoms and is not expected to be related to negative symptoms. Concurrent analysis of cognitive performance and neurochemical measures has not been investigated in a stimulant-dependent sample with psychotic symptoms. To take advantage of the co-registration of these two measures, the **sixth objective** was to predict the severity of psychotic symptoms by co-registration of ^{1}H-MRS data and processing speed and executive functioning data independently in the abstinent stimulant-dependent user sample and NSIP sample. **Hypothesis 6** was that NAA,

Glu and processing speed would predict severity of psychotic symptoms in both abstinent stimulant-dependent users and NSIP, through independent analysis.

Chapter 3: Methods and Materials

Study Design and Procedures

Study design and overview of protocol.

This study compared cognitive function and neurochemical measures of abstinent stimulant-dependent users (ASDUs) with two comparison groups: (1) a sample of non-substance-induced first episode psychosis patients (NSIPs), and (2) healthy controls (HCs) with no history of either stimulant misuse or other Axis I disorders including psychosis. NSIPs were used as a comparison group so that similarities and differences in cognitive functioning and neurochemistry could be observed between the ASDU group and individuals experiencing psychosis without a history of any drug use (i.e., a reference group of non-stimulant using individuals manifesting the clinical phenotype of interest). The HC group was recruited so that the cognitive functioning and neurochemistry of both ASDUs and NSIPs could be compared to individuals without histories of stimulant misuse or psychosis.

ASDUs were the primary group of interest in this project. Two subgroups were recruited into the ASDU sample to allow for comparison of the outcome measures across different stimulants of abuse: a group of primary cocaine users that had limited or no prior exposure to MA, and a group of primary MA users that may have used other stimulants.

All data for the ASDU and HC groups were collected by the author (BL). All data for the NSIP group were collected by the Edmonton Early Psychosis Intervention Clinic (EEPIC) staff. The NSIP sample data were collected prior to the initiation of this project; therefore, the inclusion of assessment material in this project mimicked those used in the previous EEPIC studies so that data would be directly comparable. Further, this project was initially designed on a smaller scale and expanded upon after recruitment had begun; as such, sample sizes vary by assessment.

All of the study procedures were approved by the Health Ethics Research Board at the University of Alberta.

Recruitment.

Abstinent Stimulant-Dependent Users (ASDUs). Contacts were made through unsolicited approaches to agencies and organizations providing addiction treatment and support services for substance misuse in the Edmonton area, including but not limited to: the former Alberta Alcohol and Drug Abuse Commission, 12-step meeting groups, and local detoxification or drug treatment centres. Agency contacts were informed that a study was being conducted at the University of Alberta investigating the mental health effects of MA use, and that research subjects were being recruited to participate. With agreement from the collaborating agency a schedule was set up where the author (BL) presented information about the opportunity to participate in the research to groups of drug users, or, depending the agency's preference, employees would provide study information to clients eligible to participate. Contact with all collaborating agencies was maintained on a regular basis via email.

Eligible and/or interested clients called or emailed the author (BL). The author (BL) made no unsolicited contact with potential participants. Once contacted by a potential participant, a screening interview took place to ensure that study inclusion and exclusion criteria were met by the participant, and to answer any questions or concerns about participation. All potential participants were read a description of the study, including the amount of time necessary to complete the protocol (approximately 4.5 hours), the nature of participation (including interviews, computer tests and paper-and-pencil questionnaires), the request for a urine sample, details about the MRI scan (duration approximately 1.25 hours) and compensation. All participants recruited into the ASDU sample were reimbursed at a flat rate of $50 or at the rate of $10/hour in the form of gift cards. Gift cards had been purchased prior to subject participation and were available for coffee shops, online music stores, restaurants, fast food restaurants, entertainment, or transit services.

Inclusion/exclusion criteria for the ASDU MA-using subsample were: (1) 18 to 35 years old, inclusive (2) met DSM-IV-TR criteria for amphetamine dependence (3) abstinence from cocaine, opiates and amphetamines for a

minimum of 7 days (with no maximum) (4) never diagnosed with a DSM-IV-TR Axis I disorder aside from any drug abuse or dependence or substance-induced psychosis (5) never tested positive for AIDS or HIV (6) never had a serious head injury involving loss of consciousness for longer than 30 minutes (7) never had been diagnosed with a central nervous system disorder (8) not currently pregnant (9) no contraindications for an MRI scan and (10) willing to participate and sign a consent form.

Inclusion/exclusion criteria for the ASDU cocaine-using subsample were the same, with the following amendments to the drug-dependence criteria: (1) no history of MA dependence (2) no MA use in the last 5 years (3) no MA use exceeding four uses per month (4) no MA use exceeding 3 months of use (5) no binge MA use and (6) met DSM-IV-TR criteria for cocaine dependence.

Non-Substance-Induced first episode Psychosis (NSIP) patients. NSIPs were obtained through their participation in a previous study conducted at EEPIC. All NSIP subjects participated in hospital or at EEPIC. Inclusion criteria for EEPIC patients were: (1) inpatients or outpatients with DSM-IV-TR diagnosis of schizophrenia, schizophreniform disorder or substance-induced psychotic disorder (cannabis-induced)[as determined by the Structured Clinical Interview for DSM-IV (SCID)] with active positive symptoms for less than 1 year (2) 18 to 35 years old, inclusive (3) less than 1 month of lifetime prior exposure to antipsychotic medication (4) current psychotic symptoms requiring long term antipsychotic treatment. Exclusion criteria were: (1) requiring mood stabilizers at study entry (2) head injury with greater than 29 minutes loss of consciousness (3) active (i.e., within past 30 days) substance abuse or dependence disorder other than cannabis (4) exposure to long acting depot neuroleptic medication (5) known sensitivity to olanzapine, risperidone, or quetiapine (6) serious medical illness (liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, or metabolic disturbance) and (7) unstable or poorly controlled illnesses including hypertension, angina, or diabetes. From this pool of potential EEPIC participants, additional exclusionary criteria for the purposes of this study were applied: (1) no diagnosis of affective psychosis (2) no history of

stimulant use (3) no diagnosis of substance-induced psychosis. This additional exclusionary criteria removed all substance-induced psychosis patients leaving only a sample of *de novo* schizophrenia.

Healthy Controls (HCs). The HC sample was recruited via community advertising, most often on social networking websites (i.e., www.facebook.com) or on websites advertising services (i.e., www.kijiji.ca or www.craigslist.com). Potential participants contacted the author (BL) via email or phone and a similar screening process as described for recruiting the ASDU sample took place. Interested participants were informed of the same study details, without the need for a urine sample. All HCs who completed the study were compensated for their time at a flat rate of $50 cash. Inclusion/exclusion criteria were: (1) 18 to 35 years old, inclusive (2) never diagnosed with any DSM-IV-TR Axis I disorder, with the exception of alcohol abuse or cannabis abuse (3) never used any illicit substance on a regular basis (defined at ten uses in a 1 month period) (4) never had a serious head injury involving loss of consciousness for longer than 30 minutes (5) never been diagnosed with a central nervous system disorder (6) not currently pregnant (7) no contraindications for an MRI scan and (8) willing to participate and sign a consent form.

Additional exclusionary criteria (all samples). For all participants, contraindications, and therefore further exclusionary criteria, for the MRI procedures were: (1) non-removable hearing aids or false teeth (2) cardiac pace-maker, implanted neurostimulator, implanted drug delivery system (3) surgery in the last 2 months (4) cardiac valve replacement (5) operation on the head or chest, with possibility of metal clips (6) vascular surgery (7) bone fracture or break with possibility of metal pins or screws supporting the skeletal system (8) joint replacement (9) injury by foreign metallic object that was not subsequently removed (10) work history as a welder, lathe operator or sheet metal worker (11) intra-uterine contraceptive device and (12) tattoos that were obtained outside of Canada. For any endorsement of the above-listed contraindications follow up inquiries were made. For several participants with previous surgeries including placement of pins, plates or screws, participation was allowed after approval by a

magnetic resonance specialist. For several participants endorsing a history of work as a welder, lathe operator or sheet metal worker an additional step was added to participation; these individuals were asked to consent to an orbital x-ray to search for possible metal fragments in the eye sockets. Only after clearance by a radiologist were these participants able to complete the study.

Procedure.

The author (BL) executed the study protocol for all subjects in the HC and ASDU samples at the University of Alberta. The author (BL) was trained on administration of the cognitive battery by staff at the Neuropsychology Service at Alberta Hospital Edmonton. Training on the SCID and PANSS interviews involved a series of training tapes. Assessments were reviewed by a psychiatrist. The procedure described below outlines that conducted by the author (BL) for ASDU and HC samples only.

After meeting the inclusion/exclusion criteria via a telephone or email screening process and agreeing to participate, a meeting time was set up. Participants were asked to come to the University of Alberta with the option of one half day of participation (~4.5 hours), or two consecutive sessions of approximately 2.5 hours each.

Cons ent. All participants signed an informed consent for study participation and a separate consent form for the MRI. All participants were assigned a unique identification number so that personal identification was not associated with any collected data. All participants were informed that information would be confidential and secured. All participants had the opportunity to ask questions. All participants were allowed to take breaks during participation, or to stop participation at any time. All participants signed a reimbursement receipt upon study completion.

Protocol. After signing consent forms and offering the opportunity for all participants to ask questions, the first portion of participation was a clinical diagnostic interview. This interview was used to confirm diagnosis of drug dependence in the ASDU sample and to confirm a lack of lifetime history of other

mental health disorders in all recruited samples; as such, any participant not meeting inclusion/exclusion criteria after the interview did not complete the remaining portions of the study. Each subject then participated in a cognitive battery, completed self-report questionnaires and the MRI scan.

A urine sample was collected from each participant in the ASDU sample to verify self-reported drug abstinence. In order to ensure a better likelihood of obtaining a clean urine sample, inclusion criteria for the ASDU sample was set to a minimum of 7 days abstinence because MA has a half-life of approximately 12-hours and is detectable in urine for approximately 48 hours (Winslow et al., 2007). The collected sample was refrigerated until it could be delivered to DynaLIFEDx Diagnostic Laboratory Services, always within 24 hours. DynaLIFEDx tested each urine sample for opiates, amphetamines and cocaine. Urine samples were poured into barcoded tubes and screened by an enzyme immunoassay technique on an Olympus 640 analyzer. Confirmatory analysis was not completed. Cut off points were 300ng/mL for opiates, 500 ng/mL for amphetamines, and 150 ng/mL for cocaine. These were standard values applied by DynaLIFEDx.

Measures

Clinical interview.

All subjects participated in a SCID for Axis I disorders (First, Spitzer, Gibbon, & Williams, 2002). This clinical interview was used to (1) confirm inclusion and exclusion criteria assessed in the screening process and (2) determine a detailed drug use history. The SCID involves open-ended questions about behaviours and thoughts over the subject's lifetime. The SCID is scored according to established guidelines outlining explicit details for meeting criteria for all potential Axis I diagnoses.

Each participant in the ASDU sample and NSIP sample also completed the PANSS interview (Kay et al., 1987). This interview was used to assess severity of any psychotic symptoms experienced currently or over the previous week. The PANSS consists of a semi-structured interview with questions that load onto specific symptoms of psychosis. The scale includes 7 positive symptoms, 7

negative symptoms and 16 general items. Each item is rated on a 7-point scale with higher ratings indicating greater psychopathology. The range of possible scores is 30 to 210. Psychometric analysis of the PANSS has shown at least three factor loadings in schizophrenia, consistent with the design of the scale: a positive scale, a negative scale and a disorganized scale (Peralta & Cuesta, 1994). Psychometric analysis of MA-induced psychosis has indicated two factors underlying the items: the positive scale and negative scale (Srisurapanont et al., 2003). In the current study the Cronbach alpha coefficient for the Positive subscale was 0.82 and for the Negative subscale was 0.88.

Self-report questionnaires.

Demographics and drug use patterns. Each participant completed a brief demographics form designed for the current study. Each participant in the ASDU sample also completed a self-report form on drug use patterns designed by the author (BL) for the current project. The form assessed patterns of use for the preferred stimulant, including frequency and duration of use, preferred method of drug administration, age at first use, latency from first use to regular use, duration of time abstinent, addiction treatment history, binge use, reasons for first use and self-described problems associated with use.

Psychosis-proneness. Every participant completed a set of self-report measures including the Magical Ideation Scale (MIS; Eckblad & Chapman, 1983) and the Social Anhedonia Scale (SAS; Chapman, Chapman, & Raulin, 1976) that were used to assess psychosis proneness. These are self-report questionnaires with 30 and 40 true-false items, respectively. The MIS assesses beliefs in magical thinking; the SAS assesses ability to derive pleasure from social interactions. These measures are related to schizoid and schizotypal traits (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Mishlove & Chapman, 1985) but are not specific to schizophrenia (Chapman et al., 1994). Norms for these scales were derived from published samples (Chmielewski, Fernandes, Yee, & Miller, 1995).

Comorbid symptoms. Comorbid symptoms were assessed with the Beck Depression Inventory (BDI; Beck, 1987) and the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988). The BDI consists of 21 questions, each

containing a series of statements in increasing severity of symptoms of depression. The subject was asked to circle the statement within each cluster that best represented their feelings at the time of participation and in the previous 7 days. The questionnaire was scored by summing the value of the responses, with higher scores indicating more and/or more severe symptoms of depression. The BAI contains a list of 21 symptoms of anxiety and asked the subject to check on a scale from 0 to 3 how severely they had experienced each symptom at the time of participation and in the previous 7 days. The questionnaire was scored by summing the value of the responses with higher scores indicating more and/or more severe symptoms of anxiety. The range of scores for each questionnaire is 0 to 63.

Cognitive assessment.

A cognitive battery was used in this project that allowed comparability to the data previously collected at EEPIC for the NSIP sample. Several cognitive assessments were administered as part of the procedure that were not analyzed as part of this study[3]. This battery was designed to assess several cognitive domains relevant to both psychosis and substance dependence. Where two alternate forms of the test were used, versions were alternated in order, within each study group.

Processing speed. The Stroop Colour and Word Test, Golden variant (Golden, 1975; Stroop, 1935) involves three sections, each measuring a different cognitive process. The colour reading section of this test is a simple measure of processing speed. For this task, the subject was given a page of colour words written in black ink and asked to read the words out loud as quickly as possible until being told to stop after 45 seconds. Next, a page of X's printed in coloured ink was presented and the subject was asked to read the colours of ink out loud as quickly as possible until being stopped after 45 seconds. Finally, a page was

[3] The complete battery of tests included the Peabody Picture Vocabulary Test, Weschler Memory Scale Visual Reproduction, Weschler Memory Scale Spatial Span, Rey Auditory Verbal Learning Test, Controlled Oral Word Association Test, Green Stories Recall Test, Grooved Pegboard and the Quality of Life Enjoyment and Satisfaction Questionnaire. Additional tests that were run for this project but not included in analysis were the Iowa Gambling Task and Conner's Continuous Performance Test.

presented with colour words printed in an incongruous coloured ink. The subject was asked to read the colour of ink the word was printed in (i.e., not what the word said) as quickly as possible before being stopped after 45 seconds. If any mistakes occurred the tester stopped the subject and asked for a correction before continuing. Scoring was the count of the number of items read in each trial. The outcome measure for processing speed was the number of words read in the first trial. Standardized *t*-scores were calculated based on the Stroop Colour and Word Test's manual (Golden, 1978). This task was used as the primary measure of processing speed.

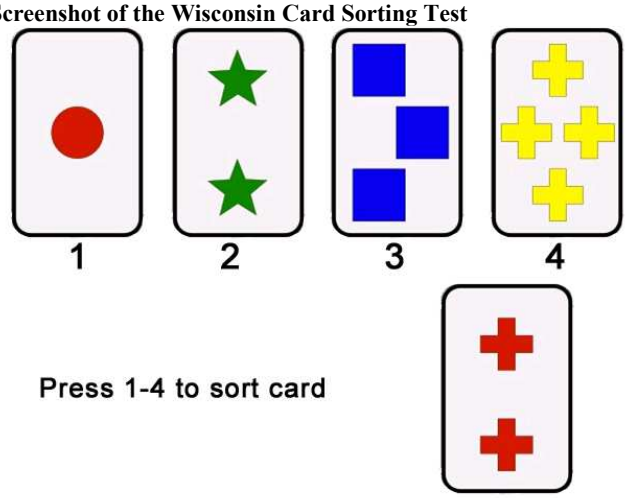
The TMT (Halstead, 1947; Reitan, 1979; War Department & Adjutant General's Office, 1944) is a two-step task that measures processing speed, attention and cognitive flexibility. The first step (TMT-A) involves a practice session where subjects were asked to draw lines between a series of numbers scattered on a page in sequential order. After a correct sample trial, the subject repeated the task with more numbers, working as quickly as possible while the tester timed the amount of time until completion. The second step (TMT-B), involves both letters and numbers. After a correct trial, the subject was asked to start with the first number (1), and draw a line to the first letter (A) and continue the alternating sequence in order until finished (e.g., 1, A, 2, B, 3, C, etc.), as quickly as possible. If the subject made an error, the tester redirected the subject to the last correct point to continue. The score for this test was the amount of time to complete the task. Independent standardization of the TMT-A and TMT-B to a *z*-score accounting for age, gender and education level was computed based on published norms (Bornstein, 1985).

The Digit Symbol Substitution Test task is part of the Wechsler Adult Intelligence Scale – Revised (Wechsler, 1981) and measures processing speed that is unaffected by intellectual prowess, memory or learning (Erber et al., 1981). The subject was presented with a single page. At the top of the page was a legend with the numbers 1 through 9. Each number was paired with a unique symbol. Below this legend was a series of numbers with an empty box below each number. The subject was asked to write the symbol in the empty box that matched

the number in the legend at the top. After seven practice trials, the subject continued until being told to stop after 2 minutes. The test was scored by counting the number of correct matches completed in the 2 minutes. The raw scores were then standardized to a *z*-score, accounting for age based on Wechsler Adult Intelligence Scale norms.

Executive function. The Wisconsin Card Sorting Test: Computer Version 3 for Windows (WCST; Heaton, 1981) is a complex test measuring thought flexibility, abstraction and set-shifting, commonly used as a measure of executive function. For this computer-based version the subject sat in front of a monitor and was shown four stimulus cards. Each stimulus card was unique with respect to colour, shape and number of objects on the card. A card from a deck was drawn and the subject was asked to match the drawn card to one of the four stimulus cards. Figure 4 depicts a screenshot of the task.

Figure 4
Screenshot of the Wisconsin Card Sorting Test



The subject was not instructed how to match the cards and had to learn via trial and error, with feedback, which element was the correct matching element. After ten sequential correct placements, the program switched matching element without notification. The subject had to learn the switch and again obtain ten sequentially correct placements. The task continued until all cards were depleted (128 cards) or the subject made ten sequentially correct placements for colour, shape, and number twice (i.e., 60 correct placements). The program recorded several measurements, including number of cards (i.e., trials) administered,

correct placements, total errors, perseverative errors, non-perseverative errors, categories completed, trials to complete first category, breaks in set and a learning measure. One of the most relevant measures to executive functioning is the perseverative error measure. Perseverative errors represent the inability to shift thinking from one previously enforced pattern to another. From the perseverative error measure a standardized *z*-score was calculated accounting for age using norms from the published manual (Heaton, Chelune, Talley, Kay, & Curtiss, 1993). This task was used as the primary measure of executive function.

A second measure of executive function was the Stroop Colour and Word Test. As described earlier, the Stroop Colour and Word Test measures several cognitive domains. The colour-word incongruent section of this task is often used as a measure of executive function (Johnson-Selfridge & Zalewski, 2001). The administration is the same as described above, but the outcome measure is the standardized interference *t*-score calculated using the following formula:

$$\text{Predicted Colour/Word Score} = \frac{(\#\ \text{Words} * \#\ \text{Colours})}{(\#\ \text{Words} + \#\ \text{Colours})}$$

$$\text{Interference Score} = \text{Colour/Words} - \text{Predicted Colour/Word}$$

Executive functioning was also assessed using the TMT-B test. As described above, the two components to the TMT task (i.e., TMT-A and TMT-B) measure different cognitive capacities. TMT-B involves cognitive flexibility, and differs from TMT-A in terms of task complexity, making it more relevant to executive function. The administration is the same as described above, but the primary outcome measure is the standardized TMT-B *z*-score.

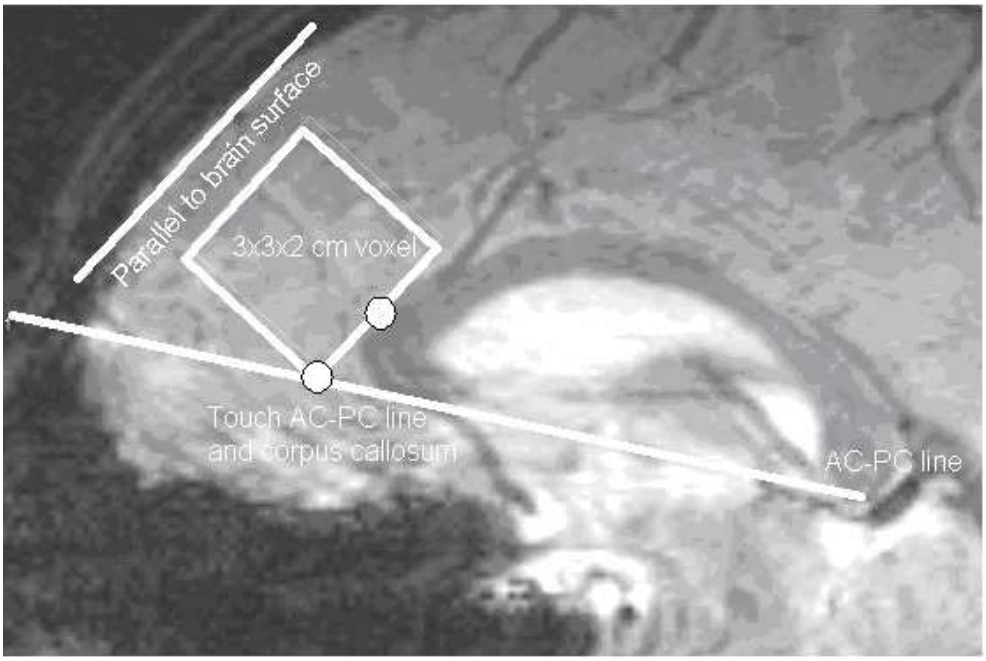
NSIP procedure

The NSIP sample completed their participation at the Neuropsychology Service of Alberta Hospital Edmonton. The SCID interview and symptom rating was completed by a neuropsychologist on the same day cognitive testing and self-report questionnaires were administered. The cognitive testing was performed by trained research staff, under the supervision of the neuropsychologist. The MRI scan was completed on a separate day, within 1 weeks' time of the previous assessments. Subjects consented to participate in a study approved by the Human Research Ethics Board at the University of Alberta. Data from this study was obtained for secondary use in the current research project with approval from the Human Research Ethics Board.

Neuroimaging: ^{1}H-MRS

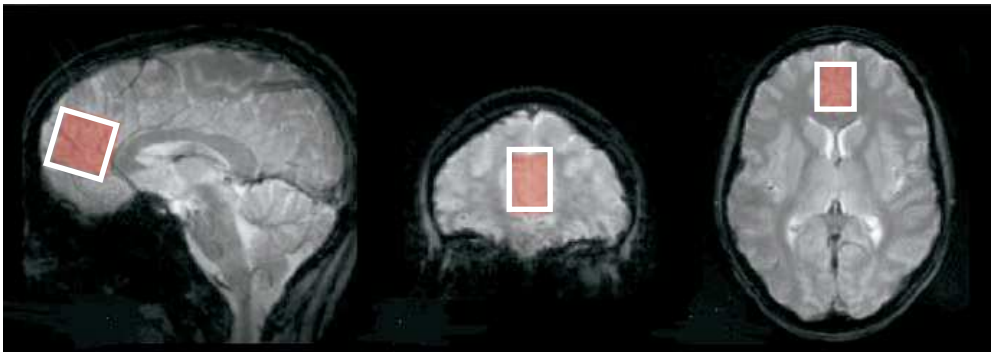
All participants completed a ^{1}H-MRS scan using a 3.0 Tesla magnet (Magnex Scientific, Concord, CA) at the Peter S. Allen MR Research Centre at the University of Alberta Hospital. A qualified technician carried out the scan sequences and prepared the output data for processing by a Faculty Service Officer IV. The magnet was equipped with actively shielded gradients, a spectrometer (Surrey Medical Imaging System, Surry, UK) and a birdcage resonator. The procedure for the scan followed those completed in previous research conducted at the Peter S. Allen MR Research Centre (see Jackson, 2007; Valiakalayil, 2006). In summary, an 18 cm^3 volume of interest (3x3x2 cm) was positioned in the mPFC such that the 2 cm dimension was centred on and parallel to the midline guided by both transverse and coronal gradient echo image series (TE = 20 ms, TR = 500 ms, 5mm slice thickness, 256 x 256 point resolution). The sagittal slice centred on the midline was then used to register the voxel, first, such that the posterior edge touched the corpus callosum and inferior edge lay along a line projecting through the anterior commissure-posterior commissure axis. The voxel was then rotated until the corners of the anterior edge were equidistant from the brain surface, while maintaining one corner contacting the anterior commissure-posterior commissure line, and one edge contacting the corpus callosum (Figure 5).

Figure 5
Selection of Voxel



Typical voxel placement in all three MRI axes (axial, coronal and sagittal) is illustrated in Figure 6.

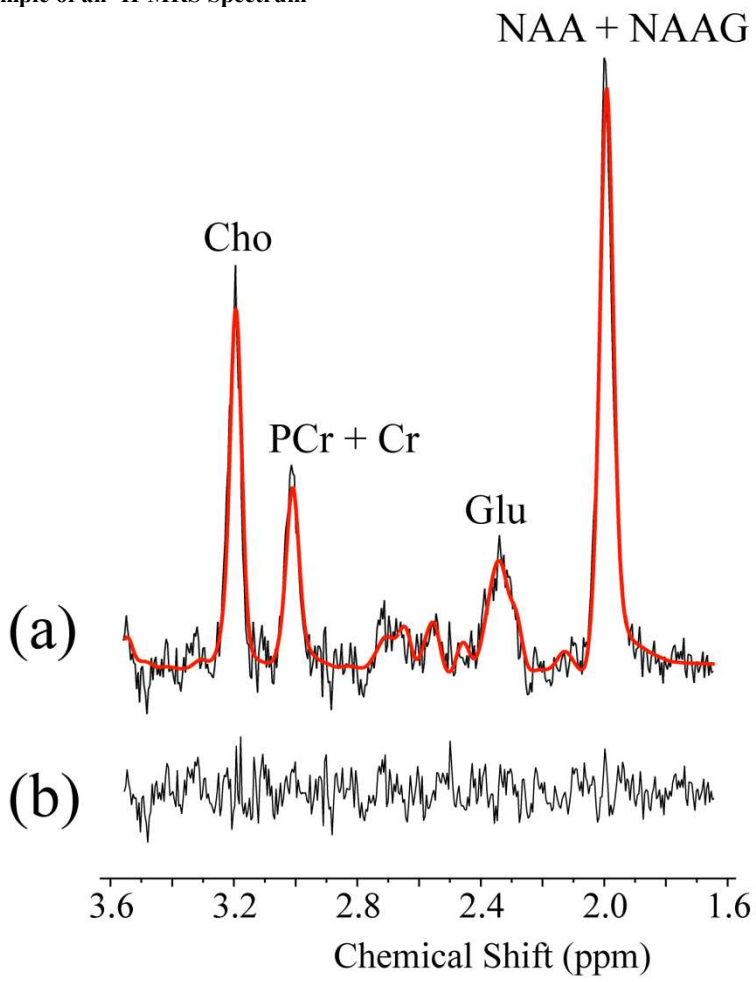
Figure 6
Voxel Placement in the mPFC



The STEAM pulse sequence timings (TE = 240ms and TM = 27ms) for optimal Glu signal contrast-to-background were determined using numerical simulation, and then implemented for the acquisition of water-suppressed spectra. The long TE time also reduced the signal contamination from macromolecules that have short T_2 relaxation time, and are reduced to < 2% of their intensity. Each spectrum was the sum of 512 averages, acquired in 16 blocks of 32 averages. Each block of data was phase corrected and frequency aligned, using the NAA singlet peak at 2.023 ppm as a reference standard, prior to summation.

Analysis of the summed data used the LCModel (version 6.0-1) analysis program, giving measures of the target metabolites Glu, NAA, Cr and Cho. LCModel analysis provides a measure of the quality of the fitted peak by estimating the Cramer-Rao lower bounds of the fit. This is represented as '%SD' in the analysis output, and must have a value less than 15% to be deemed of acceptable quality by the current research group. In the data presented in this thesis, %SD values for the target peaks were typically: for Glu < 13%, for NAA < 4%, and for Cr < 15% (Provencher, 1993). A representation spectrum analyzed using LCModel is illustrated in Figure 7, and shows the overlapping lines in (a), the experimental data (black, or noisy line) and the fitted data (red, or smoother line), and the residual spectrum (b), following subtraction of the experimental and fitted data.

Figure 7
Example of an ^{1}H-MRS Spectrum



In order to estimate the GM:WM:CSF composition of the voxel, segmentation data were acquired, using a double-inversion recovery PRESS 1-D projection method (Hanstock & Allen, 2000). These data were included to scale for differences in the composition (GM:WM) of each subject's brain in the mPFC voxel of interest, but most importantly, to allow for the elimination of the non-brain-containing-volume occupied by the CSF. The PRESS selected volume was registered precisely to the same selected region as the STEAM acquisition. Two hyperbolic secant inversion pulses (110 ms length, bandwidth = 150 Hz) were added immediately prior to the PRESS pulse sequence. The delay time between the two inversion pulses and between the last inversion pulse and the PRESS sequence was optimized to suppress two components, which included CSF and either GM or WM. Ten GM and ten WM 1D-projections were acquired, TR = 9 s, TE = 120 ms, two averages with 5 kHz sample frequency digitized over 128 data points. An additional ten CSF 1D-projections were acquired with no inversion pulses and with a TE of 500 ms. At this long TE the signal contamination from GM and WM was virtually zero (<0.2% residual signal after accounting for T_2 losses), while maintaining significant signal from CSF (~50% residual signal). All computations necessary for calculating experimental timings prior to acquisition, and for the data analysis, were performed using the MATLAB program environment.

A final series of data was acquired using the STEAM sequence without water suppression, which measured the water signal from the selected voxel at 18 TE values (TE = 20, 40, 60, 80, 100, 150, 200, 250, 300, 350, 400, 450, 500, 700, 900, 110, 1300, 1500 ms; TR = 12000ms; two averages per TE value).

Quantification of metabolite concentrations.

Three series of data were required for quantification: (1) metabolite peak area estimates were extracted from the LCModel output (M_{TE240}), (2) segmentation information for GM, WM and CSF compartment sizes were used to estimate water concentration in the selected brain voxel (W_{brain}), and (3) internal water data acquired at different TE values were used as the reference magnetic resonance signal standard (W_{TE0}).

The water data were first imported into the processing software, filtered, Fourier transformed, and phase and baseline corrected. The water peak area from each spectrum in the TE series was first determined. These area data were fitted to a multi-exponential using a non-negative-least-squares algorithm, yielding both the two T_2 components present in decay (brain (WM + GM) and CSF) and their relative proportions. In addition, this permitted an estimation of the water peak from just the brain tissue at a theoretical TE of 0 ms (W_{TE0}).

The following formulae were used to derive the metabolite "absolute" concentrations:

Metabolite and water signals derived by ^{1}H-MRS and concentrations are related by the simple expression:

$$\frac{\text{WaterSignalBrain}}{\text{WaterConcBrain}} = \frac{\text{MetaboliteSignalBrain}}{\text{MetaboliteConcBrain}}$$

Rearranging this, calculation of the metabolite concentration in brain can be achieved:

$$\text{MetaboliteConcBrain} = \frac{\text{WaterConcBrain} * \text{MetabolteSignalBrain}}{\text{WaterSignalBrain}}$$

Defining the term WaterConcBrain (M = metabolite, W = water):

$\text{PureWaterConc} = 1000 * (1000 / MW_{water})$ mM

$GM_{water} = 0.8 * \text{PureWaterConc}$

$WM_{water} = 0.65 * \text{PureWaterConc}$

$\text{WaterConcBrain} = W_{brain} = (GM_{segment} * GM_{water}) + (WM_{segment} * WM_{water})$

Inserting measured variables into the rearranged expression:

$$\text{MetaboliteConcBrain} = \frac{W_{brain} * M_{TE240}}{\text{WaterSignalBrain}}$$

W_{TE0}

Allowing for different numbers of averages and metabolite T_2 values for metabolite and water acquisitions:

Scaling Factor (SF) number of averages = $SF_{av} = sqrtM_{averages}/sqrtW_{averages}$

SF for metabolite $T_2 = SF_{MT2} = \exp(-TE/T_2)$

$MetaboliteConcBrain = SF_{T2} * ((W_{brain} * M_{TE240}) / W_{TE0}) / SF_{av}$

T_2 values for metabolites were assigned based on averaged literature values for NAA (350 ms), Cr (150 ms) and Cho (310 ms), and estimated for Glu (380 ms) based on expected normal brain concentration values for the GM:WM mix sampled in previous studies. The SF for metabolite T_2 is only to provide numerical values in the mM range, and the same values are applied to all data; this allows comparison to reported data. The data could also be reported in institutional units where:

$MetaboliteConcBrain = ((W_{brain} * M_{TE240}) / W_{TE0}) / SF_{av}$

Data selection criteria.

Finally, in post-processing data analysis, cut points were used to determine if the data were of sound quality. These cut points were based on a combination of two pieces of information, both from the LCModel output. SNR and line width are basic means of assessing spectra quality (line width is measured as full width at height maximum). If the SNR for a given subject was less than 7.5 or line width was greater than 0.075 the subject was labeled as "Review"; if the SNR was below 5, or line width was more than 0.1 the spectra quality was deemed too poor (too noisy or too broad) for adequate reliability and the data were rejected from subsequent analysis. Data labeled as review were judged on an individual basis in all subsequent analysis. Where anomalies were found the data were omitted; this will be noted in the results section. Further, the Cramer-Rao Lower Bound is the %SD that is acceptable for neurochemical measures. Less than 15% is regarded as

acceptable by the research group for NAA, Cr and Cho, while less than 20% is acceptable for Glu. Data exceeding the Cramer-Rao Lower Bound limitations were also addressed on an individual basis, and where anomalies were found, data were omitted; this will also be noted in the results section.

Procedural errors in implementing the neuroimaging protocol.

During the process of setting the scanner parameters prior to the acquisition of the metabolite spectrum, an important entry was omitted in data acquired prior to July 2007. This parameter set a frequency offset for the slice selection that accounted for chemical shift differences between water (used for segmentation and water concentration referencing) and the target metabolites, particularly Glu. In this case the frequency was misset for the water data used for quantification and resulted in a 3 mm offset in the left-right slice axis (2 cm slice), and a 4.5 mm offset in the other two slice directions. Tissue composition differences that would result from this relatively small voxel placement error were not expected to have a significant impact on the measured water reference signal. However, by the time the error was detected, four ASDUs and all NSIP data had been collected.

To summarize, prior to July 2007, the water data for segmentation and the metabolite data came from the mPFC voxel of interest, but the water-referencing data did not. No post-hoc solution to this anomaly was established as valid. As a consequence, all NSIP ^{1}H-MRS data, and four of the ASDU ^{1}H-MRS data are not directly comparable to the remaining ASDU and HC data collected after July 2007.

Chapter 4: Data Analyses and Results

All data were analyzed using PASW Statistics (V18.0). Significance levels for all statistical tests were set at $p < .05$, two-tailed, unless otherwise specified. Because most of the data for this study were manually entered into PASW, one in three subjects' hardcopies were systematically reviewed for data entry errors or missing data with the assistance of an independent, third-party judge. For the remaining data, all variables were examined for appropriate values, ranges and means.

Notes on Study Design

Treatment with psychiatric medications at the time of participation was not an exclusionary item because the inclusion and exclusion criteria for ASDUs allowed for the recruitment of stimulant users who met full criteria for stimulant-induced psychosis. However, because none of the ASDUs were seeking treatment for psychosis, subjects being treated with antidepressants, antipsychotics and anxiolytics were subsequently removed from the dataset.

As mentioned in the methods, a procedural error in the collection of ^{1}H-MRS data made some primary hypotheses for this study untestable by not allowing for a direct comparison between the ASDU and HC samples and the NSIP sample.

Finally, several of the assessments used in this study were added after initial recruitment began. As such, sample sizes differ by assessment. This is in addition to factors affecting participation on certain tasks (e.g. computer failure or colour-blindness). In addition, several variables (e.g. demographic data and some cognitive assessments) were not administered at EEPIC to the NSIP sample. All sample size variances are described below.

Sample Description

Demographics.

One-hundred eighteen participants were initially recruited into the study (36 HCs and 82 ASDUs), and 23 NSIP participants were drawn from the EEPIC database. Of these participants, 24 ASDUs were excluded from analysis (5 had positive urine screens [3 for opiate use and 2 for cocaine use]; 2 failed to provide

urine samples; 2 reported testing positive for AIDS or HIV on a self-report form (despite verbal indication otherwise); 10 reported current treatment with psychiatric medication [5 on antipsychotics, 4 on antidepressants, and 1 on an anxiolytic]; and 5 presented with Axis I disorders outside of those described in the inclusion criteria). In addition, 5 HCs were excluded from analysis (4 had abnormal scores on two psychosis proneness measures [2 HCs were >2 SD above the mean on the MIS and 2 HCs were >2 SD above the mean on the SAS], and 1 presented with an Axis I disorder outside those described in the inclusion criteria).

Of the 23 NSIP participants drawn from the EEPIC database, all presented with a primary psychotic disorder that was not substance-induced, and did not report a history of substance misuse, according to self-report measures of the Addiction Severity Index (defined as less than ten lifetime uses of stimulants, opiates and cocaine). The final sample was 112 (31 HCs, 58 ASDUs and 23 NSIPs). Table 1 provides demographic information for all study participants.

Table 1
Sample Demographics

	HCs (n = 31)	**ASDUs (n = 58)**	**NSIPs (n = 23)**	**Test Statistic**
Age (in years)	$M = 24.58_{ab}$ (SD = 5.06)	$M = 26.62_{a}$ (SD = 3.90)	$M = 22.04_{b}$ (SD = 4.47)	$F(2, 109) = 10.58$**
Gender (% Male)	74.19%	68.97%	86.96%	$\chi^2(2) = 2.78$
Handedness (% Right)	83.87%	86.21%	82.61%	$\chi^2(2) = 0.20$
Ethnicity (% Caucasian)	67.74%	72.41%	*missing data*	$\chi^2(1) = 0.21$
Marital Status (% Single)	77.42_{a}%	67.24_{a}%	100%	$\chi^2(2) = 7.24$*
Language (% English as primary)	93.55%	100%	*missing data*	$\chi^2(2) = 3.83$
Years of Education	$M = 13.29_{a}$ (SD = 2.49)	$M = 12.04_{b}$ (SD = 2.21)	$M = 12.55_{ab}$ (SD = 2.28)	$F(2, 109) = 3.36$*

Note. Values not sharing the same subscript differ from each other * $p < .05$; ** $p < .001$

Age was significantly different across the subsamples, $F(2, 109) = 10.58$, $p < .001$; ASDUs were older than NSIPs after post-hoc Bonferroni adjustment. Marital status also differed between groups, $\chi^2(2) = 7.24$, $p = .027$; significantly more ASDUs had a partner (32.76%) as compared to HCs (22.58%) and NSIPs (0%). Years of completed education also differed between groups, $F(2, 109) = 3.36$, $p = .038$, after post-hoc Bonferroni adjustment HCs had more years of education (M = 13.29, SD = 2.49) than ASDUs (M = 12.04, SD = 2.21).

There was no difference between HCs and ASDUs on the years of education for the subject's mother or father; these data were not available for the NSIP sample. HCs and ASDUs also did not differ with respect to developmental disabilities, physical injuries or head injuries; these data were not available for the NSIP group. There was a significant difference in the distribution of occupation across groups, $\chi^2(4) = 13.93$, $p = .008$; HCs (n = 25) reported employment (52%), followed by student status (28%), and unemployment (25%); ASDUs (n = 51) reported employment (49.02%), followed by unemployment (43.14%) and student status (7.84%); and NSIPs (n = 12) reported employment (66.67%) followed by student status (33.33%). The remaining sample failed to endorse any category.

Marijuana/tobacco use and legal involvement.

Table 2 presents data comparing the HCs and ASDUs on marijuana and tobacco use, as well as history of interaction with the criminal justice system; these data were not available for NSIPs.

Table 2
Marijuana and Tobacco Use, and Legal Interaction

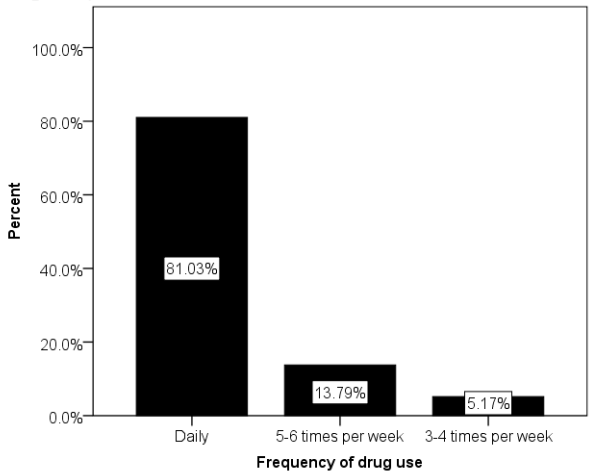
	HCs **% *: n***	**ASDU** **% *: n***	**Test Statistic**
History of marijuana use (% Yes)	54.84% : *31*	100% : *58*	χ^2 (1) = 31.08**
Current marijuana use (% Yes)	29.41%: *17*	18.87% : 53	χ^2 (1) = 0.85
Current cigarette smoking (% Yes)	19.35% : *31*	64.58% : *48*	χ^2 (2) = 16.68**
History of trouble with the law (% Yes)	6.45% : *31*	77.19% : *57*	χ^2 (1) = 40.28**

* $p < .05$; ** $p < .001$

Drug use among ASDUs.

Patterns of drug use were described on a self-report form given only to the ASDU sample. The preferred stimulant was MA for 68.97% of the ASDU sample, with the remainder (31.03%) preferring cocaine[4]. Figure 8 shows the distribution of frequency of use of the preferred stimulant.

Figure 8
Frequency of Use

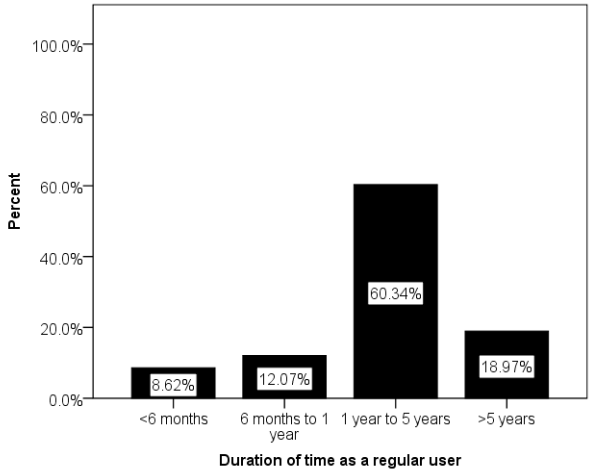


Daily use of the preferred stimulant was reported in 81.03% of ASDUs, 13.79% reported use five to six times per week, and 5.17% reported use three to four times per week (n = 58). No subject endorsed less frequent use.

Figure 9 shows the distribution of time spent as a regular stimulant user. Regular use was defined as two or more uses per week.

[4] This distribution is an artifact of recruitment strategy as MA users were recruited over a longer period of time than cocaine users

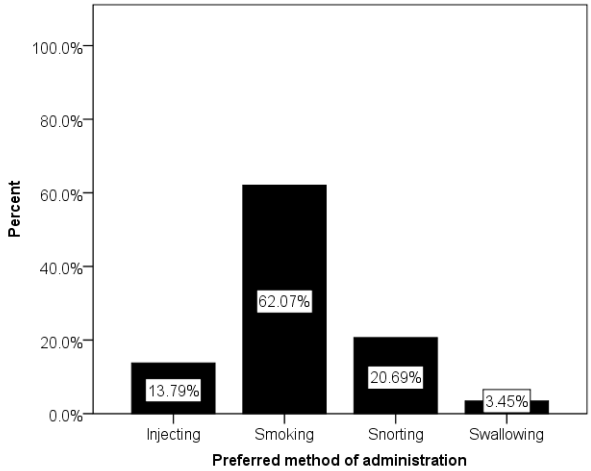
Figure 9
Duration of Time as a Regular User



Regular use for longer than 5 years was reported by 18.97% of ASDUs; regular use for 1 to 5 years was reported by 60.34% of ASDUs; and regular use for less than 1 year was reported by 20.69% (n = 58).

Figure 10 shows the preferred method of administration of the preferred stimulant. Preferred methods were not mutually exclusive from having tried other methods.

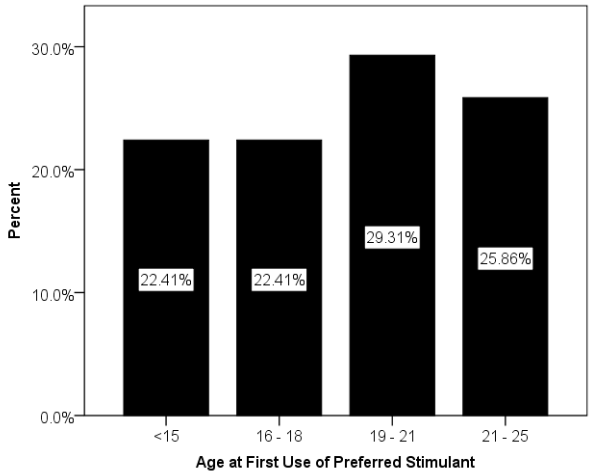
Figure 10
Preferred Method of Administration



The preferred method of administration was smoking (62.07%), followed by snorting (20.69%), injecting (13.79%) and swallowing (3.45%); 17.24% of the ASDUs reported injection use of the primary stimulant at least once (n = 58).

The mean age at first use of the preferred stimulant was 18.67 (SD = 4.29) years (n = 58). A distribution of age at first use of the preferred stimulant is presented in Figure 11.

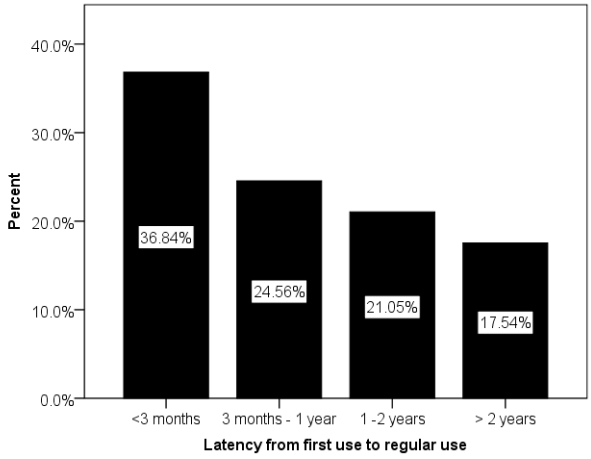
Figure 11
Age at First Use of Preferred Stimulant



All ASDUs first used the preferred stimulant between 12 and 25 years old.

Figure 12 shows the distribution of latencies from first use to regular use.

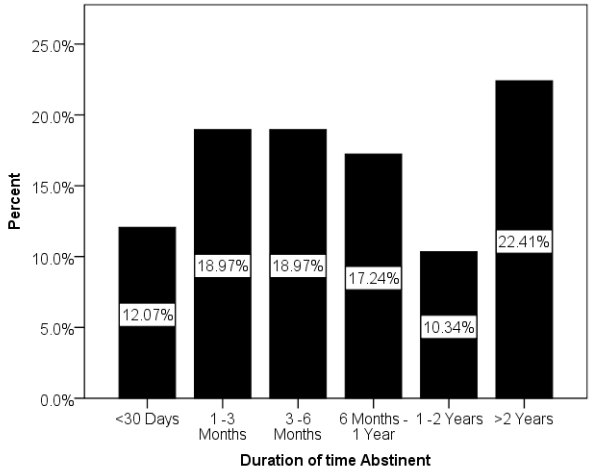
Figure 12
Latency From First Use to Regular Use



The latency period from first use to regular use (defined as two or more uses per week) was less than 1 month for 36.84% of ASDUs, 3 months to 1 year for 24.56%, 1 to 2 years for 21.05%, and longer than 2 years for 17.54% (n = 57).

Figure 13 shows the distribution of the duration of time abstinent.

Figure 13
Duration of Time Abstinent



The mean duration of time abstinent was 500 days (SD = 756); 3.45% had been abstinent < 1 week[5]; 8.62% had been abstinent 1 week to 1 month; 37.94% had been abstinent 1 month to 6 months; 17.24% had been abstinent 6 months to 1 year; 10.34% had been abstinent 1 year to 2 years; 15.51% had been abstinent 2 years to 5 years; 6.90% had been abstinent longer than 5 years.

Most (60.35%) of the ASDUs reported at least one unsuccessful previous attempt to stop using (n = 58); 63.79% reported seeking treatment for stimulant use (n = 58), and 62.07% reported seeking treatment for another substance (n = 58). The mean number of uses of the preferred stimulant in a single day was 11 (SD = 9; n = 48). Nearly all ASDUs (96.55%) reported a history of binge use (n = 58; defined as persistent use of large quantities of the preferred stimulant for a distinct period of time until running out or physical inability to use any more), with binges lasting for more than 6 days in 53.57% of the sample, and more than 10 days in 26.79% (n = 56).

A list of potential reasons for first use of the stimulant of choice was presented to the ASDUs (n = 58). Table 3 presents the percentage of ASDUs endorsing each response. As the items were not mutually exclusive, the total sums to more than 100%.

[5] Despite inclusion criteria of abstinence for longer than 7 days two subjects reported using stimulants in the previous week. Urine samples confirmed recent abstinence so data were retained.

Table 3
Reasons for First Use

Reasons for First Use	% Endorsed
For fun	84.48%
Because friends were doing it	82.76%
To get high	79.31%
To increase energy	53.45%
To "escape"	46.55%
To stay awake	41.38%
To replace another drug	37.93%
To increase attention or work performance	28.07%
For sexual properties	25.86%
To lose weight	20.69%

A list of common problems associated with drug misuse was presented (n = 58). Table 4 presents the percentage of ASDUs endorsing each response. As the items were not mutually exclusive, the total sums to more than 100%.

Table 4
Problems Associated with Use

Problems Associated with Use	% Endorsed
Weight loss	93.10%
Insomnia	93.10%
Financial problems	87.93%
Paranoia	81.03%
Problems at work	77.59%
Legal problems	68.97%
Hallucinations	68.97%
Violence/aggression	60.34%
Dental problems	51.72%
Increased blood pressure	51.72%
Skin problems	50.87%

Self-report questionnaires and symptom assessment.

Table 5 reports the means and group differences on the four self-report questionnaires (MIS, SAS, BDI, and BAI) in all three samples. PANSS data for the ASDU and NSIP samples are presented as well. All questionnaires and PANSS data are presented as sum scores.

Table 5
Self-Report Questionnaires and PANSS Scores

	HCs	ASDUs	NSIPs	
Questionnaire	**M (SD) : *n***	**M (SD) : *n***	**M (SD) : *n***	**Test Statistic**
MIS	3.35_a (2.35) : *31*	7.24_b (5.87) : *58*	11.48_c (6.76) : *23*	$F(2, 109) =$ 15.24**
SAS	7.87 (5.05) : *31*	10.95_a (6.13) : *58*	13.48_a (6.09) : *23*	$F(2, 109) =$ 7.95*
BDI	4.35 (5.72) : *26*	8.78_a (5.48) : *40*	11.00_a (6.81) : *19*	$F(2, 82) =$ 6.96*
BAI	4.42_a (4.57) : *26*	7.30_a (6.19) : *40*	14.50 (9.51) : *22*	$F(2, 85) =$ 13.85**
PANSS Positive Subscale	*N/A*	10.17 (2.86) : *58*	20.74 (3.49) : *23*	$t(79) =$ -14.06**
PANSS Negative Subscale	*N/A*	9.64 (2.91) : *58*	21.39 (4.72) : *23*	$t(28.9) =$ -11.14**
PANSS General Subscale	*N/A*	20.14 (4.21) : *58*	40.78 (7.78) : *23*	$t(27.3) =$ -12.05**

Note. Means not sharing the same subscript differ from each other * $p < .05$; ** $p < .001$

There were significant differences between groups for MIS total scores, $F(2, 109) = 15.24$, $p < .000$; post-hoc Bonferroni adjustment revealed a difference at all levels; HCs had the lowest scores, followed by higher scores for the ASDUs and even higher scores in the NSIP sample. There was also a significant group difference for SAS total scores, $F(2, 109) = 7.95$, $p = .001$; post-hoc Bonferroni adjustment revealed HCs had significantly lower scores than both ASDUs and NSIPs, with no difference between ASDUs and NSIPs. A significant between

group difference was also observed for BDI scores, $F(2, 82) = 6.96$, $p = .002$; post-hoc Bonferroni adjustment revealed significantly lower scores in HCs compared to both ASDUs and NSIPs, with no difference between ASDUs and NSIPs. A significant between group difference also existed for BAI scores, $F(2, 85) = 13.85$, $p < .001$; post-hoc Bonferroni adjustment revealed significantly higher scores in the NSIP sample compared to both HCs and ASDUs, with no difference between HCs and ASDUs.

PANSS total and subscale scores differed significantly between ASDUs and NSIPs: PANSS Total $t(28.7) = -14.63$, $p < .001$; PANSS Positive $t(79) = -14.06$, $p < .001$; PANSS Negative $t(28.90) = -11.14$, $p < .001$; PANSS General $t(27.26) = -12.05$, $p < .001$. In all cases severity of psychotic symptoms was lower in the ASDUs than in the NSIP sample.

Several between group differences were observed that are potential confounds for subsequent data analysis. These were: age, marital status, years of education, occupation status, history of cannabis dependence, current cigarette use, history of trouble with the law, and MIS, SAS, BDI and BAI scores. Only those variables with the greatest likelihood of influencing the outcome variable(s) of interest were used as covariates in subsequent analyses to assess threats to the validity of findings because of smaller sample sizes and a need to maintain statistical power.

Research Objective 1: Drug Use and Severity of Psychotic Symptoms

The first study hypothesis was that several parameters of stimulant dependence would be associated with severity and/or presence of psychotic symptoms in ASDUs. Specifically, duration of time as a regular stimulant user, MA use (as compared to cocaine use), age at first use, injection use, history of cannabis dependence and frequency of use were all hypothesized to significantly predict severity of negative symptoms of psychosis, whereas duration of time abstinent was not predicted to contribute to higher PANSS Negative symptom severity scores. To test this prediction, all ASDU data were used yielding a total sample of 58. A multiple linear regression analysis was run with the PANSS Negative scale total as the dependent variable. To avoid over-fitting the regression

model (Babyak, 2004) all seven predictor variables were entered simultaneously into the regression model including: duration of time abstinent, duration of time as a regular user, injection use (or not), daily use (or less than daily), age at first use, MA use (or not), and a history of cannabis dependence (or not). A visual examination of the scatterplot of the residuals showed significant heteroscedasticity, with variance increasing with increasing symptom score. The non-normally distributed PANSS Negative scale scores were log-transformed after being subtracted from a constant to make the lowest value one. Examination of each independent variable residual plot showed that duration of time abstinent was contributing to the heteroscedasticity. To reduce the strong skew of duration of time abstinent it was logarithmically transformed. These transformations normalized the duration of time abstinent variable, but the PANSS Negative scale score did not achieve normality. However, re-examination of the residuals showed no significant violation of assumptions. No multivariate outliers were found using $p < .001$ criterion for Mahalanobis distance. Although the overall fit of the regression model was not significant, change in $R^2 = .16$, $F(7, 50) = 1.39$, $p = .231$, MA use exhibited a trend towards a significant positive relationship with PANSS Negative symptoms, $\beta = 0.28$, $p = .051$ (see Table 6).

Table 6
Predictors of PANSS Negative Symptoms among ASDUs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		0.04	-0.73 – 0.81	.923
Duration of time abstinent (transformed)	-0.17	-0.08	-0.22 – 0.05	.233
Duration of time as a regular user	0.11	0.04	-0.07 – 0.15	.442
Injection use	-0.02	-0.02	-0.27 – 0.23	.866
Daily use	-0.04	-0.03	-0.26 – 0.19	.775
Age at first use	0.13	-0.01	0.01 – 0.033	.343
MA use	0.28	0.19	-0.001 – 0.39	.051
History of cannabis dependence	0.23	0.16	-0.03 – 0.34	.101
Model R^2			0.163	

*$p < .10$; ** $p < .05$

This regression was repeated assessing threats to validity introduced by confounding variables. Age, gender, years of education, current cigarette smoking, MIS, SAS, BDI and BAI scores could have an impact on the PANSS Negative subscale. Relationship to PANSS Negative scale score was assessed in each of these variables. Those with a significant relationship were used as covariates. Years of education, MIS and BAI scores were significantly correlated with PANSS Negative scale scores. When entered as covariates the overall model continued to lack significance, change in $R^2 = .17$, $F(10, 29) = 1.10$, $p = .393$. Again, no single variable was a significant predictor of PANSS Negative symptom severity.

A second set of regression analyses were conducted, with PANSS Positive Scale scores as the outcome variable. A visual examination of the residuals scatter plot showed significant curvilinear heteroscedasticity. The PANSS Positive scale score was log-transformed after being subtracted from a constant to make the lowest value one. Examination of each independent variable residual plot showed that duration of time abstinent was contributing to the heteroscedasticity. To reduce the strong skew of duration of time abstinent, it was logarithmically

transformed. These transformations normalized the duration of time abstinent but the PANSS Positive scale score did not achieve normality. However, re-examination of the residuals showed no significant violation of assumptions. No multivariate outliers were found using $p < .001$ criterion for Mahalanobis distance. Again, to avoid over-fitting the regression model (Babyak, 2004) all seven predictor variables were entered into the regression. Results indicated that the predictors accounted for a significant portion of variance in PANSS Positive symptom scores, change in $R^2 = .24$, $F(7, 50) = 2.25$, $p = .046$. This indicates that 13.3% (*Adjusted* R^2) of the variability in positive symptom severity in ASDUs was predicted by the seven variables. Table 7 shows the results of this regression.

Table 7
Predictors of PANSS Positive Symptoms among ASDUs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		0.65	-0.10 – 1.40	.090
Duration of time abstinent (transformed)	-0.07	-0.03	-0.16 – 0.10	.632
Duration of time as a regular user	-0.23	0.09	-0.01 – 0.20	.084
Injection use	0.18	0.17	-0.08 – 0.41	.175
Daily use	-0.26	-0.22	-0.43 – 0.002	.053
Age at first use	-0.23	-0.02	-0.04 – 0.003	.092
MA use	0.15	0.11	-0.08 – 0.30	.260
History of cannabis dependence	0.09	0.06	-0.12 – 0.15	.496
***Model* R^2**	0.24*			

* $p < .05$

As with the negative symptom analysis, this regression was repeated assessing threats to validity. Again, age, gender, years of education, current cigarette smoking, MIS, SAS, BDI and BAI were examined for significant relationship to PANSS Positive scale score and those with significant relationships were assessed as covariates. MIS and BAI scores were significantly correlated with PANSS Positive scale scores. When assessed as covariates the overall model showed a trend towards significance, change in $R^2 = .15$, $F(9, 30) =$

2.19, $p = .052$. This indicates that 21.5% (*Adjusted* R^2) of the variability in positive symptom severity in ASDUs was predicted by the seven variables, with MIS as a significant predictor.

Research Objectives 2 and 3: Neurochemical Correlates of Psychotic Symptoms in Stimulant-Dependent Users

NAA and Glu.

The second and third hypotheses were tested concurrently. They stated that NAA would be reduced in ASDUs relative to HCs and that the ASDUs would present with abnormalities of Glu as compared to HCs. To test these hypotheses all HCs and ASDUs with valid spectroscopy data were included. Four ASDUs were eliminated from analysis because they were recruited into the study prior to detection of the procedural error in the ^{1}H-MRS protocol, rendering their data incomparable to the remaining ASDU sample. The total remaining sample was 73 (27 HCs and 46 ASDUs). Preliminary analysis began with an examination of voxel tissue composition (i.e., GM, WM, and CSF). In this examination outliers were apparent. Several subjects included in this analysis had been marked as "Review" by the centre specialist. This designation implies that one of SNR or line width did not fit within the outlined parameters. Being marked "Review" may indicate, but does not necessitate, relationship to tissue composition. As such, subjects with abnormal tissue composition values (outliers) and being marked as "Review" were excluded from analysis. This reduced the final sample to 69 (25 HCs and 44 ASDUs). Analysis of the tissue composition data revealed one non-normal distribution, but due to moderate sample size ($n > 20$) analysis was considered robust to this violation. As the groups differed on age with the HCs younger than the ASDUs ($M = 23.80$, $SD = 4.66$; $M = 26.64$, $SD = 3.72$, respectively; $t(67) = -2.77$, $p = .007$) and age can significantly impact metabolite values, age was evaluated as a covariate. Age was non-normally distributed but because of adequate sample sizes, no transformation was made. Correlation analysis between the metabolites showed moderate significant negative correlations, appropriate for a MANCOVA. No multivariate outliers were found using $p < .001$ criterion for Mahalanobis distance. Assumptions of linearity,

homogeneity of variance, and homogeneity of regression were met. Age was not significantly related to tissue composition, $F(3, 64) = 1.81$, $p = .155$; while continuing to control for age, tissue composition did not differ by group, $F(3, 64) = 0.28$, $p = .830$. Re-running the analysis without the effect of age supported this finding, with no difference in tissue composition between groups, $F(3, 65) = 0.82$, $p = .490$. With no difference in tissue composition between groups, it was not a necessary covariate in analysis of metabolites.

A MANCOVA was used to test differences in metabolite data in the mPFC, with age as a covariate. Neurochemical and age data were examined; all distributions were normal. Percent standard deviations were set to <15% for NAA, Cr and Cho, and < 20% for Glu. One subject was identified as having a SD range outside of the norm for Glu (>20%) and was also identified as an outlier in Glu measures. This subject was removed from analysis. Correlation analysis revealed moderate significant correlations between the metabolites, appropriate for a MANCOVA. No multivariate outliers were found using $p < .001$ criterion for Mahalanobis distance. Assumptions of linearity, homogeneity of variance, and homogeneity of regression were met. Age was judged to be adequately reliable for covariance analysis. Using the Wilks' criterion the combined metabolites were significantly related to age $F(3, 63) = 4.20$, $p = .009$. The overall model was significant $F(3, 63) = 5.25$, $p = .003$. To investigate more specifically the power of the age to adjust the metabolites, multiple regression was run for each metabolite in turn, with age acting as a predictor. Age provided significant adjustment only for NAA, $B = -0.06$, 95% CI = -0.10 - -0.03, $t(65) = -3.44$, $p = .001$. There were no effects of age for Cho or Glu. Effects of group on the metabolites were assessed in univariate analysis. A statistically significant effect in the mPFC was present for NAA, $F(1,65) = 8.57$, $p = .005$ and Glu, $F(1, 65) = 5.51$, $p = .022$, but not for Cho, $F(1,65) = 0.53$, $p = .471$. NAA and Glu were both lower in the ASDU group as compared to the HC group. This analysis was re-run without controlling for age; the main effect was significant $F(3, 64) = 6.96$, $p < .001$. Univariate analysis shows significance for both NAA, $F(1, 66) = 15.61$, $p < .001$, and Glu, $F(1, 66)= 8.08$, $p = .006$.

This analysis was re-run covarying for the remaining potentially confounding between group differences. These included years of education, history of cannabis dependence, current cigarette smoking and MIS, BDI and SAS scores. In assessment of these potential covariates, only BDI scores were an appropriate fit for the MANCOVA. BDI total score provided significant adjustment for Cho only, B = -0.02, 95% CI = -0.031 - -0.005, $t(49) = -2.71$, p = .009 Analysis with BDI as a covariate continued to show an overall significant model $F(6, 96) = 3.68$, $p = .002$; the pattern of results remained the same. Table 8 represents the metabolite data.

Table 8
Metabolite Group Comparison

Variable	HC M (SD) n = 24	ASDU M (SD) n = 44	*p* Value
NAA	9.74 (0.60)	9.07 (0.70)	<.001
Glu	6.98 (1.05)	6.23 (1.03)	.006
Cho	1.87 (0.32)	1.81 (0.30)	.491

Research Objective 4: Cognitive Correlates of Psychotic Symptoms: Processing Speed

The fourth hypothesis was that ASDUs would present with cognitive processing speed intermediary to HCs and NSIPs and that PANSS Negative symptom severity would impact performance.

To test this hypothesis all HCs, ASDUs and NSIP patients with available standardized Stroop Colour and Word Test colour reading *t*-scores were used, yielding a total sample of 112 (31 HCs, 58 ASDUs, and 23 NSIPs). An ANCOVA was used to test for between group differences; since age and education differed between groups, and are factors that could affect processing speed, they were included as covariates. The Stroop Colour and Word Test colour reading *t*-score was normally distributed in each group according to the Shapiro-Wilk test. Assessment of test assumptions (linearity, homogeneity of regression of slopes and homogeneity of variance) were all satisfactory. The analysis revealed a main effect of group, $F(2, 107) = 10.14$, $p < .001$. Post-hoc Bonferroni adjusted

comparisons indicated that the NSIP sample exhibited significantly worse performance on cognitive processing speed as assessed by the Stroop Colour and Word Test colour reading score (M = 39.04, SD = 8.53) compared to both ASDUs (M = 46.84, SD = 7.25) and HCs (M = 49.23, SD = 8.16). ASDUs and HCs did not significantly differ from each other.

To determine whether PANSS Negative symptom severity accounted for these group differences, a supplementary ANCOVA was run comparing ASDUs and NSIPs with PANSS Negative symptom scale scores as a covariate. Examination of this variable showed a non-normal distribution. It was log-transformed after being subtracted from a constant to make the lowest value one. The result of the two-group ANCOVA showed a significant effect of this covariate that, when added to the model, eliminated the previous between-group difference between ASDUs and NSIPs, $F(1, 76) = 0.29$, $p = .593$. This analysis was re-run assessing for threats to validity, by controlling for the between group differences of MIS and BAI scores. The analysis continued to lack significance, $F(1, 55) = 3.66$, $p = .061$.

Supplemental tests of processing speed. Confirmation of these findings was tested by examining the results of two additional tests of processing speed, the TMT-A and Digit Symbol Substitution Test. In the TMT-A two extreme outliers (> three inter-quartile ranges below the first quartile) were removed from analysis, yielding a sample of 25 HCs, 40 ASDUs, and 22 NSIPs. The age, sex, and education-standardized TMT-A *z*-score showed a non-normal distribution, however equality of variances was present so the variable was not transformed. As the groups differed on age and education, they were entered as covariates in the analysis. The ANCOVA showed a trend towards significance, $F(2, 82) = 2.99$, $p = .056$ indicating no difference between group means, HC (M = 0.16, SD = 0.91), ASDU (M = -0.32, SD = 1.68), NSIP (M = -0.91, SD = 1.66). Post-hoc Bonferroni adjusted comparisons revealed a trend towards a significant difference between HCs and NSIPs ($p = .050$). No follow-up ANCOVA was performed.

Confirmation of the Stroop Colour and Word Test findings was tested by examining the Digit Symbol Substitution Test. The sample for this task was 24

HCs, 40 ASDUs and 23 NSIPs. The standardized *z*-score accounted for age, but not education. However, as age and education differed between groups, both were entered as covariates. Examination of the Digit Symbol Substitution Test score showed that it was not normally distributed; it was transformed by square root. Normalization was not achieved but equality of variances was achieved. Assessment of test assumptions (linearity, homogeneity of regression of slopes and homogeneity of variance) were all satisfactory. This analysis revealed a main effect of group, $F(2, 82) = 13.97$, $p < .001$. Post-hoc Bonferroni adjusted comparisons indicated that the NSIP group exhibited significantly worse performance on this measure of processing speed (M = -1.07, SD = 0.63) compared to both ASDUs (M = -0.37, SD = 0.92) and HCs (M = 0.28, SD = 1.02). ASDUs and HCs were not significantly different.

To determine whether severity of negative symptoms accounted for the difference between ASDUs and NSIPs group differences, a supplementary ANCOVA was run comparing ASDUs and the NSIP sample, adding PANSS Negative symptom severity as an additional covariate. Examination of this variable showed a non-normal distribution. It was log-transformed after being subtracted from a constant to make the lowest value one. The result of the two-group ANCOVA showed a significant effect of the covariate that eliminated the between-group difference between ASDUs and NSIPs, $F(1, 58) = 0.37$, $p = .543$. This finding replicated the finding on the Stroop Colour and Word Test colour reading measure.

Research Objective 5: Cognitive Correlates of Psychotic Symptoms: Executive Functioning

The fifth hypothesis was that NSIPs would present with worse performance on an executive function task as compared to ASDUs and that both NSIPs and ASDUs would perform worse than HCs. It was further hypothesized that performance on a task of executive function would not be related to negative symptoms of psychosis. To test this hypothesis all HCs, ASDUs and NSIPs with available standardized WCST perseverative error *z*-scores were used, yielding a total sample of 101 (23 HCs, 55 ASDUs, and 23 NSIPs). The calculation of the *z*-

score accounted for age. Three extreme outliers were present with very low scores in the HC group (> two standard deviations below zero). These outliers were removed from subsequent analysis, leaving 20 HCs and a total sample of 98. The WCST perseverative error *z*-score was not normally distributed between groups. It was transformed with an inverse after being subtracted from a constant to make the largest value one. After the transformation equality of variances between groups was achieved. Linearity and homogeneity of regression of slopes assumptions were met. Because education and age differed between groups and may affect performance on an executive function task, an ANCOVA was run covarying education and age. The initial three group comparison of WCST perseverative error scores showed a significant main effect, $F(2, 93) = 9.15$, $p < .001$. Post-hoc Bonferroni adjusted comparisons showed that HCs had better performance on this measure of executive function (M = -0.05, SD = 1.49) than both ASDUs (M = -0.37, SD 1.07) and NSIPs (M = -0.87, SD = 1.57), with no difference between ASDUs and NSIPs. A Kruskal-Wallis non-parametric test was run with the untransformed WCST perseverative error measure because the dependent variable had been transformed; the same pattern of results emerged, $\chi^2(2) = 17.58$, $p < .001$.

To determine whether negative symptoms accounted for these findings, a supplementary ANCOVA was run, comparing ASDUs and NSIPs, adding the additional covariate of PANSS Negative symptom severity. Examination of this variable showed a non-normal distribution. It was log-transformed after being subtracted from a constant to make the lowest value one. The result of the ANCOVA showed no effect of the covariate, and no change in the between-group comparison, $F(1, 73) = 0.03$, $p = .860$. These results remained the same when controlling for MIS and BAI scores.

Supplemental tests of executive functioning. Confirmation of this result was tested by examining the Stroop Colour and Word Test interference measure. The standardized *z*-score was examined in a sample of 30 HCs, 58 ASDUs and 23 NSIPs, and had a normal distribution according to the Shapiro-Wilk test. Assessment of test assumptions (linearity, homogeneity of regression of slopes

and homogeneity of variance) were all satisfactory. An ANCOVA was run, covarying for age and education because age and education differed between groups, and could affect task performance. This analysis revealed no significant main effect, $F(2, 106) = 0.95$, $p = .910$, indicating no difference between group means: HC (M = 0.38, SD = 0.60), ASDU (M = 0.22, SD = 0.81), and NSIP (M = 0.38, SD = 0.56). No follow-up ANCOVA with PANSS Negative symptom severity scores was run.

A second confirmatory test was the TMT-B. The standardized *z*-score showed two extreme outliers (> three inter-quartile ranges below the first quartile) that were removed from analysis, yielding a sample of 25 HCs, 40 ASDUs, and 22 NSIPs. The age, sex, and education-standardized TMT-B *z*-score showed a non-normal distribution, however equality of variances was present so the variable was not transformed. As the groups differed on age and education, they were entered as covariates in the analysis. The ANCOVA showed significance, $F(2, 82) = 12.49$, $p < .001$, indicating differences between group means. Post-hoc Bonferroni adjusted comparisons revealed a significant difference between HCs (M = 0.43, SD = 0.77) and both NSIPs (M = -0.90, SD = 1.08, $p < .001$) and ASDUs (M = -0.34, SD = 1.13, $p = .004$). There was no significant finding between ASDUs and NSIPs. No follow-up ANCOVA was performed.

Table 9 summarizes the results of cognitive correlates of psychotic symptoms between groups. Table 10 provides summarized data for the supplemental tests of processing speed and executive functioning.

Table 9
Processing Speed and Executive Functioning Group Differences

Variable	HC M (SD) *: n*	ASDU M (SD) *: n*	NSIP M (SD) *: n*	*p* Value
Stroop colour reading *t*-score	49.23_a (8.16) *: 31*	46.84_a (7.25) *: 58*	39.04 (8.53) *: 23*	< .001
Stroop Adjusted Means (controlling PANSS Negative scale score)	*N/A*	45.13 (9.37)	43.38 (11.85)	.593
WCST perseverative error *z*-score	0.46 (0.40) *: 20*	-0.37_a (1.07) : *55*	-0.87_a (1.57) *: 23*	< .001
WCST Adjusted Means (controlling PANSS Negative scale score)	*N/A*	0.31 (2.30)	0.32 (1.53)	.860

Note. Values not sharing the same subscript differ from each other

Table 10
Supplemental Tests of Processing Speed and Executive Function

Variable	HC M (SD) *: n*	ASDU M (SD) *: n*	NSIP M (SD) *: n*	*p* Value
Processing Speed				
TMT-A *z*-score	0.16_a (0.91) : *25*	-0.32_a (1.68) : *40*	-0.91 (1.66) : *22*	.056
Digit Symbol Substitution Test *z*-score	0.28 (1.02) : *24*	-0.37 (0.92) : *40*	-1.07 (0.63) : *23*	<.001
Executive Function				
Stroop Colour & Word Interference *z*-score	0.38 (0.60) : *30*	0.22 (0.81) : *58*	0.38 (0.56) : *23*	.910
TMT-B *z*-score	0.43 (0.77) : *25*	-0.34_a (1.13) : *40*	-0.90_a (1.08) : *22*	<.001

Note. Values not sharing the same subscript differ from each other

Research Objective 6: Predicting Severity of Psychotic Symptoms by Co-Registration of Cognitive and Neurochemical Measures

The sixth hypothesis stated that NAA, Glu and processing speed would predict severity of psychotic symptoms in both ASDUs and NSIPs, independently. This hypothesis was tested through a regression analysis. All ASDUs and NSIPs with WCST, Stroop Colour and Word Test and ^{1}H-MRS data were included in analysis, yielding a total sample of 67 (44 ASDUs and 23 NSIPs). Prior to

analysis, voxel tissue composition was analyzed for outliers. As in previous analysis, any subject that was an outlier and had an abnormal SNR or line width value was excluded from analysis. This resulted in excluding two ASDUs. A standard enter-method multiple regression was run with the PANSS Negative scale total as the dependent variable and NAA, Cho, Glu, WCST perseverative errors *z*-score and Stroop Colour and Word Test colour reading *t*-score as the predictor variables. Additionally, age and education were entered into a first block as control variables. The non-normally distributed PANSS Negative scale score log-transformed after being subtracted from a constant to make the lowest value one. The PANSS Negative scale score did not achieve normality, but re-examination of the residuals showed no significant violations of assumptions. WCST perseverative error *z*-score was also transformed, with an inverse after being subtracted from a constant to make the largest value one, to achieve a normal distribution. No multivariate outliers were found using $p < .001$ criterion for Mahalanobis distance. To avoid over-fitting the regression model (Babyak, 2004) all predictor variables were entered into the regression. The analysis was run independently for ASDUs and NSIPs as their spectroscopy data were not directly comparable. In ASDUs a significant relationship between the predictor variables and PANSS Negative scores emerged, $F(7, 34) = 2.46$, $p = .037$. In the NSIPs the model approached significance, $F(7,15) = 2.57$, $p = .060$. The *Adjusted* R^2 of 0.199 for ASDUs and 0.333 for NSIPS indicates that 19.9% and 33.3% (respectively) of the variance in PANSS Negative scores was accounted for by the predictor variables. Age and education as covariates did not provide a significant change in R^2 in either group: NSIP, $F(5,15) = 2.65$, $p = .065$, or ASDUs, $F(5, 34) = 1.62$, $p = .180$. In ASDUs only Cho in the mPFC contributed significantly to the model, $t = 2.67$, $p = .012$, B = .18. In NSIPs a different pattern emerged where no single predictor significantly contributed to the model. The results of these analyses are shown in Table 11 and Table 12.

Table 11
Combined Cognitive and Neurochemical Predictors of PANSS Negative Symptoms in ASDUs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		1.31	0.68 – 1.94	< .001**
Covariates				
Age	-0.16	-0.01	-0.02 – 0.01	.354
Years of Education	-0.24	-0.01	-0.03 – 0.01	.192
Main Variables				
NAA	-0.24	-0.04	-0.10 – 0.03	.248
Cho	0.49	0.18	0.04 – 0.31	.012*
Glu	0.01	0.001	-0.03 – 0.03	.973
WCST perseverative error *z*-score	0.03	0.04	-0.39 – 0.46	.170
Stroop colour reading *t*-score	-0.12	-0.002	-0.007 – 0.003	.471
Model R^2		0.336*		

* $p < .05$; ** $p < .001$

Table 12
Combined Cognitive and Neurochemical Predictors of PANSS Negative Symptoms in NSIPs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		1.64	1.16 – 2.12	< .001**
Covariates				
Age	0.01	-0.001	-0.02 – 0.02	.867
Years of Education	0.01	0.01	-0.02 – 0.04	.409
Main Variables				
NAA	-0.43	-0.04	-0.09 – 0.01	.086
Cho	-0.02	-0.01	-0.18 – 0.16	.937
Glu	0.29	0.02	-0.01 – 0.05	.156
WCST perseverative error *z*-score	-0.27	-0.27	-0.70 – 0.17	.209
Stroop colour reading *t*-score	-0.21	-0.002	-0.01 – 0.003	.367
Model R^2		0.545		

* $p < .05$; ** $p < .001$

Re-running the analysis without age and education, the predictor variables approached a significant relationship with PANSS Negative scale scores in ASDUs, $F(5, 36) = 2.47$, $p = .051$, and were significant predictors in NSIPs, $F(5, 17) = 3.71$, $p = .019$. In ASDUs, Cho was the only significant predictor for the model, $t = 2.63$, $p = .013$. In NSIPs NAA was the only significant predictor for the model, $t = -2.61$, $p = .018$. NAA was significantly negatively correlated with age only in the ASDU sample ($r = .33$, $p = .028$). NAA was not significantly correlated with education in either sample. Years of education significantly correlated negatively with PANSS Negative scale scores in the ASDU sample only ($r = -.36$, $p = .012$).

Assessing potential threats to the validity of this finding showed that none of MIS, SAS, BDI, and BAI scores, cigarette smoking nor gender showed a significant relationship with PANSS Negative scale scores.

Re-running the analysis for positive symptoms showed that the predictors approached a significant relationship to PANSS Positive symptom severity scores for ASDUs, $F(7, 34) = 2.26$, $p = .064$, but were not significant in NSIPs, $F(7, 15) = 0.19$, $p = .984$. The *Adjusted* R^2 of 0.176 for ASDUs and -0.350 for NSIPs indicates that 17.6% and 35% (respectively) of the variance of the PANSS Positive scores was accounted for by the predictor variables. Age and education as covariates provided a significant change to R^2 only in the ASDUs, $F(5, 34) = 2.74$, $p = .035$. In ASDUs, Stroop Colour and Word Test colour reading *t*-score and NAA in the mPFC were significant contributors to PANSS Positive score, $t = -2.88$, $p = .007$, B = -0.04 and $t = 2.18$, $p = .036$, B = 0.27, respectively. None of the variables were significant predictors for NSIPs. The results of these analyses are shown in 13 and Table 14.

Table 13
Combined Cognitive and Neurochemical Predictors of PANSS Positive Symptoms in ASDUs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		1.88	-0.62 – 4.37	.136
Covariates				
Age	0.24	0.03	-0.01 – 0.07	.179
Years of Education	0.002	0.01	-0.07 – 0.08	.954
Main Variables				
NAA	0.45	0.27	0.02 – 0.52	.036*
Cho	-0.24	-0.34	-0.87 – 0.20	.210
Glu	0.11	0.05	-0.08 – 0.18	.472
WCST perseverative error *z*-score	-0.18	-0.97	-2.62 – 0.69	.245
Stroop colour reading *t*-score	-0.48	-0.03	-0.05 – -0.010	.007*
Model R^2		0.317		

* $p < .05$; ** $p < .001$

Table 14
Combined Cognitive and Neurochemical Predictors of PANSS Positive Symptoms in NSIPs

Variable	Standardized Beta	*B*	95% CI	*p* Value
Constant		4.42	1.72 – 7.09	.003*
Covariates				
Age	0.22	0.03	-0.07 – 0.12	.548
Years of Education	0.04	0.01	-0.14 – 0.16	.909
Main Variables				
NAA	-0.13	-0.05	-0.30 – 0.21	.703
Cho	-0.12	-0.15	-1.09 – 0.80	.737
Glu	0.03	0.01	-0.16 – 0.18	.910
WCST perseverative error *z*-score	0.25	0.28	-2.13 – 2.69	.807
Stroop colour reading *t*-score	0.04	0.002	-0.03 – 0.03	.909
Model R^2		0.080		

* $p < .05$; ** $p < .001$

Running the analysis without controlling for age and education produced a similar pattern. The overall model was significant for ASDUs, $F(5, 36) = 2.69$, $p = .036$, but not for NSIPs, $F(5, 17) = 0.159$, $p = .974$. In ASDUs only Stroop Colour and Word Test colour reading *t*-score was a significant predictor for the model, $t = -2.81$, $p = .008$, but NAA was no longer significant, $t = 1.71$, $p = .095$. For NSIPs no single variable was a significant predictor for the model. NAA was not significantly correlated with age or positive symptom scores.

Assessing potential threats to the validity of this finding showed that in the ASDU sample BAI and MIS showed a significant relationship with PANSS Positive scale scores, whereas SAS and BDI scores, cigarette smoking and gender did not. Controlling for BAI and MIS, the overall model continued to trend towards significance, $F(9, 21) = 2.27$, $p = .059$. In the NSIP sample, BAI showed a significant relationship with PANSS Positive scale scores, whereas MIS, SAS and BDI scores, gender and cigarette smoking did not. Controlling for BAI, the overall model remained non-significant, $F(8, 13) = 0.91$, $p = .539$. In both cases, the covariates did not affect the primary findings.

In summary, Cho in the mPFC was a significant predictor of negative symptoms in ASDUs only, with and without controlling for age and education. The Stroop Colour and Word Test was a significant predictor of positive symptoms in ASDUs only, with and without controlling for age and education; NAA in the mPFC was only a significant predictor of positive symptoms in ASDUs only when age and education were controlled for. In NSIPs no included variable was a significant predictor of positive symptom scores. Only NAA in the mPFC was a significant predictor of negative symptom scores when not controlling for age and education. The individual predictors for the negative symptom severity measure differed between the two groups. NAA was the only hypothesized significant predictor of symptom severity.

Chapter 5: Discussion

The neurodevelopmental hypothesis of schizophrenia posits that insults during neurodevelopment result in pathology associated with schizophrenia. This general interpretation of the theory allows for the possibility of many definitions of "insults". Commonly a singular insult is described, involving either obstetric complications or risk-genes. An alternative interpretation to this theory is that at least two insults, or "hits", are required for the associated schizophrenia pathology to develop. This study proposed that one potential "hit" may be stimulant dependence. No studies have examined the biological and cognitive correlates of stimulant-induced psychotic symptoms in comparison to a healthy control group and a group of non-substance-induced psychosis patients. Determining the neurochemical and cognitive profile of this stimulant group may support the theory of stimulant use as a second hit, or, alternatively, may indicate that a substance-induced psychosis, though similar clinically, is a unique psychotic disorder with a unique associated pathology and cognitive profile.

This study investigated psychotic symptoms in abstinent stimulant-dependent users (ASDUs) in comparison to a healthy control (HC) group and a group of non-substance-induced first episode psychosis (NSIP) patients. The primary findings were that (1) drug use patterns were unable to predict severity of psychotic symptoms in ASDUs; however, MA dependence as opposed to cocaine dependence approached significance to be more likely associated with psychotic symptoms than cocaine dependence; (2) processing speed was associated with the presence and/or severity of negative symptoms such that worse impairment as associated with more negative symptoms of psychosis; (3) executive functioning was not associated with the presence and/or severity of negative symptoms; (4) NAA and Glu were reduced in the mPFC in ASDUs as compared to HCs; (5) Cho in the mPFC was a significant predictor of negative symptoms in ASDUs only, with and without controlling for age and education (6) the Stroop Colour and Word Test processing speed component was a significant predictor of positive symptoms in ASDUs only, with and without controlling for age and education; (7) NAA in the mPFC was only a significant predictor of positive symptoms in

ASDUs when age and education were controlled for; (8) in NSIPs no included variables were a significant predictor of positive symptom scores; (9) in NSIPs only NAA in the mPFC was a significant predictor of negative symptom scores when not controlling for age and education. Each of these findings will be discussed independently.

Groups differed on age and years of education. Where appropriate, these differences were controlled for. As expected, the ASDUs presented with less severe symptoms of psychosis across all PANSS subscales as compared to the NSIPs. As well, ASDUs had less severe symptoms of anxiety but no difference in severity of symptoms of depression as compared to NSIPs. Unexpectedly, the ASDUs collectively did not present as psychosis prone. Few ASDUs presented with the published cut-off scores for the scales. Therefore, MIS and SAS were also controlled for to account for some extreme outliers.

Research Objective 1: Drug Use and Severity of Psychotic Symptoms

Selected drug use variables were used as predictor variables in a regression analysis to determine if specific features of stimulant misuse were associated with psychotic symptoms in stimulant users, and therefore of the role of stimulant misuse as a possible 'second trigger' in the two-hit model of schizophrenia. Duration of time abstinent, duration of time using, injection use, daily use, age at first use, MA or cocaine use, and a history of cannabis use were not significant predictors of negative symptoms as measured by the PANSS negative subscale. MA use, however, approached significance as a predictor, suggesting that MA use may be a stronger predictor of negative symptom severity in abstinence than cocaine use. Future studies may benefit from a severity use index measure based on several patterns of use variables.

MA is a much more potent stimulant than cocaine, affects DA transmission in a more potent manner and has a faster transition to problematic use (Gonzalez Castro et al., 2000; Y. Zhang et al., 2001). The present results are consistent with previous reports of MA use being more likely to lead to psychotic symptoms than cocaine (Mahoney et al., 2008). It may be that the more potent action of MA on dopaminergic transmission is better able to mimic dopaminergic

changes that are associated with schizophrenia. In an already vulnerable brain, MA's aggressive action on DA may require less use and less frequent use than compared to cocaine with a similar pattern of use, explaining the higher rates of MA-induced psychosis as compared to cocaine-induced psychosis. The lack of a clearly significant finding may have been confounded by sample size effects.

History of cannabis dependence was also close to significance as a predictor of negative symptoms. The literature on the relationship between cannabis use and psychosis is substantial. Many have outlined a relationship between a pre-existing vulnerability (often genetic) and early cannabis use relating to psychosis (e.g., M. Cohen et al., 2008). The proposed mechanism may involve the ability of tetrahydrocannabinol (THC; the psychoactive ingredient in cannabis) to increase DA in the mesolimbic pathway, while reducing DA in the mPFC after chronic use (Linszen & van Amelsvoort, 2007; Luzi et al., 2008). Further, some have suggested that THC's action on the cannabinoid system during adolescence can affect growth of axons, neuron positioning, and WM integrity (Malone, Hill, & Rubino, 2010). These effects during neural development may negatively impact normal development resulting in the pathology associated with schizophrenia.

The lack of significance in the overall model and lack of significant contribution from the remaining variables is somewhat unexpected. It may be that stimulant use alone can trigger the onset of psychosis, regardless of the pattern or severity of that use. In other words, any stimulant use is sufficient to exogenously trigger the onset of psychosis in an already vulnerable population, regardless of the pattern of that use. Alternatively, these null findings may be an artifact of the inability to recruit a sample of abstinent stimulant users with a wider range of psychotic symptom scores.

There is some evidence that injection use may be related to psychotic symptoms in stimulant users (Hall et al., 1996). Hall and colleague's reported that psychotic symptom severity was related to injection use in the previous 6 months; the psychotic symptoms assessed were violent behaviour, paranoia and hallucinations. The authors offer no explanation for why injection use would

relate to more severe psychotic symptoms. Hall's study predicted primarily positive symptoms, and did not use the PANSS scale, which may account for the differences in relation to the current study.

Daily use (as opposed to less frequent use) also did not account for presence and/or severity of PANSS Negative symptoms. In the current sample 81% of the ASDUs were daily users, and the remaining 19% used three to four times per week, at minimum. It may be that the necessary frequency of use to trigger psychosis is less than three times per week so that the entire sample in this study fell within the range of frequency of use that may be sufficient to trigger psychosis, given a pre-existing vulnerability. Alternatively, it is very difficult to determine the dose of drug used and it may be that those who used less frequently used higher doses so that it is not the frequency *per se* that is critical to triggering psychosis but the amount of substance used. This interpretation is consistent with animal models, where only higher doses of MA in rats produced prepulse inhibition, an animal behaviour representative of psychosis (Hadamitzky, Markou, & Kuczenski, 2011).

The dichotomous breakdown of the duration of time as a regular user in this study was those who used longer than 5 years and those who used less than 5 years. Many (60%) of the stimulant users in the less than 5 year group had been regular users for at least 1 year. It is possible that the critical duration of use time period is substantially less than 1 year, such that most of the subjects in this study were regular users of stimulants for a duration of time longer than required to trigger the emergence of psychotic symptoms given a vulnerable state.

Duration of time abstinent was not a predictor of negative symptoms. This is consistent with the proposed model. If a vulnerability for psychosis exists in an individual who then engages in chronic stimulant use that triggers the psychotic symptoms, cessation of use would have little impact on the presence of psychotic symptoms. In this view, the second hit is a trigger for onset of psychosis, not a sustaining factor. As in NSIPs, once psychotic symptoms emerge, spontaneous cessation of symptoms over time, without treatment, is rare. This is supported by an animal model of MA-induced psychosis in rats where there was no difference

in behaviours indicative of psychosis relative to duration of time abstinent from MA; the authors suggest that the neurotoxic effects of MA do not reverse in abstinence (Huang, Tsai, Su, & Sim, 1999).

Age at first use did not predict severity of negative symptoms. In this sample the mean age at first use was 18.67 years, with 44% of the sample initiating stimulant use prior to the age of 18, and the entire sample initiating use prior to the age of 25. Because the entire sample initiated use within a period of neurodevelopment (because development continues until the third decade of life), it may be that all stimulant users in this study initiated use in an age range when stimulant drug use is capable of affecting the neurodevelopmental trajectory. While developmental is not constant, the development that occurs post-adolescence may be critical. Alternatively, 87.9% of the sample had a history of either cannabis abuse or cannabis dependence. Given the association between early cannabis use and psychosis, this may have a confounding effect on the ability to determine if the age at first use of primary stimulant was related to triggering psychosis onset, as opposed to age at first use of other drug use.

In analysis of positive symptom severity three of the seven predictor variables approached significant contributions: duration of time as a regular user, daily use and age at first use. The direction of the relationship is surprising, with less time as a regular user (under 5 years) contributing to more and/or more severe positive symptoms, use of preferred stimulant less than daily contributing to more and/or more severe positive symptoms, and an older age at first use contributing to more and/or more severe positive symptoms.

Positive symptoms that emerge during stimulant use may be more related to the acute use of the drug than with a neurodevelopmental vulnerability to psychosis. Short-term effects of MA use include paranoia, hallucination and agitation (Barr et al., 2006). Longer, heavier use of stimulants may induce a type of habituation to positive symptoms. Chronic stimulant use is no longer able to increase DA levels to the extent present in acute use. Given the relationship between positive symptoms and excess DA in the mesolimbic pathway, habituation to DA may present with a reduction in the presence or severity of

positive symptoms. The older age of first use predicting more and/or more severe positive symptoms is an unexpected finding. It may be that in this study older stimulant users were also more recent users of stimulants, with less time for DA to recover to normal levels.

Research Objective 2: Neurochemical Correlates of Psychotic Symptoms in Stimulant-Dependent Users: N-acetylaspartate

Neurochemical profiles in the mPFC were compared between HCs and ASDUs. NAA was negatively correlated with age, so age was controlled. NAA was lower in ASDUs than in HCs. Due to the procedural error described earlier, the NSIP group was not included in this analysis. Unfortunately, this error precluded the ability to test some interesting hypotheses. The analysis that could be performed supported the hypothesis that NAA in the mPFC would be reduced in ASDUs as compared to HCs. NAA is commonly regarded as a marker of neuronal integrity or neurodegeneration. Given that MA is neurotoxic to the brain, reduced NAA may represent neurotoxic effects in the mPFC region. Without the NSIPs as a comparison group it is more difficult to determine if the presence and/or severity of psychotic symptoms had an effect on NAA levels in ASDUs. NAA may be a marker of abnormal neurodevelopmental pathology in NSIPs. If reduced NAA in the mPFC represents disrupted neuronal integrity, this may explain impairment in cognitive performance, mediated by frontal lobe function.

Reduced NAA is consistently observed in MA users (Chang et al., 2007; Ernst et al., 2000; Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007; Sekine et al., 2002). Some have also related NAA levels to performance on attention tasks (Salo et al., 2007) and the presence of psychiatric symptoms (Sekine et al., 2002). There is also support that NAA may normalize with prolonged abstinence (Ernst et al., 2000; Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007; Sung et al., 2007; Taylor et al., 2007). From these published findings and the current results, it is clear that NAA is related to stimulant dependence, yet more research is required to determine the nature of the relationship.

Research Objective 3: Neurochemical Correlates of Psychotic Symptoms in Stimulant-Dependent Users: Glutamate

Glu levels were measured and compared between HCs and ASDUs. Glu was lower in the mPFC in ASDUs than in HCs. This difference supported the hypothesis that Glu would be affected in the ASDUs. Again, due to the procedural error described earlier, the NSIP group was not included in this analysis. Without the NSIP group it is difficult to determine if the presence and/or severity of psychotic symptoms has an effect on Glu levels in ASDUs.

The current consensus for Glu in schizophrenia is that Glu may be elevated in prodromal stages, while in chronic schizophrenia Glu may be reduced, possibly due to excitotoxic effects of the previous elevations (Theberge et al., 2003; Theberge et al., 2002). The observations from the current study of reduced Glu in ASDUs would suggest that ASDUs may compare more to a chronic schizophrenia sample than to a high-risk sample. In this study, NSIPs, in their first episode of psychosis, were defined as having active positive symptoms for less than 1 year. In ASDUs, several participants (33%) were abstinent for longer than 1 year. Given that symptoms of psychosis likely emerge during active drug use, any symptoms present in the current sample may have been present for longer than 1 year. It is possible that the ASDUs with symptoms of psychosis in the current study were more representative of a chronic course of untreated schizophrenia.

Glutamatergic alterations are inherently difficult to interpret. Because of constant Glu-Gln conversion cycle, and Glu's many roles as both a metabolite and a neurotransmitter, the functional effect of a change in Glu is difficult to predict. Recently it was proposed that ^{1}H-MRS observations of Glu differences in clinical samples most likely reflects a change in function of glutamatergic neurotransmission (Yüksel & Öngür, 2010). In the current study it may be that reduced Glu reflects a hypoglutamatergic state that emerged after excessive neurotoxic damage. In previous reports of reduced Glu in chronic schizophrenia, authors concluded that it supported a progression of the illness (Ohrmann et al., 2005) and may be related to neurodegeneration (Theberge et al., 2003). The

inability to include the NSIPs in this analysis prevented determining if the Glu alterations were related to the stimulant dependence or the presence of psychotic symptoms.

Research Objective 4: Cognitive Correlates of Psychotic Symptoms: Processing Speed

Processing speed was assessed in a three-group comparison using the Stroop Colour and Word Test colour reading standardized *t*-score as the primary measure. NSIPs had worse (i.e., slower) processing speed as compared to both the HC and ASDU samples. Controlling for negative symptom severity eliminated the previous difference between NSIPs and ASDUs. The results of the analysis of the Stroop Colour and Word Test processing speed measure indicate that deficits in processing speed may be related to presentation of negative symptoms, and therefore may reflect an underlying vulnerability. It may be that because of the heterogeneous make-up of the ASDU group (i.e., those with a potential underlying neuropathological vulnerability and those without), that only those with the proposed vulnerability may also have a pathology accounting for the processing speed deficits. The initial difference between ASDUs and NSIP was likely confounded by this heterogeneity, where those without the vulnerability did not show processing speed deficits. The lack of difference after controlling for negative symptom severity scores supports the hypothesis that negative symptoms may have an impact on processing speed. However, this result is weakened because of the lack of association between the Stroop and Colour Word Test measure and negative symptom severity in subsequent analyses. Further research is required to examine processing speed as an endophenotype.

In supplemental tests using the TMT-A, the overall model lacked significance. The supplemental test using the Digit Symbol Substitution Test, however, supported the Stroop Colour and Word Test colour reading results. The Digit Symbol Substitution Test is more commonly used as a measure of processing speed, and is the measure with the strongest findings in schizophrenia literature (Dickinson, 2008; Dickinson et al., 2007; Mesholam-Gately et al., 2009).

Processing speed is garnering interest as a strong candidate for an endophenotype for schizophrenia. Endophenotypes must be heritable, state-independent, associated with illness in the population and must co-segregate within families (Joo, 2008). Several studies have tested processing speed against these criteria and it passes, including the heritability factor (Bertisch, Li, Hoptman, & Delisi, 2010; Bertisch et al., 2009; Dickinson et al., 2007; Husted, Lim, Chow, Greenwood, & Bassett, 2009). The results of the current project support this idea, showing that processing speed is disrupted in abstinent stimulant-dependent users who present with negative symptoms, which may be associated with an underlying vulnerability.

Research Objective 5: Cognitive Correlates of Psychotic Symptoms: Executive Functioning

Executive functioning was assessed in a three-group comparison using the WCST perseverative error standardized *z*-score as the primary measure. The overall model was significant with worse performance in ASDUs and NSIPs as compared to the HCs. When assessing the effects of negative symptom severity there was no change in the previous lack of significant difference between the two groups. The results of the WCST indicate that ASDUs, regardless of presentation of psychotic symptoms, may have impairment of executive function that is indistinguishable from an NSIP sample. Executive function impairment is not sensitive to ASDUs who may have a pre-existing vulnerability to psychosis compared to ASDUs who do not. In supplemental tests using the Stroop Colour and Word Test interference *t*-score, no significant difference was observed between any of the groups; neither the ADSU nor NSIP groups differed from HCs. In the second supplemental test using the TMT-B, a similar pattern emerged as observed for the WCST perseverative error measure; both NSIPs and ASDUs presented with worse performance as compared to HCs. An alternative explanation is that executive function impairments in ASDUs differ in construct from the executive function impairments in NSIPs and future research may benefit from investigating distinct executive functioning features. For example, it

may be that ASDUs are impaired in decision making whereas NSIPs are impaired in concept formation or thought flexibility.

Executive function may be more closely related to the phenotype than the genotype of schizophrenia (Purdon et al., 2008). This is evident in the lack of reliable findings of executive function deficits in relatives of schizophrenia patients and high-risk samples (Brewer et al., 2005). The results from the current study support the hypothesis that executive function deficits in schizophrenia are a symptom of the disorder, and hold less potential as an endophenotype. The lack of any group difference on the Stroop Colour and Word Test interference score is unexpected. It may be that because the interference measure is dependent on the performance of the colour naming and colour reading measures, and that this assessment is not an adequate measure of executive function without controlling for earlier performance.

Executive functioning in schizophrenia is associated with self-care skills, insight, occupational functioning, independent living and use of treatment services (Bowie & Harvey, 2005; Raffard et al., 2009; Sharma & Antonova, 2003). For these reasons many are interested in improving executive functioning in schizophrenia with goals of improving daily living, arguably the most desired treatment outcome. Executive functioning may hold more value as a predictor of functional outcome.

Executive function impairment is also evident in substance dependence (Crews & Boettiger, 2009; Yucel et al., 2007). Deficits in executive function may pre-date the onset of substance use, affecting decision making and inhibitory behaviours creating susceptibility to drug dependence. Certainly these behaviours are affected during use, and act to perpetuate use (Gonzalez et al., 2007). Though the effect size of impairment is reportedly less in MA dependence than schizophrenia (Jacobs et al., 2008; Mesholam-Gately et al., 2009; Scott et al., 2007), this relationship makes it difficult to distinguish ASDUs based on a potential relationship between executive function and psychotic symptoms.

The results described here support the hypothesis that executive functioning is more likely a symptom of schizophrenia than an endophenotype.

This cognitive domain has less value in examining the etiology of substance-induced psychosis given the confounding independent impairment of executive function in stimulant users.

Research Objective 6: Predicting Severity of Psychotic Symptoms by Co-Registration of Cognitive and Neurochemical Measures

A unique feature of this study was the ability to investigate cognitive factors and neurochemical profiles in the mPFC together in relation to psychotic symptoms. The co-registration of neurochemical and neurocognitive factors may aid in the discovery of combination endophenotypes, adding predictive power in high-risk populations. Glu, NAA, Cho, an executive functioning measure and a processing speed measure were assessed as predictors of PANSS Negative scale scores. A separate analysis was applied to each of the NSIP and ASDU samples because of the procedural error in the spectroscopy data collection.

In NSIPs the combined neurochemical and cognitive factors approached a significant association with PANSS Negative symptoms. No single predictor reached significance but NAA in the mPFC trended to significance. With the removal of age and education as covariates, and therefore an increase in power, the overall model was significant, and NAA was a significant predictor. The added power may account for differences in these two tests. Because of the proposed frontal pathology described, it is not unexpected to show reduced levels of a marker of neuronal integrity in the frontal lobes associated with negative symptoms. Others have supported an inverse relationship between NAA and negative symptoms (Aydin et al., 2008; Callicott et al., 2000; Sigmundsson et al., 2003; Tanaka et al., 2006; Yamasue et al., 2002). This relationship may represent neuronal dysfunction or pathology (Callicott et al., 2000; Yamasue et al., 2002), or NAA may be a marker of disease severity (Sigmundsson et al., 2003). The functional effects of reductions in NAA is not clear as it serves many roles; NAA stores aspartate, is the metabolic pathway for glutamate, is involved in myelin lipid synthesis, neuronal energy metabolism, production of fatty acid and steroids, neuronal osmoregulation and axon-glial signaling and nitrogen balance, has bioenergetic role in neuronal mitochondria, enhances mitochondrial energy

production from Glu, and is a marker for neuronal health, viability and number (Moffett et al., 2007). Callicott and colleagues (2000) suggest that NAA does not cause schizophrenia *per* se but may be a marker for frontal cortex pathology unrelated to neuron loss.

In ASDUs Cho in the mPFC was the only significant predictor of negative symptoms in the overall significant model. This finding is unexpected and worthy of future examination. Cho is regarded as a product of myelin breakdown (Salibi & Brown, 1998) and increased signals in Cho may reflect gliosis. The positive association between Cho and negative symptoms may reflect gliosis and neuronal damage in the mPFC in stimulant users but not in NSIPs, suggesting that the mechanism or pathway to the negative symptoms differs between the two groups. Elevations of Cho in MA users have been observed previously (Chang et al., 2007; Chang, Ernst, Strickland et al., 1999; Ernst et al., 2000; Nordahl et al., 2005; Nordahl et al., 2002; Salo et al., 2007; Sekine et al., 2002), including a relationship to presence of psychotic symptoms (Iyo et al., 2004). Increases of Cho may reflect membrane damage or synthesis, inflammation or glial activation or proliferation (Ernst et al., 2000; Nordahl et al., 2005). In a rat study after MA exposure, rat brains showed a response to injury that involved reactive gliosis thereby elevating Cho levels (Pennypacker, Kassed, Eidizadeh, & O'Callaghan, 2000). With relation to symptoms of psychosis, the ratio of Cr/Cho has been associated with positive symptoms in MA users; the authors suggest that decreased Cr/Cho is accounted for by increases in Cho (Sekine et al., 2002). The neurotoxic effects of MA may induce gliosis, thereby elevating Cho levels and relating to the emergence and persistence of psychotic symptoms (Sekine et al., 2002). As this was an unpredicted result, further research is required to examine the potential mechanism for this finding.

The lack of association between the Stroop Colour and Word Test colour reading measure and negative symptoms weakens the previous theory of processing speed as an endophenotype of psychosis, as this association would be expected. However, processing speed may be associated with the presence of psychotic symptoms and not the severity.

In assessing positive symptom scores, the overall model was not significant in the NSIP sample, and no single predictor was related to positive symptoms regardless of covariance with age and education. In previous literature, associations with positive symptoms and neurochemical and neurocognitive measures were less consistent than with negative symptoms. These findings support the theory that negative symptoms of schizophrenia represent an independent construct from the positive symptoms, and that positive symptoms may be more related to the acute disease state, i.e., are symptoms rather than markers. An endophenotype presents before illness onset and is a reliable marker for that disorder. A symptom presents with illness onset and has no value in predicting the presentation of the disorder.

In ASDUs, the combined neurochemical and cognitive assessment factors approached significance with covariance of age and education. Running the analysis without adjusting for these covariates, and therefore increasing power, showed a significant result. The Stroop Colour and Word Test processing speed measure and NAA in the mPFC were significant predictors of positive symptoms. The relationship between NAA and positive symptoms has been an inconsistent finding. However, some studies have described negative correlations with positive symptoms (Callicott et al., 2000; Martinez-Granados et al., 2008; Premkumar et al., 2010; Sigmundsson et al., 2003; Theberge et al., 2004). In the current study however, the association between NAA and positive symptoms was positive, so that higher levels of NAA predicted more and/more severe positive symptoms. In ASDUs NAA may normalize with abstinence. Given that the range of duration of time abstinent in the study was 2 days to 10 years, it may be that the variance in NAA with abstinence accounts for these elevations. However, the relationship with positive symptoms is unexpected and further research is required to explore this association.

The association between processing speed and positive symptom severity is also an unexpected finding; however a few studies have observed a similar association (Lipkovich et al., 2009; Rund et al., 2004; Suslow, Junghanns, Weitzsch, & Arolt, 1998). Processing speed and positive symptoms have

independently been associated with functional outcome in schizophrenia. It may be that the relationship in ASDUs is mediated by a measure of functional ability, or, perhaps more likely, a third factor may be influencing both processing speed performance and positive symptom presentation with end impact on functionality.

Summary.

The pattern of results described here suggests that stimulant-induced psychotic symptoms may differ biologically and cognitively from *de novo* schizophrenia. The co-registration of biological and cognitive measures did not substantially increase the predictability of positive or negative symptoms in either group. The two samples differed on individual predictors, and only in the ASDU sample did a cognitive measure (processing speed) predict symptom presentation. While a stimulant-induced psychosis and schizophrenia may present as clinically similar, the other associated factors, neurochemical profiles and cognitive performance, may differ. This is supported by the finding that MA-induced psychosis did not present with the same P300 attenuated wave amplitudes commonly observed in schizophrenia (Iwanami, Suga, Kaneko, Sugiyama, & Nakatani, 1994).

Strengths and Limitations

A unique aspect of this study design was that the target sample was a group of ASDUs with and without symptoms of psychosis, as opposed to a sample of schizophrenia patients with and without a history of substance abuse or dependence. This is a unique approach to the study of the etiology of schizophrenia, and allows for the focus on symptoms of psychosis as opposed to the impact of substance use. Determining the etiology of schizophrenia and independently, the etiology of substance-induced psychosis, or substance-induced persistent symptoms of psychosis, will better aid in treatment services. Understanding the mechanism by which substances impact neuropathology and neurotransmission may aid in learning about the mechanism of psychosis.

Community sampling as a recruitment method in this study allowed for greater ecological validity, as opposed to ruling out participation for those with poly-drug use. The drug use patterns and demographic profiles of the ASDUs in

this study are consistent with profiles of MA users previously published (for example Brecht, Greenwell, & Anglin, 2007; Hall et al., 1996). This allowed for generalizability of findings.

Regarding the ^{1}H-MRS measures, this study had the advantage of use of a stronger magnet (3 Tesla) allowing for better separation of Glu from Gln, better quantification techniques for Glu, the acquisition of segmentation data allowing more accurate comparison between groups, and quantification of water as a standard, precluding the need to rely on metabolite ratios that would make interpretation of findings more difficult. These ^{1}H-MRS methods in future research allow for more reliable findings.

This study had several limitations. A history of birth and obstetric complications was not recorded, nor were subjects sampled for known risk-genes for schizophrenia. These variables would have added strength to the proposed "two-hit" model theory, without reliance on negative symptoms as a potential representation of neuropathology.

Unfortunately a procedural error in ^{1}H-MRS precluded the ability to compare NSIPs to both the HCs and ASDUs. This prevented the testing of some hypotheses regarding the relationship between neurochemical profiles and symptoms of psychosis.

Community recruitment for the ASDUs, while allowing for generalizability, produced a sample of individuals with a range of currently experienced psychotic symptoms, with no single user meeting full criteria for psychosis at the time of participation, limiting the ability to draw conclusions about whether subjects with subclinical symptoms of psychosis would progress to develop full psychosis. Community recruitment produced a group of ASDUs with a narrow range of symptom severity scores, and a somewhat narrow range of drug use patterns; all users were heavy, chronic, regular users of stimulants. These limited ranges likely impacted ability to detect change. Additionally, the cross-sectional nature of the study design did not allow for the detection of change over time.

As is the case for most research of individuals with a substance dependence disorder, many of the reported patterns of use variables were self-report. Retrospective self-report data always has the risk of being inaccurate (Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). However, many suggest that self-report data from substance abusers do provide useful estimates of use (Del Boca & Darkes, 2003; Del Boca & Noll, 2000).

Finally, as described in the introduction subsection in ^{1}H-MRS, there are several limitations inherent in spectroscopy, including further exclusionary criteria to population sampling. In this case, many recruited ASDUs were excluded because of concern for MRI contraindications. Even when eligibility for the scan was allowed, problems of subject movement and inter-individual variability always exist. As well, there have been some suggestion that time of day, time point in menstrual cycle and gender may have an effect on findings (Soreni, Noseworthy, Konyer, Pullenayegum, & Schachar, 2010; Tayoshi et al., 2009; Wallace et al., 2010).

The samples in the study differed in some demographic data, despite attempts to match for age and education during recruitment. These differences were controlled for in relevant analyses. Small sample sizes were also a factor in this study. However, the *a priori* power analysis demonstrated that the sample sizes were adequate to power analyses of ^{1}H-MRS measures.

Future studies are required to replicate these findings. Unfortunately, due to the procedural error in the ^{1}H-MRS data collection, this study was limited in the ability to compare the HC and ASDU samples to the NSIP sample. Future imaging studies are needed to investigate these interesting comparisons. While this study was unique in the recruitment of ASDUs with and without symptoms of psychosis, this study would have benefitted from recruitment of a sample with full stimulant-induced psychosis to compare to a sample meeting full criteria without substance use (i.e., NSIPs).

Longitudinal studies offer some of the greatest insight into the etiology of schizophrenia. A study following individuals from active substance dependence through treatment and into prolonged abstinence may offer a unique opportunity

to study the emergence and persistence of psychotic symptoms in a stimulant using sample.

Conclusions

This study has contributed to the understanding of the potential differences between a stimulant-induced psychosis and *de novo* schizophrenia. This study has demonstrated that these disorders may differ in the biological correlates of symptom presentation. This observation has significant implications to the treatment of psychosis and the etiology of schizophrenia.

There are several implications to the findings described. This study examined drug use patterns with respect to prediction of severity of psychotic symptoms in abstinent stimulant-dependent users. MA, as compared to cocaine use, was trended towards a significant predictor, while other factors failed to show association. This suggests that the variables in this study may not have accurately captured what level of severity of stimulant drug use may be required to trigger psychosis, but suggests that the required use is minimal given that stimulant users in this study were heavy, chronic users. This has implications for recreational drug users and suggests that many individuals may be at risk for substance-induced mental illness, if given a vulnerable brain state. Alternatively, drug use patterns may have no effect on the ability of stimulants to induce psychotic symptoms.

This study demonstrated that processing speed was affected by the presence and/or severity of negative symptoms in both *de novo* schizophrenia and abstinent stimulant-dependent users with symptoms of psychosis. This supports previous assertions that processing speed holds significant potential as an endophenotype for psychosis.

Executive function impairments were evident in the abstinent stimulant-dependent user sample, suggesting that executive function impairments are not valuable in distinguishing a substance-induced psychosis from a *de novo* psychosis. Executive functioning is not specific to stimulant drug users who may be at risk of psychosis. Executive functioning impairments may be more related to the phenotype of schizophrenia than to a genotype or endophenotype.

In comparison between the abstinent stimulant-dependent users and healthy controls, the user group had lower measures of NAA and Glu. Unfortunately, the direct impact of psychosis on these neurochemicals was not assessed. This finding may support a role for Glu in schizophrenia. The implication of glutamatergic findings in schizophrenia has potential to impact treatment options and opens a host of new drug target areas. To date, research on the glycine modulatory site of the NMDA receptor and even on the AMPA, kainate, and metabotropic receptors have provided positive feedback into the development of new and potentially more effective antipsychotic drugs than those currently being used (Javitt, 2004). Trials have described evidence of improvement in cognitive functioning and negative symptoms with glutamatergic agents (Moghaddam, 2003).

The combination of neurochemical and neurocognitive measures provided evidence of different correlates of symptoms in abstinent stimulant-dependent users and *de novo* schizophrenia. In the user group Cho was a significant predictor of negative symptoms, while processing speed and NAA predicted positive symptoms. Conversely, in the schizophrenia group no measure significantly predicted positive symptoms, while only NAA approached a significant predictor of negative symptoms. These results suggest that the substance-induced persistent psychotic symptoms differed biologically and cognitively from *de novo* schizophrenia, and may warrant different treatment approaches.

An understanding of the etiology of schizophrenia is important for treatment, prevention and identification of individuals who may be at greater risk of developing psychosis. The search for biological, genetic or cognitive markers of the disorder have identified several potential candidate endophenotypes including GM reduction, cortical inhibition, prepulse inhibition, electrophysiological measures, hypofrontality, eye movement dysfunction, and candidate risk genes, including GAD1, GAD67, DAOA, GRM3, dysbindin, COMT, and NRG1 (Bender, Weisbrod, & Resch, 2007). To date no single test or construct completely separates schizophrenia from healthy controls (Heinrichs & Zakzanis, 1998). This project provided new information on substance-induced

psychotic symptoms, suggesting that this substance-induced symptoms, though similar phenotypically to schizophrenia, may have different cognitive and neural correlates. This may be due to a completely different etiological pathway, or it may be that this unique pathway, with stimulants triggering the onset of psychosis in a vulnerable brain, presents with different cognitive and neural correlates.

References

Abbott, C., & Bustillo, J. (2006). What have we learned from proton magnetic resonance spectroscopy about schizophrenia? A critical update. *Current Opinion in Psychiatry, 19*(2), 135-139.

Addington, J., & Addington, D. (1997). Substance abuse and cognitive functioning in schizophrenia. *Journal of Psychiatry and Neuroscience, 22*(2), 99-104.

Adinoff, B. (2004). Neurobiologic processes in drug reward and addiction. *Harvard Review of Psychiatry, 12*(6), 305-320.

Adlaf, E. M., Begin, P., & Sawka, E. (Eds.). (2005). *Canadian Addiction Survey (CAS): A national survey of Canadians' use of alcohol and other drugs: Prevalence of use and related harms: Detailed report*. Ottawa: Canadian Centre on Substance Abuse.

Advokat, C. (2010). What are the cognitive effects of stimulant medications? Emphasis on adults with attention-deficit/hyperactivity disorder (ADHD). *Neuroscience and Biobehavioral Reviews, 34*(8), 1256-1266.

Akiyama, K., Saito, A., & Shimoda, K. (2011). Chronic methamphetamine psychosis after long-term abstinence in Japanese incarcerated patients. *American Journal on Addictions, 20*(3), 240-249.

Allen, A. J., Griss, M. E., Folley, B. S., Hawkins, K. A., & Pearlson, G. D. (2009). Endophenotypes in schizophrenia: A selective review. *Schizophrenia Research, 109*(1-3), 24-37.

Allott, K., Liu, P., Proffitt, T. M., & Killackey, E. (2011). Cognition at illness onset as a predictor of later functional outcome in early psychosis: Systematic review and methodological critique. *Schizophrenia Research, 125*(2-3), 221-235.

American Psychiatric Association. (2000). *Diagnostic and Statistical Manual of Mental Disorders* (IV, Text Revised ed.). Washington DC.

Anderson, J. E, O'Donnell, B. F., McCarley, R. W., & Shenton, M. E. (1998). Progressive changes in schizophrenia: Do they exist and what do they mean? *Restorative Neurology and Neuroscience, 12*, 175-185.

Anderson, S. W., Damasio, H., Jones, R. D., & Tranel, D. (1991). Wisconsin Card Sorting Test Performance as a Measure of Frontal Lobe Damage. *Journal of Clinical and Experimental Neuropsychology, 13*(6), 909-922.

Antonova, E., Sharma, T., Morris, R., & Kumari, V. (2004). The relationship between brain structure and neurocognition in schizophrenia: A selective review. *Schizophrenia Research, 70*(2-3), 117-145.

Aydin, K., Ucok, A., & Cakir, S. (2007). Quantitative proton MR spectroscopy findings in the corpus callosum of patients with schizophrenia suggest callosal disconnection. *American Journal of Neuroradiology, 28*(10), 1968-1974.

Aydin, K., Ucok, A., & Guler, J. (2008). Altered metabolic integrity of corpus callosum among individuals at ultra high risk of schizophrenia and first-episode patients. *Biological Psychiatry, 64*(9), 750-757.

Babyak, M. A. (2004). What you see may not be what you get: A brief, nontechnical introduction to overfitting in regression-type models. *Psychosomatic Medicine, 66*(3), 411-421.

Backstrom, P., & Hyytia, P. (2005). Suppression of alcohol self-administration and cue-induced reinstatement of alcohol seeking by the mGlu2/3 receptor agonist LY379268 and the mGlu8 receptor agonist (S)-3,4-DCPG. *European Journal of Pharmacology, 528*(1-3), 110-118.

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

Baker, A., & Dawe, S. (2005). Amphetamine use and co-occurring psychological problems: Review of the literature and implications for treatment. *Australian Psychologist, 40*(2), 88-95.

Baker, D. A., Cornish, J. L., & Kalivas, P. W. (2003). Glutamate and Dopamine Interactions in the Motive Circuit. In BH Herman (Ed.), *Glutamate and Addiction*. Totowa, New Jersey: Human Press Inc.

Baker, D. A., McFarland, K., Lake, R. W., Shen, H., Tang, X. C., Toda, S., & Kalivas, P. W. (2003). Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. *Nature Neuroscience, 6*(7), 743-749.

Barker, M. J., Greenwood, K. M., Jackson, M., & Crowe, S. F. (2004). Persistence of cognitive effects after withdrawal from long-term benzodiazepine use: A meta-analysis. *Archives of Clinical Neuropsychology, 19*(3), 437-454.

Barr, A. M., Panenka, W. J., Macewan, G. W., Thornton, A. E., Lang, D. J., Honer, W. G., & Lecomte, T. (2006). The need for speed: An update on methamphetamine addiction. *Journal of Psychiatry and Neuroscience, 31*(5), 301-313.

Bartha, R., al-Semaan, Y. M., Williamson, P. C., Drost, D. J., Malla, A. K., Carr, T. J., . . . Neufeld, R. W. (1999). A short echo proton magnetic resonance spectroscopy study of the left mesial-temporal lobe in first-onset schizophrenic patients. *Biological Psychiatry, 45*, 1403-1411.

Bartha, R., Williamson, P. C., Drost, D. J., Malla, A., Carr, T. J., Cortese, L., . . . Neufeld, R. W. (1997). Measurement of glutamate and glutamine in the medial prefrontal cortex of never-treated schizophrenic patients and healthy controls by proton magnetic resonance spectroscopy. *Archives of General Psychiatry, 54*(10), 959-965.

Bartsch, A. J., Homola, G., Biller, A., Smith, S. M., Weijers, H. G., Wiesbeck, G. A., . . . Bendszus, M. (2007). Manifestations of early brain recovery associated with abstinence from alcoholism. *Brain, 130*, 36-47.

Batki, S. L., & Harris, D. S. (2004). Quantitative drug levels in stimulant psychosis: Relationship to symptom severity, catecholamines and hyperkinesia. *American Journal on Addictions, 13*(5), 461-470.

Battaglia, M., Abbruzzese, M., Ferri, S., Scarone, S., Bellodi, L., & Smeraldi, E. (1994). An assessment of the Wisconsin Card Sorting Test as an indicator of liability to schizophrenia. *Schizophrenia Research, 14*(1), 39-45.

Bayer, T. A., Falkai, P., & Maier, W. (1999). Genetic and non-genetic vulnerability factors in schizophrenia: The basis of the "two hit hypothesis". *Journal of Psychiatric Research, 33*(6), 543-548.

Beck, A. T. (1987). *Beck Depression Inventory Manual*. San Antonio, Texas: Psychological Corporation.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*(6), 893-897.

Behrendt, S., Beesdo-Baum, K., Zimmermann, P., Hofler, M., Perkonigg, A., Buhringer, G., . . . Wittchen, H. U. (2011). The role of mental disorders in the risk and speed of transition to alcohol use disorders among community youth. *Psychological Medicine, 41*(5), 1073-1085.

Benaiges, I., Prat, G., & Adan, A. (2010). Neuropsychological aspects of dual diagnosis. *Current Drug Abuse Reviews, 3*(3), 175-188.

Bender, S., Weisbrod, M., & Resch, F. (2007). Which perspectives can endophenotypes and biological markers offer in the early recognition of schizophrenia? *Journal of Neural Transmission, 114*(9), 1199-1215.

Bendszus, M., Weijers, H. G., Wiesbeck, G., Warmuth-Metz, M., Bartsch, A. J., Engels, S., . . . Solymosi, L. (2001). Sequential MR imaging and proton MR spectroscopy in patients who underwent recent detoxification for chronic alcoholism: Correlation with clinical and neuropsychological data. *American Journal of Neuroradiology, 22*(10), 1926-1932.

Berman, S., O'Neill, J., Fears, S., Bartzokis, G., & London, E. D. (2008). Abuse of amphetamines and structural abnormalities in the brain. *Annals of the New York Academy of Sciences, 1141*, 195-220.

Bernier, D., & Tibbo, P. (2010). *Proton Magnetic Resonance Spectroscopy Studies of Schizophrenia: A Selected Review*. Unpublished manuscript, Department of Psychiatry, Dalhousie University.

Bertisch, H., Li, D., Hoptman, M. J., & Delisi, L. E. (2010). Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. *American Journal Medical Genetics B Neuropsychiatric Genetics, 153B*(4), 885-894.

Bertisch, H., Mesen-Fainardi, A., Martin, M. V., Perez-Vargas, V., Vargas-Rodriguez, T., Delgado, G., . . . DeLisi, L. E. (2009). Neuropsychological performance as endophenotypes in extended schizophrenia families from the Central Valley of Costa Rica. *Psychiatric Genetics, 19*(1), 45-52.

Bertolino, A., Callicott, J. H., Elman, I., Mattay, V. S., Tedeschi, G., Frank, J. A., . . . Weinberger, D. R. (1998). Regionally specific neuronal pathology in untreated patients with schizophrenia: A proton magnetic resonance spectroscopic imaging study. *Biological Psychiatry, 43*(9), 641-648.

Bertolino, A., Callicott, J. H., Mattay, V. S., Weidenhammer, K. M., Rakow, R., Egan, M. F., & Weinberger, D. R. (2001). The effect of treatment with antipsychotic drugs on brain N-acetylaspartate measures in patients with schizophrenia. *Biological Psychiatry, 49*(1), 39-46.

Bertolino, A., Callicott, J. H., Nawroz, S., Mattay, V. S., Duyn, J. H., Tedeschi, G., . . . Weinberger, D. R. (1998). Reproducibility of proton magnetic resonance spectroscopic imaging in patients with schizophrenia. *Neuropsychopharmacology, 18*(1), 1-9.

Bertolino, A., Esposito, G., Callicott, J. H., Mattay, V. S., Van Horn, J. D., Frank, J. A., . . . Weinberger, D. R. (2000). Specific relationship between prefrontal neuronal N-acetylaspartate and activation of the working memory cortical network in schizophrenia. *American Journal of Psychiatry, 157*(1), 26-33.

Bertolino, A., Kumra, S., Callicott, J. H., Mattay, V. S., Lestz, R. M., Jacobsen, L., . . . Weinberger, D. R. (1998). Common pattern of cortical pathology in childhood-onset and adult-onset schizophrenia as identified by proton magnetic resonance spectroscopic imaging. *American Journal of Psychiatry, 155*(10), 1376-1383.

Bertolino, A., Sciota, D., Brudaglio, F., Altamura, M., Blasi, G., Bellomo, A., . . . Nardini, M. (2003). Working memory deficits and levels of N-acetylaspartate in patients with schizophreniform disorder. *American Journal of Psychiatry, 160*(3), 483-489.

Bertolino, A., & Weinberger, D. R. (1999). Proton magnetic resonance spectroscopy in schizophrenia. *European Journal of Radiology, 30*(2), 132-141.

Birkett, P., Sigmundsson, T., Sharma, T., Toulopoulou, T., Griffiths, T. D., Reveley, A., & Murray, R. (2008). Executive function and genetic

predisposition to schizophrenia--the Maudsley family study. *American Journal Medical Genetics B Neuropsychiatric Genetics, 147*(3), 285-293.

Bizzarri, J. V., Rucci, P., Sbrana, A., Gonnelli, C., Massei, G. J., Ravani, L., . . . Cassano, G. B. (2007). Reasons for substance use and vulnerability factors in patients with substance use disorder and anxiety or mood disorders. *Addictive Behaviors, 32*(2), 384-391.

Blasi, G., Bertolino, A., Brudaglio, F., Sciota, D., Altamura, M., Antonucci, N., . . . Nardini, M. (2004). Hippocampal neurochemical pathology in patients at first episode of affective psychosis: A proton magnetic resonance spectroscopic imaging study. *Psychiatry Research, 131*, 95-105.

Block, W., Bayer, T. A., Tepest, R., Traber, F., Rietschel, M., Muller, D. J., . . . Falkai, P. (2000). Decreased frontal lobe ratio of N-acetyl aspartate to choline in familial schizophrenia: A proton magnetic resonance spectroscopy study. *Neuroscience Letters, 289*(2), 147-151.

Bokat, C. E., & Goldberg, T. E. (2003). Letter and category fluency in schizophrenic patients: A meta-analysis. *Schizophrenia Research, 64*(1), 73-78.

Bora, E., Yucel, M., & Pantelis, C. (2009). Cognitive functioning in schizophrenia, schizoaffective disorder and affective psychoses: Meta-analytic study. *The British Journal of Psychiatry, 195*(6), 475-482.

Bora, E., Yucel, M., & Pantelis, C. (2010). Cognitive impairment in schizophrenia and affective psychoses: Implications for DSM-V criteria and beyond. *Schizophrenia Bulletin, 36*(1), 36-42.

Borison, R. L., & Diamond, B. I. (1978). A new animal model for schizophrenia: Interactions with adrenergic mechanisms. *Biological Psychiatry, 13*(2), 217-225.

Bornstein, RA. (1985). Normative data on selected neuropsychological measures from a nonclincal sample. *Journal of Clinical Psychology, 41*(5), 651-659.

Bossong, M. G., & Niesink, R. J. (2010). Adolescent brain maturation, the endogenous cannabinoid system and the neurobiology of cannabis-induced schizophrenia. *Progress in Neurobiology, 92*(3), 370-385.

Bowie, C. R., & Harvey, P. D. (2005). Cognition in schizophrenia: Impairments, determinants, and functional importance. *Psychiatric Clinics of North America, 28*(3), 613-633.

Bozikas, V. P., & Andreou, C. (2011). Longitudinal studies of cognition in first episode psychosis: A systematic review of the literature. *Australian and New Zealand Journal of Psychiatry, 45*(2), 93-108.

Bracken, B. K., Jensen, J. E., Prescot, A. P., Cohen, B. M., Renshaw, P. F., & Ongur, D. (2011). Brain metabolite concentrations across cortical regions in healthy adults. *Brain Research, 1369*, 89-94.

Brake, W. G., Sullivan, R. M., & Gratton, A. (2000). Perinatal distress leads to lateralized medial prefrontal cortical dopamine hypofunction in adult rats. *The Journal of Neuroscience, 20*(14), 5538-5543.

Brecht, M. L., Greenwell, L., & Anglin, M. D. (2007). Substance use pathways to methamphetamine use among treated users. *Addictive Behaviors, 32*(1), 24-38.

Bressan, R. A., & Pilowsky, L. S. (2000). Imaging the glutamatergic system in vivo--relevance to schizophrenia. *European Journal of Nuclear Medicine, 27*(11), 1723-1731.

Breton, F., Plante, A., Legauffre, C., Morel, N., Ades, J., Gorwood, P., . . . Dubertret, C. (2011). The executive control of attention differentiates patients with schizophrenia, their first-degree relatives and healthy controls. *Neuropsychologia, 49*(2), 203-208.

Brewer, W. J., Francey, S. M., Wood, S. J., Jackson, H. J., Pantelis, C., Phillips, L. J., . . . McGorry, P. D. (2005). Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *American Journal of Psychiatry, 162*(1), 71-78.

Brewer, W. J., Wood, S. J., Phillips, L. J., Francey, S. M., Pantelis, C., Yung, A. R., . . . McGorry, P. D. (2006). Generalized and specific cognitive performance in clinical high-risk cohorts: A review highlighting potential vulnerability markers for psychosis. *Schizophrenia Bulletin, 32*(3), 538-555.

Brooks, W. M., Hodde-Vargas, J., Vargas, L. A., Yeo, R. A., Ford, C. C., & Hendren, R. L. (1998). Frontal lobe of children with schizophrenia spectrum disorders: A proton magnetic resonance spectroscopic study. *Biological Psychiatry, 43*(4), 263-269.

Broome, M. R., Woolley, J. B., Tabraham, P., Johns, L. C., Bramon, E., Murray, G. K., . . . Murray, R. M. (2005). What causes the onset of psychosis? *Schizophrenia Research, 79*(1), 23-34.

Brugger, S., Davis, J. M., Leucht, S., & Stone, J. M. (2011). Proton magnetic resonance spectroscopy and illness stage in schizophrenia-a systematic review and meta-analysis. *Biological Psychiatry, 69*(5), 495-503.

Burrows, K. B., & Meshul, C. K. (1997). Methamphetamine alters presynaptic glutamate immunoreactivity in the caudate nucleus and motor cortex. *Synapse, 27*(2), 133-144.

Bustillo, J. R., Lauriello, J., Rowland, L. M., Jung, R. E., Petropoulos, H., Hart, B. L., . . . Brooks, W. M. (2001). Effects of chronic haloperidol and clozapine treatments on frontal and caudate neurochemistry in schizophrenia. *Psychiatry Research, 107*, 135-149.

Bustillo, J. R., Lauriello, J., Rowland, L. M., Thomson, L. M., Petropoulos, H., Hammond, R., . . . Brooks, W. M. (2002). Longitudinal follow-up of neurochemical changes during the first year of antipsychotic treatment in schizophrenia patients with minimal previous medication exposure. *Schizophrenia Research, 58*, 313-321.

Bustillo, J. R., Rowland, L. M., Jung, R., Brooks, W. M., Qualls, C., Hammond, R., . . . Lauriello, J. (2008). Proton magnetic resonance spectroscopy during initial treatment with antipsychotic medication in schizophrenia. *Neuropsychopharmacology, 33*(10), 2456-2466.

Bustillo, J. R., Rowland, L. M., Mullins, P., Jung, R., Chen, H., Qualls, C., . . . Lauriello, J. (2010). 1H-MRS at 4 tesla in minimally treated early schizophrenia. *Molecular Psychiatry, 15*(6), 629-636.

Byun, M. S., Choi, J. S., Yoo, S. Y., Kang, D. H., Choi, C. H., Jang, D. P., . . . Kwon, J. S. (2009). Depressive symptoms and brain metabolite alterations in subjects at ultra-high risk for psychosis: A preliminary study. *Psychiatry Investigation, 6*(4), 264-271.

Cador, M., Bjijou, Y., Cailhol, S., & Stinus, L. (1999). D-amphetamine-induced behavioral sensitization: Implication of a glutamatergic medial prefrontal cortex-ventral tegmental area innervation. *Neuroscience, 94*(3), 705-721.

Callicott, J. H., Bertolino, A., Egan, M. F., Mattay, V. S., Langheim, F. J., & Weinberger, D. R. (2000). Selective relationship between prefrontal N-acetylaspartate measures and negative symptoms in schizophrenia. *American Journal of Psychiatry, 157*(10), 1646-1651.

Callicott, J. H., Egan, M. F., Bertolino, A., Mattay, V. S., Langheim, F. J., Frank, J. A., & Weinberger, D. R. (1998). Hippocampal N-acetyl aspartate in unaffected siblings of patients with schizophrenia: a possible intermediate neurobiological phenotype. *Biological Psychiatry, 44*, 941-950.

Cannon, M., Jones, P. B., & Murray, R. M. (2002). Obstetric complications and schizophrenia: Historical and meta-analytic review. *American Journal of Psychiatry, 159*(7), 1080-1092.

Cantor-Graae, E., Nordstrom, L. G., & McNeil, T. F. (2001). Substance abuse in schizophrenia: A review of the literature and a study of correlates in Sweden. *Schizophrenia Research, 48*(1), 69-82.

Cardno, A. G., & Gottesman, I. I. (2000). Twin studies of schizophrenia: From bow-and-arrow concordances to Star Wars Mx and functional genomics. *American Journal of Medical Genetics, 97*(1), 12-17.

Cardoso, B. M., Kauer Sant'Anna, M., Dias, V. V., Andreazza, A. C., Cereser, K. M., & Kapczinski, F. (2008). The impact of co-morbid alcohol use disorder in bipolar patients. *Alcohol, 42*(6), 451-457.

Carey, K. B., Carey, M. P., & Simons, J. S. (2003). Correlates of substance use disorder among psychiatric outpatients: Focus on cognition, social role functioning, and psychiatric status. *Journal of Nervous and Mental Disease, 191*(5), 300-308.

Carlsson, M. L., Carlsson, A., & Nilsson, M. (2004). Schizophrenia: From dopamine to glutamate and back. *Current Medicinal Chemistry, 11*(3), 267-277.

Cecil, K. M., Lenkinski, R. E., Gur, R. E., & Gur, R. C. (1999). Proton magnetic resonance spectroscopy in the frontal and temporal lobes of neuroleptic naive patients with schizophrenia. *Neuropsychopharmacology, 20*(2), 131-140.

Censits, D. M., Ragland, J. D., Gur, R. C., & Gur, R. E. (1997). Neuropsychological evidence supporting a neurodevelopmental model of schizophrenia: A longitudinal study. *Schizophrenia Research, 24*(3), 289-298.

Chambers, R. A., Krystal, J. H., & Self, D. W. (2001). A neurobiological basis for substance abuse comorbidity in schizophrenia. *Biological Psychiatry, 50*(2), 71-83.

Chang, L., Alicata, D., Ernst, T., & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction, 102 Suppl 1*, 16-32.

Chang, L., Cloak, C., Yakupov, R., & Ernst, T. (2006). Combined and independent effects of chronic marijuana use and HIV on brain metabolites. *Journal of Neuroimmune Pharmacology, 1*(1), 65-76.

Chang, L., Ernst, T., Grob, C. S., & Poland, R. E. (1999). Cerebral (1)H MRS alterations in recreational 3, 4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. *Journal of Magnetic Resonance Imaging, 10*, 521-526.

Chang, L., Ernst, T., Speck, O., & Grob, C. S. (2005). Additive effects of HIV and chronic methamphetamine use on brain metabolite abnormalities. *American Journal of Psychiatry, 162*(2), 361-369.

Chang, L., Ernst, T., Speck, O., Patel, H., DeSilva, M., Leonido-Yee, M., & Miller, E. N. (2002). Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. *Psychiatry Research, 114*(2), 65-79.

Chang, L., Ernst, T., Strickland, T., & Mehringer, C. M. (1999). Gender effects on persistent cerebral metabolite changes in the frontal lobes of abstinent cocaine users. *American Journal of Psychiatry, 156*(5), 716-722.

Chang, L., & Haning, W. (2006). Insights from recent positron emission tomographic studies of drug abuse and dependence. *Current Opinion in Psychiatry, 19*(3), 246-252.

Chang, L., Mehringer, C. M., Ernst, T., Melchor, R., Myers, H., Forney, D., & Satz, P. (1997). Neurochemical alterations in asymptomatic abstinent cocaine users: A proton magnetic resonance spectroscopy study. *Biological Psychiatry, 42*(12), 1105-1114.

Chapman, L. J., Chapman, J. P., Kwapil, T. R., Eckblad, M., & Zinser, M. C. (1994). Putatively psychosis-prone subjects 10 years later. *Journal of Abnormal Psychology, 103*(2), 171-183.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1976). Scales for physical and social anhedonia. *Journal of Abnormal Psychology, 85*(4), 374-382.

Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh, E. W., Hsiao, C. C., . . . Murray, R. M. (2003). Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychological Medicine, 33*(8), 1407-1414.

Chen, C. K., Lin, S. K., Sham, P. C., Ball, D., Loh el, W., & Murray, R. M. (2005). Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *American Journal of Medical Genetics Part B Neuropsychiatric Genetics, 136*(1), 87-91.

Chkonia, E., Roinishvili, M., Makhatadze, N., Tsverava, L., Stroux, A., Neumann, K., . . . Brand, A. (2010). The shine-through masking paradigm is a potential endophenotype of schizophrenia. *PloS one, 5*(12), e14268.

Chmielewski, P. M., Fernandes, L. O., Yee, C. M., & Miller, G. A. (1995). Ethnicity and gender in scales of psychosis proneness and mood disorders. *Journal of Abnormal Psychology, 104*(3), 464-470.

Chung, A., Lyoo, I. K., Kim, S. J., Hwang, J., Bae, S. C., Sung, Y. H., . . . Renshaw, P. F. (2007). Decreased frontal white-matter integrity in abstinent methamphetamine abusers. *International Journal of Neuropsychopharmacology, 10*(6), 765-775.

Cirillo, M. A., & Seidman, L. J. (2003). Verbal declarative memory dysfunction in schizophrenia: From clinical assessment to genetics and brain mechanisms. *Neuropsychology Review, 13*(2), 43-77.

Cohen, A. S., Saperstein, A. M., Gold, J. M., Kirkpatrick, B., Carpenter, W. T., Jr., & Buchanan, R. W. (2007). Neuropsychology of the deficit syndrome: New data and meta-analysis of findings to date. *Schizophrenia Bulletin, 33*(5), 1201-1212.

Cohen, M., Solowij, N., & Carr, V. (2008). Cannabis, cannabinoids and schizophrenia: Integration of the evidence. *Australian and New Zealand Journal of Psychiatry, 42*(5), 357-368.

Collier, D. A., & Li, T. (2003). The genetics of schizophrenia: Glutamate not dopamine? *European Journal of Pharmacology, 480*(1-3), 177-184.

Copersino, M. L., Serper, M. R., Vadhan, N., Goldberg, B. R., Richarme, D., Chou, J. C., . . . Cancro, R. (2004). Cocaine craving and attentional bias in cocaine-dependent schizophrenic patients. *Psychiatry Research, 128*(3), 209-218.

Cornblatt, B. A., Lencz, T., Smith, C. W., Correll, C. U., Auther, A. M., & Nakayama, E. (2003). The schizophrenia prodrome revisited: A neurodevelopmental perspective. *Schizophrenia Bulletin, 29*(4), 633-651.

Cornish, J. L., & Kalivas, P. W. (2000). Glutamate transmission in the nucleus accumbens mediates relapse in cocaine addiction. *The Journal of Neuroscience, 20*(15), RC89.

Cowan, R. L., Bolo, N. R., Dietrich, M., Haga, E., Lukas, S. E., & Renshaw, P. F. (2007). Occipital cortical proton MRS at 4 Tesla in human moderate MDMA polydrug users. *Psychiatry Research, 155*, 179-188.

Coyle, J. T. (1996). The glutamatergic dysfunction hypothesis for schizophrenia. *Harvard Review of Psychiatry, 3*(5), 241-253.

Coyle, J. T. (2006a). Glutamate and schizophrenia: Beyond the dopamine hypothesis. *Cellular and Molecular Neurobiology, 4-6*(365-384)

Coyle, J. T. (2006b). Substance use disorders and schizophrenia: A question of shared glutamatergic mechanisms. *Neurotoxicology Research, 10*(3-4), 221-233.

Coyle, J. T., Tsai, G., & Goff, D. (2003). Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. *Annals of the New York Academy of Science, 1003*, 318-327.

Crespo-Facorro, B., Barbadillo, L., Pelayo-Teran, J. M., & Rodriguez-Sanchez, J. M. (2007). Neuropsychological functioning and brain structure in schizophrenia. *International Review of Psychiatry, 19*(4), 325-336.

Crews, F. T., & Boettiger, C. A. (2009). Impulsivity, frontal lobes and risk for addiction. *Pharmacology, Biochemistry and Behavior, 93*(3), 237-247.

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

Curran, C., Byrappa, N., & McBride, A. (2004). Stimulant psychosis: Systematic review. *British Journal of Psychiatry, 185*, 196-204.

Daumann, J., Fischermann, T., Pilatus, U., Thron, A., Moeller-Hartmann, W., & Gouzoulis-Mayfrank, E. (2004). Proton magnetic resonance spectroscopy in ecstasy (MDMA) users. *Neuroscience Letters, 362*(2), 113-116.

de Gracia Dominguez, M., Viechtbauer, W., Simons, C. J. P., & Van Os, J. (2009). Are psychotic psychopathology and neurocognition orthogonal? A systematic review of their associations. *Psychological Bulletin, 135*(1), 157-171.

de la Fuente-Sandoval, C., Leon-Ortiz, P., Favila, R., Stephano, S., Mamo, D., Ramirez-Bermudez, J., & Graff-Guerrero, A. (2011). Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology, 36*, 1781–1791.

de Win, M. M., Reneman, L., Jager, G., Vlieger, E. J., Olabarriaga, S. D., Lavini, C., . . . van den Brink, W. (2007). A prospective cohort study on sustained effects of low-dose ecstasy use on the brain in new ecstasy users. *Neuropsychopharmacology, 32*, 458-470.

Deakin, J. F., & Simpson, M. D. (1997). A two-process theory of schizophrenia: Evidence from studies in post-mortem brain. *Journal of Psychiatric Research, 31*(2), 277-295.

Degenhardt, L., Hall, W., & Lynskey, M. (2004). What is comorbidity and why does it occur? In Teesson M. & Proudfoot H. (Eds.), *Comorbid mental disorders and substance use disorders: Epidemiology, prevention and treatment* (pp. 10-25). Sydney: Australian Government Department of Health and Ageing.

Degenhardt, L., & Topp, L. (2003). 'Crystal meth' use among polydrug users in Sydney's dance party subculture: Characteristics, use patterns and associated harm. *International Journal of Drug Policy, 14*, 17-24.

Deicken, R. F., Zhou, L., Schuff, N., Fein, G., & Weiner, M. W. (1998). Hippocampal neuronal dysfunction in schizophrenia as measured by proton magnetic resonance spectroscopy. *Biological Psychiatry, 43*(7), 483-488.

Deicken, R. F., Zhou, L., Schuff, N., & Weiner, M. W. (1997). Proton magnetic resonance spectroscopy of the anterior cingulate region in schizophrenia. *Schizophrenia Research, 27*(1), 65-71.

Del Boca, F. K., & Darkes, J. (2003). The validity of self-reports of alcohol consumption: State of the science and challenges for research. *Addiction, 98*, 1-12.

Del Boca, F. K., & Noll, J. A. (2000). Truth or consequences: The validity of self-report data in health services research on addictions. *Addiction, 95 Suppl 3*, S347-360.

Delamillieure, P., Constans, J., Fernandez, J., Brazo, P., & Dollfus, S. (2000). Proton magnetic resonance spectroscopy (1H-MRS) of the thalamus in schizophrenia. *European Psychiatry, 15*(8), 489-491.

Delamillieure, P., Constans, J. M., Fernandez, J., Brazo, P., Benali, K., Courtheoux, P., . . . Dollfus, S. (2002). Proton magnetic resonance spectroscopy (1H MRS) in schizophrenia: Investigation of the right and left hippocampus, thalamus, and prefrontal cortex. *Schizophrenia Bulletin, 28*(2), 329-339.

Delamillieure, P., Constans, J. M., Fernandez, J., Brazo, P., & Dollfus, S. (2004). Relationship between performance on the Stroop test and N-acetylaspartate in the medial prefrontal cortex in deficit and nondeficit schizophrenia: Preliminary results. *Psychiatry Research, 132*, 87-89.

Delamillieure, P., Fernandez, J., Constans, J. M., Brazo, P., Benali, K., Abadie, P., . . . Dollfus, S. (2000). Proton magnetic resonance spectroscopy of the medial prefrontal cortex in patients with deficit schizophrenia: Preliminary report. *American Journal of Psychiatry, 157*(4), 641-643.

DeLisi, L. E., Szulc, K. U., Bertisch, H. C., Majcher, M., & Brown, K. (2006). Understanding structural brain changes in schizophrenia. *Dialogues in Clinical Neuroscience, 8*(1), 71-78.

Dell, C. A., & Garabedian, K. (2003). 2002 National Report Drug Trends and the CCENDU network. Ottawa, ON: Canadian Community Epidemiology Network on Drug Use.

Denny, D. R., & Lynch, S. G. (2009). The impact of multiple sclerosis on patients' performance on the Stroop Test: Processing speed versus interference. *Journal of the International Neuropsychological Society, 15*(03), 451-458.

Dibben, C. R., Rice, C., Laws, K., & McKenna, P. J. (2009). Is executive impairment associated with schizophrenic syndromes? A meta-analysis. *Psychological Medicine, 39*(3), 381-392.

Dickinson, D. (2008). Digit symbol coding and general cognitive ability in schizophrenia: Worth another look? *The British Journal of Psychiatry, 193*(5), 354-356.

Dickinson, D., Ragland, J. D., Gold, J. M., & Gur, R. E. (2008). General and specific cognitive deficits in schizophrenia: Goliath defeats David? *Biological Psychiatry, 64*(9), 823-827.

Dickinson, D., Ramsey, M. E., & Gold, J. M. (2007). Overlooking the obvious: A meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia. *Archives of General Psychiatry, 64*(5), 532-542.

Donohoe, G., Corvin, A., & Robertson, I. H. (2005). Are the cognitive deficits associated with impaired insight in schizophrenia specific to executive

task performance? *Journal of Nervous and Mental Disease, 193*(12), 803-808.

Donohoe, G., & Robertson, I. H. (2003). Can specific deficits in executive functioning explain the negative symptoms of schizophrenia? A review. *Neurocase, 9*(2), 97-108.

Dore, G., & Sweeting, M. (2006). Drug-induced psychosis associated with crystalline methamphetamine. *Australas Psychiatry, 14*(1), 86-89.

Doughty, O. J., & Done, D. J. (2009). Is semantic memory impaired in schizophrenia? A systematic review and meta-analysis of 91 studies. *Cognitive Neuropsychiatry, 14*(6), 473-509.

Drewe, M., Drewe, J., & Riecher-Rossler, A. (2004). Cannabis and risk of psychosis. *Swiss Medical Weekly, 134*(45-46), 659-663.

Duan, J., Sanders, A. R., & Gejman, P. V. (2010). Genome-wide approaches to schizophrenia. *Brain Research Bulletin, 83*(3-4), 93-102.

Dubertret, C., Bidard, I., Ades, J., & Gorwood, P. (2006). Lifetime positive symptoms in patients with schizophrenia and cannabis abuse are partially explained by co-morbid addiction. *Schizophrenia Research, 86*(1-3), 284-290.

Durazzo, T. C., Gazdzinski, S., Banys, P., & Meyerhoff, D. J. (2004). Cigarette smoking exacerbates chronic alcohol-induced brain damage: A preliminary metabolite imaging study. *Alcoholism: Clinical and Experimental Research, 28*, 1849-1860.

Durazzo, T. C., Gazdzinski, S., Rothlind, J. C., Banys, P., & Meyerhoff, D. J. (2006). Brain metabolite concentrations and neurocognition during short-term recovery from alcohol dependence: Preliminary evidence of the effects of concurrent chronic cigarette smoking. *Alcoholism: Clinical and Experimental Research, 30*(3), 539-551.

Durazzo, T. C., Gazdzinski, S., Yeh, P. H., & Meyerhoff, D. J. (2008). Combined neuroimaging, neurocognitive and psychiatric factors to predict alcohol consumption following treatment for alcohol dependence. *Alcohol and Alcoholism, 43*, 683-691.

Durazzo, T. C., Pathak, V., Gazdzinski, S., Mon, A., & Meyerhoff, D. J. (2010). Metabolite levels in the brain reward pathway discriminate those who remain abstinent from those who resume hazardous alcohol consumption after treatment for alcohol dependence. *Journal of Studies on Alcohol and Drugs, 71*(2), 278-289.

Duva, S. M., Silverstein, S. M., & Spiga, R. (2011). Impulsivity and risk-taking in co-occurring psychotic disorders and substance abuse. *Psychiatry Research, 186*(2-3), 351-355.

Eckblad, M., & Chapman, L. J. (1983). Magical ideation as an indicator of schizotypy. *Journal of Consulting and Clinical Psychology, 51*(2), 215-225.

Eisenberg, D. P., & Berman, K. F. (2010). Executive function, neural circuitry, and genetic mechanisms in schizophrenia. *Neuropsychopharmacology, 35*(1), 258-277.

Elliott, R., Rees, G., & Dolan, R. J. (1999). Ventromedial prefrontal cortex mediates guessing. *Neuropsychologia, 37*(4), 403-411.

Ellison, G. (1994). Stimulant-induced psychosis, the dopamine theory of schizophrenia, and the habenula. *Brain Research Reviews, 19*(2), 223-239.

Ende, G., Braus, D. F., Walter, S., Weber-Fahr, W., Soher, B., Maudsley, A. A., & Henn, F. A. (2000). Effects of age, medication, and illness duration on the N-acetyl aspartate signal of the anterior cingulate region in schizophrenia. *Schizophrenia Research, 41*, 389-395.

Ende, G., Walter, S., Welzel, H., Demirakca, T., Wokrina, T., Ruf, M., . . . Mann, K. (2006). Alcohol consumption significantly influences the MR signal of frontal choline-containing compounds. *Neuroimage, 32*, 740-746.

Ende, G., Welzel, H., Walter, S., Weber-Fahr, W., Diehl, A., Hermann, D., . . . Mann, K. (2005). Monitoring the effects of chronic alcohol consumption and abstinence on brain metabolism: A longitudinal proton magnetic resonance spectroscopy study. *Biological Psychiatry, 58*, 974-980.

Erber, J. T., Botwinick, J., & Storandt, M. (1981). The impact of memory on age differences in digit symbol performance. *Journal of Gerontology, 36*(5), 586-590.

Erfan, S., Hashim, A. H., Shaheen, M., & Sabry, N. (2010). Effect of comorbid depression on substance use disorders. *Substance Abuse, 31*(3), 162-169.

Ernst, T., & Chang, L. (2008). Adaptation of brain glutamate plus glutamine during abstinence from chronic methamphetamine use. *Journal of Neuroimmune Pharmacology, 3*(3), 165-172.

Ernst, T., Chang, L., Leonido-Yee, M., & Speck, O. (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. *Neurology, 54*(6), 1344-1349.

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

Ertugrul, A., Volkan-Salanci, B., Basar, K., Karli Oguz, K., Demir, B., Ergun, E. L., . . . Ulug, B. (2009). The effect of clozapine on regional cerebral blood flow and brain metabolite ratios in schizophrenia: Relationship with treatment response. *Psychiatry Research, 174*(2), 121-129.

Estrada, G., Fatjó-Vilas, M., Muñoz, M. J., Pulido, G., Miñano, M. J., Toledo, E., . . . Fañanás, L. (2011). Cannabis use and age at onset of psychosis: Further evidence of interaction with COMT Val158Met polymorphism. *Acta Psychiatrica Scandinavica, 123*(6), 485-492.

Fernandez-Serrano, M. J., Perez-Garcia, M., & Verdejo-Garcia, A. (2011). What are the specific vs. generalized effects of drugs of abuse on neuropsychological performance? *Neuroscience and Biobehavioral Reviews, 35*(3), 377-406.

Fioravanti, M., Carlone, O., Vitale, B., Cinti, M. E., & Clare, L. (2005). A meta-analysis of cognitive deficits in adults with a diagnosis of schizophrenia. *Neuropsychology Review, 15*(2), 73-95.

First, M. B., Spitzer, R. L., Gibbon, M., & Williams, J. B. W. (2002). Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version,

Patient Edition (SCID-I/P). New York: Biometrics Research, New York State Psychiatric Institute.

Fischer, B., Rehm, J., & Hall, W. (2009). Cannabis use in Canada: The need for a 'public health' approach. *Canadian Journal of Public Health, 100*(2), 101-103.

Fishbein, D., Hyde, C., Eldreth, D., London, E. D., Matochik, J., Ernst, M., . . . Kimes, A. (2005). Cognitive performance and autonomic reactivity in abstinent drug abusers and nonusers. *Experimental and Clinical Psychopharmacology, 13*(1), 25-40.

Forbes, N. F., Carrick, L. A., McIntosh, A. M., & Lawrie, S. M. (2009). Working memory in schizophrenia: A meta-analysis. *Psychological Medicine, 39*(6), 889-905.

Forn, C., Belenguer, A., Belloch, V., Sanjuan, A., Parcet, M. A., & Ávila, C. (2010). Anatomical and functional differences between the Paced Auditory Serial Addition Test and the Symbol Digit Modalities Test. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 42-50.

Freedman, D., & Brown, A. S. (2011). The developmental course of executive functioning in schizophrenia. *International Journal of Developmental Neuroscience, 29*(3), 237-243.

Fusar-Poli, P., Stone, J. M., Broome, M. R., Valli, I., Mechelli, A., McLean, M. A., . . . McGuire, P. K. (2011). Thalamic glutamate levels as a predictor of cortical response during executive functioning in subjects at high risk for psychosis. *Archives of General Psychiatry, 68*(9), 881-890.

Galinska, B., Szulc, A., Tarasow, E., Kubas, B., Dzienis, W., Czernikiewicz, A., & Walecki, J. (2009). Duration of untreated psychosis and proton magnetic resonance spectroscopy (1H-MRS) findings in first-episode schizophrenia. *Medical Science Monitor, 15*, CR82-88.

Galinska, B., Szulc, A., Tarasow, E., Kubas, B., Dzienis, W., Siergiejczyk, L., . . . Walecki, J. (2007). Relationship between frontal N-acetylaspartate and cognitive deficits in first-episode schizophrenia. *Medical Science Monitor, 13 Suppl 1*, 11-16.

Garavan, H., & Hester, R. (2007). The role of cognitive control in cocaine dependence. *Neuropsychology Review, 17*(3), 337-345.

Geddes, J. R., & Lawrie, S. M. (1995). Obstetric complications and schizophrenia: A meta-analysis. *The British Journal of Psychiatry, 167*(6), 786-793.

Giakoumaki, S. G., Roussos, P., Pallis, E. G., & Bitsios, P. (2011). Sustained attention and working memory deficits follow a familial pattern in schizophrenia. *Archives of Clinical Neuropsychology, 26*(7), 687-695.

Gillard, J. H., Waldman, A., & Barker, P. B. (Eds.). (2004). *Clinical MR Neuroimaging: Diffusion, Perfusion and Spectroscopy*: Cambridge University Press.

Glahn, D. C., Almasy, L., Blangero, J., Burk, G. M., Estrada, J., Peralta, J. M., . . . Escamilla, M. A. (2007). Adjudicating neurocognitive endophenotypes for schizophrenia. *American Journal Medical Genetics B Neuropsychiatric Genetics, 144B*(2), 242-249.

Goff, D. C., & Coyle, J. T. (2001). The emerging role of glutamate in the pathophysiology and treatment of schizophrenia. *American Journal of Psychiatry, 158*(9), 1367-1377.

Goff, D. C., Hennen, J., Lyoo, I. K., Tsai, G., Wald, L. L., Evins, A. E., . . . Renshaw, P. F. (2002). Modulation of brain and serum glutamatergic concentrations following a switch from conventional neuroleptics to olanzapine. *Biological Psychiatry, 51*(6), 493-497.

Goff, D. C., & Wine, L. (1997). Glutamate in schizophrenia: Clinical and research implications. *Schizophrenia Research, 27*(2-3), 157-168.

Gold, J. M., Hahn, B., Strauss, G. P., & Waltz, J. A. (2009). Turning it upside down: Areas of preserved cognitive function in schizophrenia. *Neuropsychology Review, 19*(3), 294-311.

Goldberg, T. E., Torrey, E. F., Gold, J. M., Ragland, J. D., Bigelow, L. B., & Weinberger, D. R. (1993). Learning and memory in monozygotic twins discordant for schizophrenia. *Psychological Medicine, 23*(1), 71-85.

Golden, C. J. (1975). A group version of the Stroop Color and Word Test. *Journal of Personality Assessment, 39*(4), 386-388.

Golden, C. J. (1978). Stroop color and word test: A manual for clinical and experimental uses. Chicago, IL: Stoelting Co.

Goldstein, R. Z., Leskovjan, A. C., Hoff, A. L., Hitzemann, R., Bashan, F., Khalsa, S. S., . . . Volkow, N. D. (2004). Severity of neuropsychological impairment in cocaine and alcohol addiction: Association with metabolism in the prefrontal cortex. *Neuropsychologia, 42*(11), 1447-1458.

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

Gonzales, R., Mooney, L., & Rawson, R. A. (2010). The methamphetamine problem in the United States. *Annual Review of Public Health, 31*, 385-398.

Gonzalez Castro, F., Barrington, E. H., Walton, M. A., & Rawson, R. A. (2000). Cocaine and methamphetamine: Differential addiction rates. *Psychology of Addictive Behaviors, 14*(4), 390-396.

Gonzalez, R., Bechara, A., & Martin, E. M. (2007). Executive functions among individuals with methamphetamine or alcohol as drugs of choice: Preliminary observations. *Journal of Clinical and Experimental Neuropsychology, 29*(2), 155-159.

Gonzalez, R., Rippeth, J. D., Carey, C. L., Heaton, R. K., Moore, D. J., Schweinsburg, B. C., . . . Grant, I. (2004). Neurocognitive performance of methamphetamine users discordant for history of marijuana exposure. *Drug and Alcohol Dependence, 76*(2), 181-190.

Gorber, S. C., Schofield-Hurwitz, S., Hardt, J., Levasseur, G., & Tremblay, M. (2009). The accuracy of self-reported smoking: A systematic review of the relationship between self-reported and cotinine-assessed smoking status. *Nicotine & Tobacco Research, 11*(1), 12-24.

Goto, N., Yoshimura, R., Kakeda, S., Moriya, J., Hayashi, K., Ikenouchi-Sugita, A., . . . Nakamura, J. (2011). Comparison of brain N-acetylaspartate levels

and serum brain-derived neurotrophic factor (BDNF) levels between patients with first-episode schizophrenia psychosis and healthy controls. *European Psychiatry, 26*(1), 57-63.

Goudsmit, N., Wolitzky, R., Seckinger, R. A., Corcoran, C., Stanford, A., Rosenfield, P., . . . Malaspina, D. (2004). Trail making and olfaction in schizophrenia: Implications for processing speed. *CNS spectrums, 9*(5), 344-349, 356.

Gouzoulis-Mayfrank, E., & Daumann, J. . (2006). The confounding problem of polydrug use in recreational ecstasy/MDMA users: A brief overview. *Journal of Psychopharmacology, 20*, 188-193.

Grace, A. A. (2000). The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and psychostimulant craving. *Addiction, 95 Suppl 2*, S119-128.

Grant, I., Gonzalez, R., Carey, C. L., Natarajan, L., & Wolfson, T. (2003). Non-acute (residual) neurocognitive effects of cannabis use: A meta-analytic study. *Journal of the International Neuropsychological Society, 9*(5), 679-689.

Grant, S., Contoreggi, C., & London, E. D. (2000). Drug abusers show impaired performance in a laboratory test of decision making. *Neuropsychologia, 38*(8), 1180-1187.

Green, A. I. (2007). Pharmacotherapy for schizophrenia and co-occurring substance use disorders. *Neurotoxicology Research, 11*(1), 33-40.

Gregg, L., Barrowclough, C., & Haddock, G. (2007). Reasons for increased substance use in psychosis. *Clinical Psychology Review, 27*(4), 494-510.

Griffith, J. J., Oates, J., & Cavanaugh, J. (1968). Paranoid episodes induced by drugs. *JAMA, 205*(11), 39.

Gur, R. E., Cowell, P. E., Latshaw, A., Turetsky, B. I., Grossman, R. I., Arnold, S. E., . . . Gur, R. C. (2000). Reduced dorsal and orbital prefrontal gray matter volumes in schizophrenia. *Archives of General Psychiatry, 57*(8), 761-768.

Gur, R. E., & Gur, R. C. (2010). Functional magnetic resonance imaging in schizophrenia. *Dialogues in Clinical Neuroscience, 12*(3), 333-343.

Gureje, O. (1989). Correlates of positive and negative schizophrenic syndromes in Nigerian patients. *The British Journal of Psychiatry, 155*, 628-632.

Hadamitzky, M., Markou, A., & Kuczenski, R. (2011). Extended access to methamphetamine self-administration affects sensorimotor gating in rats. *Behavioural Brain Research, 217*(2), 386-390.

Hagino, H., Suzuki, M., Mori, K., Nohara, S., Yamashita, I., Takahashi, T., . . . Kurachi, M. (2002). Proton magnetic resonance spectroscopy of the inferior frontal gyrus and thalamus and its relationship to verbal learning task performance in patients with schizophrenia: A preliminary report. *Psychiatry and Clinical Neurosciences, 56*, 499-507.

Hall, W., & Degenhardt, L. (2000). Cannabis use and psychosis: A review of clinical and epidemiological evidence. *Australian and New Zealand Journal of Psychiatry, 34*(1), 26-34.

Hall, W., Hando, J., Darke, S., & Ross, J. (1996). Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. *Addiction, 91*(1), 81-87.

Hall, W., Teesson, M., Lynskey, M., & Degenhardt, L. (1999). The 12-month prevalence of substance use and ICD-10 substance use disorders in Australian adults: Findings from the National Survey of Mental Health and Well-Being. *Addiction, 94*(10), 1541-1550.

Halstead, W. C. (1947). *Brain and Intelligence.* Chicago: University of Chicago Press.

Hanson, K. L., Winward, J. L., Schweinsburg, A. D., Medina, K. L., Brown, S. A., & Tapert, S. F. (2010). Longitudinal study of cognition among adolescent marijuana users over three weeks of abstinence. *Addictive Behaviors, 35*(11), 970-976.

Hanstock, C., & Allen, P. (2000). *Segmentation of brain from a PRESS localised single volume using Double Inversion Recovery for simultaneous T1 nulling.* Paper presented at the International Society for Magnetic Resonance Imaging, Denver, Co.

Hardoy, M. C., Carta, M. G., Catena, M., Hardoy, M. J., Cadeddu, M., Dell'Osso, L., . . . Carpiniello, B. (2004). Impairment in visual and spatial perception in schizophrenia and delusional disorder. *Psychiatry Research, 127*(1-2), 163-166.

Harris, G. C., & Aston-Jones, G. (2003). Critical role for ventral tegmental glutamate in preference for a cocaine-conditioned environment. *Neuropsychopharmacology, 28*(1), 73-76.

Harrison, P. J., & Owen, M. J. (2003). Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet, 361*(9355), 417-419.

Hashimoto, K., Engberg, G., Shimizu, E., Nordin, C., Lindstrom, L. H., & Iyo, M. (2005). Elevated glutamine/glutamate ratio in cerebrospinal fluid of first episode and drug naive schizophrenic patients. *BMC Psychiatry, 5*, 6.

Heaton, R. (1981). Wisconsin Card Sorting Test: Manual. Odessa, FL: Psychological Assessment Resources.

Heaton, R., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). Wisconsin Card Sorting Test manual: Revised and expanded. Odessa, FL: Psychological Assessment Resources.

Heinrichs, R. W., & Zakzanis, K. K. (1998). Neurocognitive deficit in schizophrenia: A quantitative review of the evidence. *Neuropsychology, 12*(3), 426-445.

Henry, J. D., & Crawford, J. R. (2005). A meta-analytic review of verbal fluency deficits in schizophrenia relative to other neurocognitive deficits. *Cognitive Neuropsychiatry, 10*(1), 1-33.

Herman, M. (2004). Neurocognitive functioning and quality of life among dually diagnosed and non-substance abusing schizophrenia inpatients. *International Journal of Mental Health Nursing, 13*(4), 282-291.

Hermann, D., Sartorius, A., Welzel, H., Walter, S., Skopp, G., Ende, G., & Mann, K. (2007). Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. *Biological Psychiatry, 61*, 1281-1289.

Hilti, C. C., Hilti, L. M., Heinemann, D., Robbins, T., Seifritz, E., & Cattapan-Ludewig, K. (2010). Impaired performance on the Rapid Visual Information Processing task (RVIP) could be an endophenotype of schizophrenia. *Psychiatry Research, 177*(1-2), 60-64.

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

Hotsenpiller, G., Giorgetti, M., & Wolf, M. E. (2001). Alterations in behaviour and glutamate transmission following presentation of stimuli previously associated with cocaine exposure. *European Journal of Neuroscience, 14*(11), 1843-1855.

Howell, L. L., & Kimmel, H. L. (2008). Monoamine transporters and psychostimulant addiction. *Biochemical Pharmacology, 75*(1), 196-217.

Huang, Y. H., Tsai, S. J. , Su, T. W., & Sim, C. B. (1999). Effects of repeated high-dose methamphetamine on local cerebral glucose utilization in rats. *Neuropsychopharmacology, 21*(3), 427-434.

Hunt, D, Kuck, S, & Truitt, L. (2006). *Methamphetamine use: Lessons learned*.

Husted, J. A., Lim, S., Chow, E. W., Greenwood, C., & Bassett, A. S. (2009). Heritability of neurocognitive traits in familial schizophrenia. *American Journal Medical Genetics B Neuropsychiatric Genetics, 150B*(6), 845-853.

Hyman, S. E. (2005). Addiction: A disease of learning and memory. *American Journal of Psychiatry, 162*(8), 1414-1422.

Isohanni, M., Isohanni, I., Koponen, H., Koskinen, J., Laine, P., Lauronen, E., . . . Murray, G. (2004). Developmental precursors of psychosis. *Current Psychiatry Reports, 6*(3), 168-175.

Iwanami, A., Suga, I., Kaneko, T., Sugiyama, A., & Nakatani, Y. (1994). P300 component of event-related potentials in methamphetamine psychosis and schizophrenia. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 18*(3), 465-475.

Iyo, M., Sekine, Y., & Mori, N. (2004). Neuromechanism of developing methamphetamine psychosis: A neuroimaging study. *Annals of the New York Academy of Science, 1025*, 288-295.

Jackson, Y. (2007). *The investigation of neuroactive steroids, kynurenine metabolites and glutamate in schizophrenia.* Doctoral Dissertation, University of Alberta, Edmonton.

Jacobs, E., Fujii, D., Schiffman, J., & Bello, I. (2008). An exploratory analysis of neurocognition in methamphetamine-induced psychotic disorder and paranoid schizophrenia. *Cognitive and Behavioral Neurology, 21*(2), 98-103.

Jagannathan, N. R., Desai, N. G., & Raghunathan, P. (1996). Brain metabolite changes in alcoholism: An in vivo proton magnetic resonance spectroscopy (MRS) study. *Magnetic Resonance Imaging, 14*(5), 553-557.

Javitt, D. C. (2004). Glutamate as a therapeutic target in psychiatric disorders. *Molecular Psychiatry, 9*(11), 984-997, 979.

Javitt, D. C., & Zukin, S. R. (1991). Recent advances in the phencyclidine model of schizophrenia. *American Journal of Psychiatry, 148*(10), 1301-1308.

Jensen, A. R. (1965). Scoring the Stroop Test. *Acta Pscyhologica, 24*, 398-408.

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

Jessen, F., Scherk, H., Traber, F., Theyson, S., Berning, J., Tepest, R., . . . Block, W. (2006). Proton magnetic resonance spectroscopy in subjects at risk for schizophrenia. *Schizophrenia Research, 87*, 81-88.

Johnson-Selfridge, M., & Zalewski, C. (2001). Moderator variables of executive functioning in schizophrenia: Meta-analytic findings. *Schizophrenia Bulletin, 27*(2), 305-316.

Joo, Y. H. (2008). Neurophyisological and neurocognitive endophenotypes for schizophrenia genetics research. *Psychiatry Investigation, 5*(4), 199-202.

Jovanovski, D., Erb, S., & Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: A quantitative review of the evidence. *Journal of Clinical and Experimental Neuropsychology, 27*(2), 189-204.

Kalechstein, A. D., De La Garza, R., 2nd, Mahoney, J. J., 3rd, Fantegrossi, W. E., & Newton, T. F. (2007). MDMA use and neurocognition: A meta-analytic review. *Psychopharmacology, 189*(4), 531-537.

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

Kalivas, P. W., McFarland, K., Bowers, S., Szumlinski, K., Xi, Z. X., & Baker, D. (2003). Glutamate transmission and addiction to cocaine. *Annals of the New York Academy of Sciences, 1003*, 169-175.

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

Karler, R., Calder, L. D., Chaudhry, I. A., & Turkanis, S. A. (1989). Blockade of "reverse tolerance" to cocaine and amphetamine by MK-801. *Life Sciences, 45*(7), 599-606.

Karler, R., Thai, D. K., & Calder, L. D. (2003). Interactions of dopamine, glutamate, and GABA systems in mediating amphetamine- and cocaine-induced stereotypy and behavioral sensitization. In BH Herman (Ed.), *Glutamate and addiction*. Totowa, New Jersey: Human Press Inc.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276.

Keefe, R. S. (2007). Cognitive deficits in patients with schizophrenia: Effects and treatment. *Journal of Clinical Psychiatry, 68 Suppl 14*, 8-13.

Keefe, R. S., & Fenton, W. S. (2007). How should DSM-V criteria for schizophrenia include cognitive impairment? *Schizophrenia Bulletin, 33*(4), 912-920.

Keefe, R. S., Perkins, D. O., Gu, H., Zipursky, R. B., Christensen, B. K., & Lieberman, J. A. (2006). A longitudinal study of neurocognitive function in individuals at-risk for psychosis. *Schizophrenia Research, 88*(1-3), 26-35.

Kegeles, L. S., Humaran, T. J., & Mann, J. J. (1998). In vivo neurochemistry of the brain in schizophrenia as revealed by magnetic resonance spectroscopy. *Biological Psychiatry, 44*(6), 382-398.

Kelsey, J. E., Newport, D. J., & Nemeroff, C. B. (2006). Sleep disorders *Principles of psychopharmacology for mental health professionals*. Hoboken, New Jersey: John Wiley & Sons Inc.

Keshavan, M. S., Dick, R. M., Diwadkar, V. A., Montrose, D. M., Prasad, K. M., & Stanley, J. A. (2009). Striatal metabolic alterations in non-psychotic adolescent offspring at risk for schizophrenia: a (1)H spectroscopy study. *Schizophrenia Research, 115*, 88-93.

Keshavan, M. S., & Hogarty, G. E. (1999). Brain maturational processes and delayed onset in schizophrenia. *Development and Psychopathology, 11*(3), 525-543.

Keshavan, M. S., Kulkarni, S., Bhojraj, T., Francis, A., Diwadkar, V., Montrose, D. M., . . . Sweeney, J. (2010). Premorbid cognitive deficits in young relatives of schizophrenia patients. *Frontiers in Human Neuroscience, 3*, 62.

Keshavan, M. S., Montrose, D. M., Pierri, J. N., Dick, E. L., Rosenberg, D., Talagala, L., & Sweeney, J. A. (1997). Magnetic resonance imaging and spectroscopy in offspring at risk for schizophrenia: preliminary studies. *Progress in Neuropsychopharmacology and Biological Psychiatry, 21*, 1285-1295.

Keshavan, M. S., Stanley, J. A., & Pettegrew, J. W. (2000). Magnetic resonance spectroscopy in schizophrenia: methodological issues and findings--part II. *Biological Psychiatry, 48*(5), 369-380.

Khantzian, E. J. (1985). The self-medication hypothesis of addictive disorders: Focus on heroin and cocaine dependence. *American Journal of Psychiatry, 142*(11), 1259-1264.

Khantzian, E. J. (1997). The self-medication hypothesis of substance use disorders: A reconsideration and recent applications. *Harvard Review of Psychiatry, 4*(5), 231-244.

Kim, J. S., Kornhuber, H. H., Schmid-Burgk, W., & Holzmuller, B. (1980). Low cerebrospinal fluid glutamate in schizophrenic patients and a new hypothesis on schizophrenia. *Neuroscience Letters, 20*(3), 379-382.

Kim, S. J., Lyoo, I. K., Hwang, J., Chung, A., Hoon Sung, Y., Kim, J., . . . Renshaw, P. F. (2006). Prefrontal grey-matter changes in short-term and

long-term abstinent methamphetamine abusers. *International Journal of Neuropsychopharmacology, 9*(2), 221-228.

Kinney, D. K., Yurgelun-Todd, D. A., Waternaux, C. M., & Matthysse, S. (1994). Obstetrical complications and trail making deficits discriminate schizophrenics from unaffected siblings and controls. *Schizophrenia Research, 12*(1), 63-73.

Klar, A. A., Ballmaier, M., Leopold, K., Hake, I., Schaefer, M., Bruhl, R., . . . Gallinat, J. (2010). Interaction of hippocampal volume and N-acetylaspartate concentration deficits in schizophrenia: A combined MRI and 1H-MRS study. *Neuroimage, 53*(1), 51-57.

Klasser, G. D., & Epstein, J. (2005). Methamphetamine and its impact on dental care. *Journal of the Canadian Dental Association, 71*(10), 759-762.

Knable, M., & Weinberger, D. R. (1995). Are mental diseases brain diseases? The contribution of neuropathology to understanding of schizophrenic psychoses. *European Archives of Psychiatry and Clinical Neuroscience, 245*(4), 224-230.

Knowles, E. E., David, A. S., & Reichenberg, A. (2010). Processing speed deficits in schizophrenia: Reexamining the evidence. *American Journal of Psychiatry, 167*(7), 828-835.

Konradi, C., & Heckers, S. (2001). Antipsychotic drugs and neuroplasticity: Insights into the treatment and neurobiology of schizophrenia. *Biological Psychiatry, 50*(10), 729-742.

Konradi, C., & Heckers, S. (2003). Molecular aspects of glutamate dysregulation: Implications for schizophrenia and its treatment. *Pharmacology and Therapeutics, 97*(2), 153-179.

Koob, G. F., Ahmed, S. H., Boutrel, B., Chen, S. A., Kenny, P. J., Markou, A., . . . Sanna, P. P. (2004). Neurobiological mechanisms in the transition from drug use to drug dependence. *Neuroscience and Biobehavioral Reviews, 27*(8), 739-749.

Koren, D., Seidman, L. J., Harrison, R. H., Lyons, M. J., Kremen, W. S., Caplan, B., . . . Tsuang, M. T. (1998). Factor structure of the Wisconsin Card Sorting Test: Dimensions of deficit in schizophrenia. *Neuropsychology, 12*(2), 289-302.

Kosmidis, M. H., Bozikas, V. P., Zafiri, M., & Karavatos, A. (2006). Shared cognitive processes underlying performance on the Wisconsin Card Sorting Test and the Stroop Test in patients with schizophrenia: A measurement artifact? *Neuroscience Letters, 409*(3), 234-238.

Kurtz, M. M. (2005). Neurocognitive impairment across the lifespan in schizophrenia: An update. *Schizophrenia Research, 74*(1), 15-26.

Kurtz, M. M. (2011). Neurocognition as a predictor of response to evidence-based psychosocial interventions in schizophrenia: What is the state of the evidence? *Clinical Psychology Review, 31*(4), 663-672.

Lapish, C. C., Seamans, J. K., & Chandler, L. J. (2006). Glutamate-dopamine cotransmission and reward processing in addiction. *Alcoholism: Clinical and Experimental Research, 30*(9), 1451-1465.

Laruelle, M., Kegeles, L. S., & Abi-Dargham, A. (2003). Glutamate, dopamine, and schizophrenia: From pathophysiology to treatment. *Annals of the New York Academy of Science, 1003*, 138-158.

Laurent, A., Biloa-Tang, M., Bougerol, T., Duly, D., Anchisi, A., Bosson, J., . . . Dalery, J. (2000). Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. *Schizophrenia Research, 46*(2-3), 269-283.

Leavitt, V. M., & Goldberg, T. E. (2009). Episodic memory in schizophrenia. *Neuropsychology Review, 19*(3), 312-323.

Lee, E., Jang, D. P., Kim, J. J., An, S. K., Park, S., Kim, I. Y., . . . Namkoong, K. (2007). Alteration of brain metabolites in young alcoholics without structural changes. *Neuroreport, 18*, 1511-1514.

Lee, J., & Park, S. (2005). Working memory impairments in schizophrenia: A meta-analysis. *Journal of Abnormal Psychology, 114*(4), 599-611.

Leeson, V. C., Barnes, T. R., Harrison, M., Matheson, E., Harrison, I., Mutsatsa, S. H., . . . Joyce, E. M. (2010). The relationship between IQ, memory, executive function, and processing speed in recent-onset psychosis: 1-year stability and clinical outcome. *Schizophrenia Bulletin, 36*(2), 400-409.

Lencz, T., Smith, C. W., McLaughlin, D., Auther, A., Nakayama, E., Hovey, L., & Cornblatt, B. A. (2006). Generalized and specific neurocognitive deficits in prodromal schizophrenia. *Biological Psychiatry, 59*(9), 863-871.

Lewandowski, K. E., Cohen, B. M., & Ongur, D. (2011). Evolution of neuropsychological dysfunction during the course of schizophrenia and bipolar disorder. *Psychological Medicine, 41*(2), 225-241.

Lewis, D. A., & Moghaddam, B. (2006). Cognitive dysfunction in schizophrenia: Convergence of gamma-aminobutyric acid and glutamate alterations. *Archives of Neurology, 63*(10), 1372-1376.

Li, S. J., Wang, Y., Pankiewicz, J., & Stein, E. A. (1999). Neurochemical adaptation to cocaine abuse: reduction of N-acetyl aspartate in thalamus of human cocaine abusers. *Biological Psychiatry, 45*, 1481-1487.

Licata, S. C., & Renshaw, P. F. (2009). Neurochemistry of drug action: Insights from proton magnetic resonance spectroscopic imaging and their relevance to addiction. *Annals of the New York Academy of Sciences, 1187*, 148-171.

Lichlyter, B., Purdon, S., & Tibbo, P. (2010). Predictors of psychosis severity in individuals with primary stimulant addictions. *Addictive Behaviors, 36*(1-2), 137-139.

Liddle, P. F. (1987). Schizophrenic syndromes, cognitive performance and neurological dysfunction. *Psychological Medicine, 17*(1), 49-57.

Lim, K. O., Adalsteinsson, E., Spielman, D., Sullivan, E. V., Rosenbloom, M. J., & Pfefferbaum, A. (1998). Proton magnetic resonance spectroscopic imaging of cortical gray and white matter in schizophrenia. *Archives of General Psychiatry, 55*(4), 346-352.

Lineberry, T. W., & Bostwick, J. M. (2006). Methamphetamine abuse: A perfect storm of complications. *Mayo Clinic Proceedings., 81*(1), 77-84.

Lingford-Hughes, A. (2005). Human brain imaging and substance abuse. *Current Opinion in Pharmacology, 5*(1), 42-46.

Lingford-Hughes, A, Davies, S. J., McIver, S., Williams, T. M., Daglish, M. R., & Nutt, D. J. (2003). Addiction. *British Medical Bulletin, 65*, 209-222.

Linszen, D., & van Amelsvoort, T. (2007). Cannabis and psychosis: An update on course and biological plausible mechanisms. *Current Opinion in Psychiatry, 20*(2), 116-120.

Lipkovich, I. A., Deberdt, W., Csernansky, J. G., Sabbe, B., Keefe, R. S., & Kollack-Walker, S. (2009). Relationships among neurocognition, symptoms and functioning in patients with schizophrenia: A path-analytic approach for associations at baseline and following 24 weeks of antipsychotic drug therapy. *BMC Psychiatry, 9*, 44.

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

Lundqvist, T. (2005). Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. *Pharmacology, Biochemistry and Behavior, 81*(2), 319-330.

Lutkenhoff, E. S., van Erp, T. G., Thomas, M. A., Therman, S., Manninen, M., Huttunen, M. O., . . . Cannon, T. D. (2010). Proton MRS in twin pairs discordant for schizophrenia. *Molecular Psychiatry, 15*(3), 308-318.

Luzi, S., Morrison, P. D., Powell, J., di Forti, M., & Murray, R. M. (2008). What is the mechanism whereby cannabis use increases risk of psychosis? *Neurotoxicology Research, 14*(2-3), 105-112.

Lysaker, P. H., Bell, M. D., Bioty, S. M., & Zito, W. S. (1997). Cognitive impairment and substance abuse history as predictors of the temporal stability of negative symptoms in schizophrenia. *Journal of Nervous and Mental Disease, 185*(1), 21-26.

Ma, X., Wang, Q., Sham, P. C., Liu, X., Rabe-Hesketh, S., Sun, X., . . . Li, T. (2007). Neurocognitive deficits in first-episode schizophrenic patients and their first-degree relatives. *American Journal Medical Genetics B Neuropsychiatric Genetics, 144B*(4), 407-416.

Maccabe, J. H. (2008). Population-based cohort studies on premorbid cognitive function in schizophrenia. *Epidemiologic Reviews, 30*, 77-83.

Machielsen, M., van der Sluis, S., & de Haan, L. (2010). Cannabis use in patients with a first psychotic episode and subjects at ultra high risk of psychosis: Impact on psychotic- and pre-psychotic symptoms. *Australian and New Zealand Journal of Psychiatry, 44*(8), 721-728.

Machiyama, Y. (1992). Chronic methamphetamine intoxication model of schizophrenia in animals. *Schizophrenia Bulletin, 18*(1), 107-113.

Mahoney, J. J., 3rd, Kalechstein, A. D., De La Garza, R., 2nd, & Newton, T. F. (2008). Presence and persistence of psychotic symptoms in cocaine- versus methamphetamine-dependent participants. *American Journal on Addictions, 17*(2), 83-98.

Mahurin, R. K., Velligan, D. I., & Miller, A. L. (1998). Executive-frontal lobe cognitive dysfunction in schizophrenia: a symptom subtype analysis. *Psychiatry Research, 79*(2), 139-149.

Maier, M., & Ron, M. A. (1996). Hippocampal age-related changes in schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Research, 22*, 5-17.

Maki, P., Veijola, J., Jones, P. B., Murray, G. K., Koponen, H., Tienari, P., . . . Isohanni, M. (2005). Predictors of schizophrenia--a review. *British Medical Bulletin, 73-74*, 1-15.

Makinen, J., Miettunen, J., Isohanni, M., & Koponen, H. (2008). Negative symptoms in schizophrenia: A review. *Nordic Journal of Psychiatry, 62*(5), 334-341.

Malone, D. T., Hill, M. N., & Rubino, T. (2010). Adolescent cannabis use and psychosis: Epidemiology and neurodevelopmental models. *British Journal of Pharmacology, 160*(3), 511-522.

Manning, V., Betteridge, S., Wanigaratne, S., Best, D., Strang, J., & Gossop, M. (2009). Cognitive impairment in dual diagnosis inpatients with schizophrenia and alcohol use disorder. *Schizophrenia Research, 114*(1-3), 98-104.

Manning, V., Wanigaratne, S., Best, D., Strathdee, G., Schrover, I., & Gossop, M. (2007). Screening for cognitive functioning in psychiatric outpatients with schizophrenia, alcohol dependence, and dual diagnosis. *Schizophrenia Research, 91*(1-3), 151-158.

Marsden, J., Gossop, M., Stewart, D., Rolfe, A., & Farrell, M. (2000). Psychiatric symptoms among clients seeking treatment for drug dependence. Intake data from the National Treatment Outcome Research Study. *The British Journal of Psychiatry, 176*, 285-289.

Marshall, B. D., & Werb, D. (2010). Health outcomes associated with methamphetamine use among young people: A systematic review. *Addiction, 105*(6), 991-1002.

Martin, P. R., Gibbs, S. J., Nimmerrichter, A. A., Riddle, W. R., Welch, L. W., & Willcott, M. R. (1995). Brain proton magnetic resonance spectroscopy studies in recently abstinent alcoholics. *Alcoholism: Clinical and Experimental Research, 19*(4), 1078-1082.

Martinez-Granados, B., Brotons, O., Martinez-Bisbal, M. C., Celda, B., Marti-Bonmati, L., Aguilar, E. J., . . . Sanjuan, J. (2008). Spectroscopic metabolomic abnormalities in the thalamus related to auditory hallucinations in patients with schizophrenia. *Schizophrenia Research, 104*(1-3), 13-22.

Martino, D. J., Bucay, D., Butman, J. T., & Allegri, R. F. (2007). Neuropsychological frontal impairments and negative symptoms in schizophrenia. *Psychiatry Research, 152*(2-3), 121-128.

Mathias, S., Lubman, D. I., & Hides, L. (2008). Substance-induced psychosis: A diagnostic conundrum. *Journal of Clinical Psychiatry, 69*(3), 358-367.

Maton, B. M., & Kuzniecky, R. I. (2000). Proton MRS: N-acetyl aspartate, creatine, and choline. In T. R. Henry, J. S. Duncan & S. F Berkovic (Eds.), *Functional imaging in the epilepsies*. Philadelphia: Lippincott Williams & Wilkins.

Maxwell, J. C. (2005). Emerging research on methamphetamine. *Current Opinion in Psychiatry, 18*(3), 235-242.

Maynard, T. M., Sikich, L., Lieberman, J. A., & LaMantia, A. S. (2001). Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. *Schizophrenia Bulletin, 27*(3), 457-476.

McDowd, J., Tang, T., Tsai, P., Wang, S., & Su, C. (2011). The association between verbal memory, processing speed, negative symptoms and functional capacity in schizophrenia. *Psychiatry Research, 187*(3), 329-334.

McFarland, K., Davidge, S. B., Lapish, C. C., & Kalivas, P. W. (2004). Limbic and motor circuitry underlying footshock-induced reinstatement of cocaine-seeking behavior. *The Journal of Neuroscience, 24*(7), 1551-1560.

McFarland, K., Lapish, C. C., & Kalivas, P. W. (2003). Prefrontal glutamate release into the core of the nucleus accumbens mediates cocaine-induced reinstatement of drug-seeking behavior. *The Journal of Neuroscience, 23*(8), 3531-3537.

McGeehan, A. J., & Olive, M. F. (2003). The mGluR5 antagonist MPEP reduces the conditioned rewarding effects of cocaine but not other drugs of abuse. *Synapse, 47*(3), 240-242.

McGrath, J. J., Feron, F. P., Burne, T. H., Mackay-Sim, A., & Eyles, D. W. (2003). The neurodevelopmental hypothesis of schizophrenia: A review of recent developments. *Annals of Medicine, 35*(2), 86-93.

McKetin, R., Hickey, K., Devlin, K., & Lawrence, K. (2010). The risk of psychotic symptoms associated with recreational methamphetamine use. *Drug and Alcohol Review, 29*(4), 358-363.

McKetin, R., McLaren, J., Lubman, D. I., & Hides, L. (2006). The prevalence of psychotic symptoms among methamphetamine users. *Addiction, 101*(10), 1473-1478.

McKetin, R., Ross, J., Kelly, E., Baker, A., Lee, N., Lubman, D. I., & Mattick, R. (2008). Characteristics and harms associated with injecting versus smoking methamphetamine among methamphetamine treatment entrants. *Drug and Alcohol Review, 27*(3), 277-285.

Meador-Woodruff, J. H., & Healy, D. J. (2000). Glutamate receptor expression in schizophrenic brain. *Brain Research Reviews, 31*(2-3), 288-294.

Meltzer, H. Y., Thompson, P. A., Lee, M. A., & Ranjan, R. (1996). Neuropsychologic deficits in schizophrenia: relation to social function and effect of antipsychotic drug treatment. *Neuropsychopharmacology, 14*(3 Suppl), 27S-33S.

Meredith, C. W., Jaffe, C., Ang-Lee, K., & Saxon, A. J. (2005). Implications of chronic methamphetamine use: a literature review. *Harvard Review of Psychiatry, 13*(3), 141-154.

Mesholam-Gately, R. I., Giuliano, A. J., Goff, K. P., Faraone, S. V., & Seidman, L. J. (2009). Neurocognition in first-episode schizophrenia: A meta-analytic review. *Neuropsychology, 23*(3), 315-336.

Mikami, T., Naruse, N., Fukura, Y., Ohkubo, H., Ohkubo, T., Matsuura, M., . . . Kojima, T. (2003). Determining vulnerability to schizophrenia in methamphetamine psychosis using exploratory eye movements. *Psychiatry and Clinical Neurosciences, 57*(4), 433-440.

Milner, B. (1963). Effects of different brain lesions on card sorting: The role of the frontal lobes. *Archives of Neurology, 9*(1), 90-100.

Ministry of Justice. (1996). *Controlled Drugs and Substances Act*.

Minzenberg, M. J., Laird, A. R., Thelen, S., Carter, C. S., & Glahn, D. C. (2009). Meta-analysis of 41 functional neuroimaging studies of executive function in schizophrenia. *Archives of General Psychiatry, 66*(8), 811-822.

Mishlove, M., & Chapman, L. J. (1985). Social anhedonia in the prediction of psychosis proneness. *Journal of Abnormal Psychology, 94*(3), 384-396.

Moffett, J. R., Ross, B., Arun, P., Madhavarao, C. N., & Namboodiri, A. M. (2007). N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Progress in Neurobiology, 81*, 89-131.

Moghaddam, B. (2003). Bringing order to the glutamate chaos in schizophrenia. *Neuron, 40*(5), 881-884.

Moghaddam, B. (2004). Targeting metabotropic glutamate receptors for treatment of the cognitive symptoms of schizophrenia. *Psychopharmacology, 174*(1), 39-44.

Moghaddam, B., & Jackson, M. E. (2003). Glutamatergic animal models of schizophrenia. *Annals of the New York Academy of Science, 1003*, 131-137.

Molina, V., Sanchez, J., Reig, S., Sanz, J., Benito, C., Santamarta, C., . . . Desco, M. (2005). N-acetyl-aspartate levels in the dorsolateral prefrontal cortex in the early years of schizophrenia are inversely related to disease duration. *Schizophrenia Research, 73*, 209-219.

Molitor, F., Ruiz, J. D., Flynn, N., Mikanda, J. N., Sun, R. K., & Anderson, R. (1999). Methamphetamine use and sexual and injection risk behaviors among out-of-treatment injection drug users. *American Journal of Drug and Alcohol Abuse, 25*(3), 475-493.

Monterosso, J. R., Ainslie, G., Xu, J., Cordova, X., Domier, C. P., & London, E. D. (2006). Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Human Brain Mapping, 8*(5), 383-393.

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

Moon, M., Do, K. S., Park, J., & Kim, D. (2007). Memory impairment in methamphetamine dependent patients. *International Journal of Neuroscience, 117*(1), 1-9.

Moritz, S., Andresen, B., Perro, C., Schickel, M., Krausz, M., & Naber, D. (2002). Neurocognitive performance in first-episode and chronic schizophrenic patients. *European Archives of Psychiatry and Clinical Neuroscience, 252*(1), 33-37.

Morris, B. J., Cochran, S. M., & Pratt, J. A. (2005). PCP: From pharmacology to modelling schizophrenia. *Current Opinion in Pharmacology, 5*(1), 101-106.

Mueser, K. T., Drake, R. E., & Wallach, M. A. (1998). Dual diagnosis: A review of etiological theories. *Addictive Behaviors, 23*(6), 717-734.

Mueser, K. T., Noordsy, D. L., Drake, R. E., & Fox, L. (2003). *Integrated Treatment for Dual Disorders: A Guide to Effective Practice*. New York, New York: The Guildford Press.

Mueser, K. T., Yarnold, P. R., & Bellack, A. S. (1992). Diagnostic and demographic correlates of substance abuse in schizophrenia and major affective disorder. *Acta Psychiatrica Scandinavica, 85*(1), 48-55.

Mullins, P. G., Rowland, L., Bustillo, J., Bedrick, E. J., Lauriello, J., & Brooks, W. M. (2003). Reproducibility of 1H-MRS measurements in schizophrenic patients. *Magnetic Resonance in Medicine, 50*(4), 704-707.

Nakama, H., Chang, L., Cloak, C., Jiang, C., Alicata, D., & Haning, W. (2008). Association between psychiatric symptoms and craving in methamphetamine users. *American Journal on Addictions, 17*(5), 441-446.

Nakamura, K., Chen, C. K., Sekine, Y., Iwata, Y., Anitha, A., Loh el, W., . . . Mori, N. (2006). Association analysis of SOD2 variants with methamphetamine psychosis in Japanese and Taiwanese populations. *Human Genetics, 120*(2), 243-252.

Newton, T. F., Kalechstein, A. D., Duran, S., Vansluis, N., & Ling, W. (2004). Methamphetamine abstinence syndrome: Preliminary findings. *American Journal on Addictions, 13*(3), 248-255.

Niendam, T. A., Bearden, C. E., Johnson, J. K., McKinley, M., Loewy, R., O'Brien, M., . . . Cannon, T. D. (2006). Neurocognitive performance and functional disability in the psychosis prodrome. *Schizophrenia Research, 84*(1), 100-111.

Nixon, S. J., Hallford, H. G., & Tivis, R. D. (1996). Neurocognitive function in alcoholic, schizophrenic, and dually diagnosed patients. *Psychiatry Research, 64*(1), 35-45.

Nordahl, T. E., Salo, R., & Leamon, M. (2003). Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: A review. *Journal of Neuropsychiatry and Clinical Neuroscience, 15*(3), 317-325.

Nordahl, T. E., Salo, R., Natsuaki, Y., Galloway, G. P., Waters, C., Moore, C. D., . . . Buonocore, M. H. (2005). Methamphetamine users in sustained

abstinence: A proton magnetic resonance spectroscopy study. *Archives of General Psychiatry, 62*(4), 444-452.

Nordahl, T. E., Salo, R., Possin, K., Gibson, D. R., Flynn, N., Leamon, M., . . . Sullivan, E. V. (2002). Low N-acetyl-aspartate and high choline in the anterior cingulum of recently abstinent methamphetamine-dependent subjects: A preliminary proton MRS study. Magnetic resonance spectroscopy. *Psychiatry Research, 116*(1-2), 43-52.

Nuechterlein, K. H. (1986). Childhood precursors of adult schizophrenia. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 27*(2), 133-144.

Nuechterlein, K. H., Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research, 72*(1), 29-39.

O'Connor, M., Harris, J. M., McIntosh, A. M., Owens, D. G. C., Lawrie, S. M., & Johnstone, E. C. (2009). Specific cognitive deficits in a group at genetic high risk of schizophrenia. *Psychological Medicine, 39*(10), 1649-1655.

O'Donnell, P., & Grace, A. A. (1998). Dysfunctions in multiple interrelated systems as the neurobiological bases of schizophrenic symptom clusters. *Schizophrenia Bulletin, 24*(2), 267-283.

O'Leary, D. S., Flaum, M., Kesler, M. L., Flashman, L. A., Arndt, S., & Andreasen, N. C. (2000). Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences, 12*(1), 4-15.

O'Tuathaigh, C. M. P., Harte, M., O'Leary, C., O'Sullivan, G. J., Blau, C., Lai, D., . . . Waddington, J. L. (2010). Schizophrenia-related endophenotypes in heterozygous neuregulin-1 'knockout' mice. *European Journal of Neuroscience, 31*(2), 349-358.

Oertel-Knochel, V., Bittner, R. A., Knochel, C., Prvulovic, D., & Hampel, H. (2011). Discovery and development of integrative biological markers for schizophrenia. *Progress in Neurobiology*

Oetting, E. R., Deffenbacher, J. L., Taylor, M. J., Luther, N., Beauvais, F., & Edwards, R. W. (2000). Methamphetamine use by high school students: Recent trends, gender and ethnicity differences, and use of other drugs. *Journal of Child & Adolescent Substance Abuse, 10*(1), 33-50.

Ohmori, T., Abekawa, T., Muraki, A., & Koyama, T. (1994). Competitive and noncompetitive NMDA antagonists block sensitization to methamphetamine. *Pharmacology Biochemistry and Behavior, 48*(3), 587-591.

Ohrmann, P., Kugel, H., Bauer, J., Siegmund, A., Kolkebeck, K., Suslow, T., . . . Pedersen, A. (2008). Learning potential on the WCST in schizophrenia is related to the neuronal integrity of the anterior cingulate cortex as measured by proton magnetic resonance spectroscopy. *Schizophrenia Research, 106*(2-3), 156-163.

Ohrmann, P., Siegmund, A., Suslow, T., Pedersen, A., Spitzberg, K., Kersting, A., . . . Pfleiderer, B. (2006). Cognitive impairment and in vivo metabolites in first-episode neuroleptic-naive and chronic medicated schizophrenic

patients: A proton magnetic resonance spectroscopy study. *Journal of Psychiatric Research, 41*(8), 625-634.

Ohrmann, P., Siegmund, A., Suslow, T., Spitzberg, K., Kersting, A., Arolt, V., . . . Pfleiderer, B. (2005). Evidence for glutamatergic neuronal dysfunction in the prefrontal cortex in chronic but not in first-episode patients with schizophrenia: a proton magnetic resonance spectroscopy study. *Schizophrenia Research, 73*(2-3), 153-157.

Olbrich, H. M., Valerius, G., Rusch, N., Buchert, M., Thiel, T., Hennig, J., . . . Van Elst, L. T. (2008). Frontolimbic glutamate alterations in first episode schizophrenia: Evidence from a magnetic resonance spectroscopy study. *World Journal of Biological Psychiatry, 9*, 59-63.

Olney, J. W., & Farber, N. B. (1995). Glutamate receptor dysfunction and schizophrenia. *Archives of General Psychiatry, 52*(12), 998-1007.

Olney, J. W., Newcomer, J. W., & Farber, N. B. (1999). NMDA receptor hypofunction model of schizophrenia. *Journal of Psychiatric Research, 33*(6), 523-533.

Ongur, D., Prescot, A. P., Jensen, J. E., Cohen, B. M., & Renshaw, P. F. (2009). Creatine abnormalities in schizophrenia and bipolar disorder. *Psychiatry Research, 172*(1), 44-48.

Ornstein, T. J., Iddon, J. L., Baldacchino, A. M., Sahakian, B. J., London, M., Everitt, B. J., & Robbins, T. W. (2000). Profiles of cognitive dysfunction in chronic amphetamine and heroin abusers. *Neuropsychopharmacology, 23*(2), 113-126.

Palmer, B. W., Dawes, S. E., & Heaton, R. K. (2009). What do we know about neuropsychological aspects of schizophrenia? *Neuropsychology Review, 19*(3), 365-384.

Pantelis, C., Stuart, G. W., Nelson, H. E., Robbins, T. W., & Barnes, T. R. (2001). Spatial working memory deficits in schizophrenia: Relationship with tardive dyskinesia and negative symptoms. *American Journal of Psychiatry, 158*(8), 1276-1285.

Pantelis, C., Yucel, M., Wood, S. J., McGorry, P. D., & Velakoulis, D. (2003). Early and late neurodevelopmental disturbances in schizophrenia and their functional consequences. *Australian and New Zealand Journal of Psychiatry, 37*(4), 399-406.

Pantelis, C., Yucel, M., Wood, S. J., Velakoulis, D., Sun, D., Berger, G., . . . McGorry, P. D. (2005). Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophrenia Bulletin, 31*(3), 672-696.

Park, W. K., Bari, A. A., Jey, A. R., Anderson, S. M., Spealman, R. D., Rowlett, J. K., & Pierce, R. C. (2002). Cocaine administered into the medial prefrontal cortex reinstates cocaine-seeking behavior by increasing AMPA receptor-mediated glutamate transmission in the nucleus accumbens. *The Journal of Neuroscience, 22*(7), 2916-2925.

Parks, M. H., Dawant, B. M., Riddle, W. R., Hartmann, S. L., Dietrich, M. S., Nickel, M. K., . . . Martin, P. R. (2002). Longitudinal brain metabolic characterization of chronic alcoholics with proton magnetic resonance

spectroscopy. *Alcoholism: Clinical and Experimental Research, 26*(9), 1368-1380.

Paulus, M. P., Hozack, N. E., Zauscher, B. E., Frank, L., Brown, G. G., Braff, D. L., & Schuckit, M. A. (2002). Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology, 26*(1), 53-63.

Paulus, M. P., Hozack, N., Frank, L., Brown, G. G., & Schuckit, M. A. (2003). Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. *Biological Psychiatry, 53*(1), 65-74.

Peer, J., Bennett, M. E., & Bellack, A. S. (2009). Neurocognitive characteristics of individuals with schizophrenia and cocaine dependence: Comparison of currently dependent and remitted groups. *The Journal of Nervous and Mental Disease, 197*(8), 631-634.

Pencer, A., & Addington, J. (2003). Substance use and cognition in early psychosis. *Journal of Psychiatry and Neuroscience, 28*(1), 48-54.

Pennypacker, K. R., Kassed, C. A., Eidizadeh, S., & O'Callaghan, J. P. (2000). Brain injury: Prolonged induction of transcription factors. *Acta Neurobiologiae Experimentalis, 60*(4), 515-530.

Peralta, V., & Cuesta, M. J. (1994). Psychometric properties of the positive and negative syndrome scale (PANSS) in schizophrenia. *Psychiatry Research, 53*(1), 31-40.

Perry, T. L. (1982). Normal cerebrospinal fluid and brain glutamate levels in schizophrenia do not support the hypothesis of glutamatergic neuronal dysfunction. *Neuroscience Letters, 28*(1), 81-85.

Pierce, R. C., Bell, K., Duffy, P., & Kalivas, P. W. (1996). Repeated cocaine augments excitatory amino acid transmission in the nucleus accumbens only in rats having developed behavioral sensitization. *The Journal of Neuroscience, 16*(4), 1550-1560.

Piskulic, D., Olver, J. S., Norman, T. R., & Maruff, P. (2007). Behavioural studies of spatial working memory dysfunction in schizophrenia: A quantitative literature review. *Psychiatry Research, 150*(2), 111-121.

Pomarol-Clotet, E., Canales-Rodriguez, E. J., Salvador, R., Sarro, S., Gomar, J. J., Vila, F., . . . McKenna, P. J. (2010). Medial prefrontal cortex pathology in schizophrenia as revealed by convergent findings from multimodal imaging. *Molecular Psychiatry, 15*(8), 823-830.

Pope, H. G., Jr., Gruber, A. J., Hudson, J. I., Huestis, M. A., & Yurgelun-Todd, D. (2002). Cognitive measures in long-term cannabis users. *Journal of Clinical Pharmacology, 42*(11 Suppl), 41S-47S.

Potvin, S., Joyal, C. C., Pelletier, J., & Stip, E. (2008). Contradictory cognitive capacities among substance-abusing patients with schizophrenia: A meta-analysis. *Schizophrenia Research, 100*(1-3), 242-251.

Potvin, S., Pampoulova, T., Lipp, O., Ait Bentaleb, L., Lalonde, P., & Stip, E. (2008). Working memory and depressive symptoms in patients with

schizophrenia and substance use disorders. *Cognitive Neuropsychiatry, 13*(4), 357-366.

Premkumar, P., Parbhakar, V. A., Fannon, D., Lythgoe, D., Williams, S. C., Kuipers, E., & Kumari, V. (2010). N-acetyl aspartate concentration in the anterior cingulate cortex in patients with schizophrenia: A study of clinical and neuropsychological correlates and preliminary exploration of cognitive behaviour therapy effects. *Psychiatry Research, 182*(3), 251-260.

Prentice, K. J., Gold, J. M., & Buchanan, R. W. (2007). The Wisconsin Card Sorting impairment in schizophrenia is evident in the first four trials. *Schizophrenia Research, 106*(1), 81-87.

Provencher, S. W. (1993). Estimation of metabolite concentrations from localized in vivo proton NMR spectra. *Magnetic Resonance in Medicine, 30*(6), 672-679.

Pukrop, R., & Klosterkotter, J. (2010). Neurocognitive indicators of clinical high-risk states for psychosis: A critical review of the evidence. *Neurotoxicology Research, 18*(3-4), 272-286.

Purdon, S. E., Labelle, A., & Boulay, L. (2001). Neuropsychological change in schizophrenia after 6 weeks of clozapine. *Schizophrenia Research, 48*(1), 57-67.

Purdon, S. E., Valiakalayil, A., Hanstock, C. C., Seres, P., & Tibbo, P. (2008). Elevated 3T proton MRS glutamate levels associated with poor

Continuous Performance Test (CPT-0X) scores and genetic risk for schizophrenia. *Schizophrenia Research, 99*(1-3), 218-224.

Purdon, S. E., Waldie, B., Woodward, N. D., Wilman, A. H., & Tibbo, P. G. (2011). Procedural learning in first episode schizophrenia investigated with functional magnetic resonance imaging. *Neuropsychology, 25*(2), 147-158.

Radlow, R. (1994). A quantitative theory of acute tolerance to alcohol. *Psychopharmacology, 114*(1), 1-8.

Raffard, S., Bayard, S., Gely-Nargeot, M. C., Capdevielle, D., Maggi, M., Barbotte, E., . . . Boulenger, J. P. (2009). Insight and executive functioning in schizophrenia: A multidimensional approach. *Psychiatry Research, 167*(3), 239-250.

Rapoport, J. L., Addington, A., & Frangou, S. (2005). The neurodevelopmental model of schizophrenia: What can very early onset cases tell us? *Current Psychiatry Reports, 7*(2), 81-82.

Rector, N. A., Beck, A. T., & Stolar, N. (2005). The negative symptoms of schizophrenia: A cognitive perspective. *Canadian Journal of Psychiatry, 50*(5), 247-257.

Rehm, J., Baliunas, D., Brochu, S., Fischer, B., Gnam, W., Patra, J., . . . Taylor, B. (2006). *The Costs of Substance Abuse In Canada 2002 Highlights*: Canadian Centre on Substance Abuse.

Rehman, I. U., & Farooq, S. (2007). Schizophrenia and comorbid self reported cannabis abuse: Impact on course, functioning and services use. *Journal of the Pakistan Medical Association, 57*(2), 60-64.

Rehn, A. E., & Rees, S. M. (2005). Investigating the neurodevelopmental hypothesis of schizophrenia. *Clinical and Experimental Pharmacology and Physiology, 32*(9), 687-696.

Reichenberg, A. (2010). The assessment of neuropsychological functioning in schizophrenia. *Dialogues in Clinical Neuroscience, 12*(3), 383-392.

Reid, M. A., Stoeckel, L. E., White, D. M., Avsar, K. B., Bolding, M. S., Akella, N. S., . . . Lahti, A. C. (2010). Assessments of function and biochemistry of the anterior cingulate cortex in schizophrenia. *Biological Psychiatry, 68*(7), 625-633.

Reid, M. S., & Berger, S. P. (1996). Evidence for sensitization of cocaine-induced nucleus accumbens glutamate release. *Neuroreport, 7*(7), 1325-1329.

Reitan, R. M. (1979). *Manual for the Administration of Neuropsychological Test Batteries for Adults and Children*. Tucson: Neuropsychology Press.

Reneman, L., Majoie, C. B., Flick, H., & den Heeten, G. J. (2002). Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (Ecstasy) users: Preliminary results. *American Journal of Neuroradiology, 23*(2), 231-237.

Reneman, L., Majoie, C. B., Schmand, B., van den Brink, W., & den Heeten, G. J. (2001). Prefrontal N-acetylaspartate is strongly associated with memory

performance in (abstinent) ecstasy users: Preliminary report. *Biological Psychiatry, 50*(7), 550-554.

Rogers, R. D., Everitt, B. J., Baldacchino, A., Blackshaw, A. J., Swainson, R., Wynne, K., . . . Robbins, T. W. (1999). Dissociable deficits in the decision-making cognition of chronic amphetamine abusers, opiate abusers, patients with focal damage to prefrontal cortex, and tryptophan-depleted normal volunteers: Evidence for monoaminergic mechanisms. *Neuropsychopharmacology, 20*(4), 322-339.

Ross, A. J., & Sachdev, P. S. (2004). Magnetic resonance spectroscopy in cognitive research. *Brain Research Reviews, 44*(2-3), 83-102.

Rund, B. R. , Egeland, J., Sundet, K., Asbjørnsen, A., Hugdahl, K., Landrø, N. I., . . . Stordal, K. I. (2004). Early visual information processing in schizophrenia compared to recurrent depression. *Schizophrenia Research, 68*(2-3), 111-118.

Rusch, N., Tebartz van Elst, L., Valerius, G., Buchert, M., Thiel, T., Ebert, D., . . . Olbrich, H. M. (2008). Neurochemical and structural correlates of executive dysfunction in schizophrenia. *Schizophrenia Research, 99*(1-3), 155-163.

Rush, B., Urbanoski, K., Bassani, D., Castel, S., Wild, T. C., Strike, C., . . . Somers, J. (2008). Prevalence of co-occurring substance use and other mental disorders in the Canadian population. *Canadian Journal of Psychiatry, 53*(12), 800-809.

Russell, K., Dryden, D. M., Liang, Y., Friesen, C., O'Gorman, K., Durec, T., . . . Klassen, T. P. (2008). Risk factors for methamphetamine use in youth: A systematic review. *BMC Pediatrics, 8*, 48.

Rutten, B. P., & Mill, J. (2009). Epigenetic mediation of environmental influences in major psychotic disorders. *Schizophrenia Bulletin, 35*(6), 1045-1056.

Sadock, B. J., & Sadock, V. A. (2003). *Kaplan & Sadock's Synopsis of Psychiatry* (9th Edition ed.): Lippincott Williams & Wilkins.

Saha, S., Chant, D., & McGrath, J. J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry, 64*(10), 1123-1131.

Salibi, N., & Brown, M. A. (1998). *Clinical MR Spectroscopy First Principles*. New York: Wiley-Liss Inc.

Salo, R., Flower, K., Kielstein, A., Leamon, M. H., Nordahl, T. E., & Galloway, G. P. (2011). Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Research, 186*(2-3), 356-361.

Salo, R., Leamon, M. H., Natsuaki, Y., Moore, C., Waters, C., & Nordahl, T. E. (2008). Findings of preserved implicit attention in methamphetamine dependent subjects. *Progress in Neuropsychopharmacology & Biological Psychiatry, 32*(1), 217-223.

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

Salo, R., Nordahl, T. E., Natsuaki, Y., Leamon, M. H., Galloway, G. P., Waters, C., . . . Buonocore, M. H. (2007). Attentional control and brain metabolite levels in methamphetamine abusers. *Biological Psychiatry, 61*(11), 1272-1280.

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

Sanches, R. F., Crippa, J. A., Hallak, J. E., Araujo, D., & Zuardi, A. W. (2004). Proton magnetic resonance spectroscopy of the frontal lobe in schizophrenics: A critical review of the methodology. *Revista do Hospital Das Clinicas; Faculdade de Medicina da Universidade de Sao Paulo, 59*(3), 145-152.

Sanchez, P., Ojeda, N., Pena, J., Elizagarate, E., Yoller, A. B., Gutierrez, M., & Ezcurra, J. (2009). Predictors of longitudinal changes in schizophrenia: The role of processing speed. *Journal of Clinical Psychiatry, 70*(6), 888-896.

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

Sato, M., Numachi, Y., & Hamamura, T. (1992). Relapse of paranoid psychotic state in methamphetamine model of schizophrenia. *Schizophrenia Bulletin, 18*(1), 115-122.

Schenk, S., Valadez, A., McNamara, C., House, D. T., Higley, D., Bankson, M. G., . . . Horger, B. A. (1993). Development and expression of sensitization to cocaine's reinforcing properties: Role of NMDA receptors. *Psychopharmacology, 111*(3), 332-338.

Schmidt, L. M., Hesse, M., & Lykke, J. (2011). The impact of substance use disorders on the course of schizophrenia-A 15-year follow-up study Dual diagnosis over 15 years. *Schizophrenia Research, 130*(1-3), 228-233.

Schoenbaum, G., Roesch, M. R., & Stalnaker, T. A. (2006). Orbitofrontal cortex, decision-making and drug addiction. *Trends in Neuroscience, 29*(2), 116-124.

Schultz, W. (2006). Behavioral theories and the neurophysiology of reward. *Annual Review of Psychology, 57*, 87-115.

Schweinsburg, A. D., Brown, S. A., & Tapert, S. F. (2008). The influence of marijuana use on neurocognitive functioning in adolescents. *Current Drug Abuse Reviews, 1*(1), 99-111.

Schweinsburg, B. C., Alhassoon, O. M., Taylor, M. J., Gonzalez, R., Videen, J. S., Brown, G. G., . . . Grant, I. (2003). Effects of alcoholism and gender on brain metabolism. *American Journal of Psychiatry, 160*(6), 1180-1183.

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

Seidman, L. J., Giuliano, A. J., Meyer, E. C., Addington, J., Cadenhead, K. S., Cannon, T. D., . . . Cornblatt, B. A. (2010). Neuropsychology of the prodrome to psychosis in the NAPLS consortium: Relationship to family history and conversion to psychosis. *Archives of General Psychiatry, 67*(6), 578-588.

Seidman, L. J., Yurgelun-Todd, D., Kremen, W. S., Woods, B. T., Goldstein, J. M., Faraone, S. V., & Tsuang, M. T. (1994). Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. *Biological Psychiatry, 35*(4), 235-246.

Sekine, Y., Minabe, Y., Kawai, M., Suzuki, K., Iyo, M., Isoda, H., . . . Mori, N. (2002). Metabolite alterations in basal ganglia associated with methamphetamine-related psychiatric symptoms. A proton MRS study. *Neuropsychopharmacology, 27*(3), 453-461.

Sekine, Y., Minabe, Y., Ouchi, Y., Takei, N., Iyo, M., Nakamura, K., . . . Mori, N. (2003). Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. *American Journal of Psychiatry, 160*(9), 1699-1701.

Selemon, L. D., & Goldman-Rakic, P. S. (1999). The reduced neuropil hypothesis: A circuit based model of schizophrenia. *Biological Psychiatry, 45*(1), 17-25.

Serper, M. R., Bergman, A., Copersino, M. L., Chou, J. C., Richarme, D., & Cancro, R. (2000). Learning and memory impairment in cocaine-

dependent and comorbid schizophrenic patients. *Psychiatry Research, 93*(1), 21-32.

Serper, M. R., Copersino, M. L., Richarme, D., Vadhan, N., & Cancro, R. (2000). Neurocognitive functioning in recently abstinent, cocaine-abusing schizophrenic patients. *Journal of Substance Abuse, 11*(2), 205-213.

Sevy, S., Kay, S. R., Opler, L. A., & van Praag, H. M. (1990). Significance of cocaine history in schizophrenia. *Journal of Nervous and Mental Disease, 178*(10), 642-648.

Shad, M. U., Tamminga, C. A., Cullum, M., Haas, G. L., & Keshavan, M. S. (2006). Insight and frontal cortical function in schizophrenia: A review. *Schizophrenia Research, 86*(1-3), 54-70.

Shansky, R. M., & Morrison, J. H. (2009). Stress-induced dendritic remodeling in the medial prefrontal cortex: Effects of circuit, hormones and rest. *Brain Research, 1293*, 108-113.

Sharma, T., & Antonova, L. (2003). Cognitive function in schizophrenia. Deficits, functional consequences, and future treatment. *Psychiatric Clinics of North America, 26*(1), 25-40.

Shenton, M. E., Dickey, C. C., Frumin, M., & McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophrenia Research, 49*(1-2), 1-52.

Shenton, M. E., Whitford, T. J., & Kubicki, M. (2010). Structural neuroimaging in schizophrenia: From methods to insights to treatments. *Dialogues in Clinical Neuroscience, 12*(3), 317-332.

Shirayama, Y., Obata, T., Matsuzawa, D., Nonaka, H., Kanazawa, Y., Yoshitome, E., . . . Iyo, M. (2010). Specific metabolites in the medial prefrontal cortex are associated with the neurocognitive deficits in schizophrenia: A preliminary study. *Neuroimage, 49*(3), 2783-2790.

Sigmundsson, T., Maier, M., Toone, B. K., Williams, S. C., Simmons, A., Greenwood, K., & Ron, M. A. (2003). Frontal lobe N-acetylaspartate correlates with psychopathology in schizophrenia: A proton magnetic resonance spectroscopy study. *Schizophrenia Research, 64*(1), 63-71.

Sigmundsson, T., Suckling, J., Maier, M., Williams, S., Bullmore, E., Greenwood, K., . . . Toone, B. (2001). Structural abnormalities in frontal, temporal, and limbic regions and interconnecting white matter tracts in schizophrenic patients with prominent negative symptoms. *American Journal of Psychiatry, 158*(2), 234-243.

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

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

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

Simpson, M. D., Slater, P., & Deakin, J. F. (1998). Comparison of glutamate and gamma-aminobutyric acid uptake binding sites in frontal and temporal lobes in schizophrenia. *Biological Psychiatry, 44*(6), 423-427.

Sinclair, J. M., Nausheen, B., Garner, M. J., & Baldwin, D. S. (2010). Attentional biases in clinical populations with alcohol use disorders: Is co-morbidity ignored? *Human Psychopharmacology, 25*(7-8), 515-524.

Smelson, D. A., Davis, C. W., Di Pano, R., Johnson, V., Losonczy, M. F., & Ziedonis, D. (2002). Executive and motor skill functioning among cocaine-dependent schizophrenics and non-drug-abusing schizophrenics. *Journal of Nervous and Mental Disease, 190*(3), 200-202.

Smelson, D. A., Davis, C. W., Eisenstein, N., Engelhart, C., Williams, J., Losonczy, M. F., & Ziedonis, D. (2003). Cognitive disparity in schizophrenics with and without cocaine dependency. *Journal of Substance Abuse Treatment, 24*(1), 75-79.

Smith, M. J., Thirthalli, J., Abdallah, A. B., Murray, R. M., & Cottler, L. B. (2009). Prevalence of psychotic symptoms in substance users: A comparison across substances. *Comprehensive Psychiatry, 50*(3), 245-250.

Snider, J., & Choi, D. W. (2003). Glutamate and Neurotoxicity. In BH Herman (Ed.), *Glutamate and Addiction*. Totowa, New Jersey: Human Press Inc.

Solowij, N., & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: A review. *Current Drug Abuse Reviews, 1*(1), 81-98.

Sommers, I., Baskin, D., & Baskin-Sommers, A. (2006). Methamphetamine use among young adults: Health and social consequences. *Addictive Behaviors, 31*(8), 1469-1476.

Soreni, N., Noseworthy, M. D., Konyer, N. B., Pullenayegum, E., & Schachar, R. (2010). Interindividual, repositioning, and time-of-day effects on single voxel proton MR spectroscopy of the anterior cingulate cortex. *Journal of Magnetic Resonance Imaging, 32*(2), 276-282.

Spann, M. D., McGwin, G., Jr., Kerby, J. D., George, R. L., Dunn, S., Rue, L. W., 3rd, & Cross, J. M. (2006). Characteristics of burn patients injured in methamphetamine laboratory explosions. *Journal of Burn Care Research, 27*(4), 496-501.

Spreen, O., & Strauss, E. (1991). *A Compendium of Neuropsychological Tests*. New York: Oxford University Press.

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

Srisurapanont, M., Ali, R., Marsden, J., Sunga, A., Wada, K., & Monteiro, M. (2003). Psychotic symptoms in methamphetamine psychotic in-patients. *International Journal of Neuropsychopharmacology, 6*(4), 347-352.

Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R., & Kongsakon, R. (2011). Comparisons of methamphetamine psychotic and schizophrenic symptoms: A differential item functioning analysis.

Progress in Neuro-Psychopharmacology and Biological Psychiatry, 35(4), 959-964.

Stahl, S. M. (2008). Stahl's Essential Psychopharmacology Online Retrieved from http://stahlonline.cambridge.org/essential_chapter.jsf?page=chapter9.htm&name=Chapter%209&title=Symptom%20dimensions%20in%20schizophrenia

Stanley, J. A., Pettegrew, J. W., & Keshavan, M. S. (2000). Magnetic resonance spectroscopy in schizophrenia: Methodological issues and findings--part I. *Biological Psychiatry, 48*(5), 357-368.

Stanley, J. A., Vemulapalli, M., Nutche, J., Montrose, D. M., Sweeney, J. A., Pettegrew, J. W., . . . Keshavan, M. S. (2007). Reduced N-acetyl-aspartate levels in schizophrenia patients with a younger onset age: A single-voxel 1H spectroscopy study. *Schizophrenia Research, 93*, 23-32.

Stanley, J. A., Williamson, P. C., Drost, D. J., Rylett, R. J., Carr, T. J., Malla, A., & Thompson, R. T. (1996). An in vivo proton magnetic resonance spectroscopy study of schizophrenia patients. *Schizophrenia Bulletin, 22*(4), 597-609.

Steen, R. G., Hamer, R. M., & Lieberman, J. A. (2005). Measurement of brain metabolites by 1H magnetic resonance spectroscopy in patients with schizophrenia: A systematic review and meta-analysis. *Neuropsychopharmacology, 30*(11), 1949-1962.

Stewart, S. A. (2005). The effects of benzodiazepines on cognition. *Journal of Clinical Psychiatry, 66 Suppl 2*, 9-13.

Stilo, S. A., & Murray, R. M. (2010). The epidemiology of schizophrenia: Replacing dogma with knowledge. *Dialogues in Clinical Neuroscience, 12*(3), 305-315.

Stone, J. M., Bramon, E., Pauls, A., Sumich, A., & McGuire, P. K. (2010). Thalamic neurochemical abnormalities in individuals with prodromal symptoms of schizophrenia - relationship to auditory event-related potentials. *Psychiatry Research, 183*(2), 174-176.

Stone, J. M., Day, F., Tsagaraki, H., Valli, I., McLean, M. A., Lythgoe, D. J., . . . McGuire, P. K. (2009). Glutamate dysfunction in people with prodromal symptoms of psychosis: Relationship to gray matter volume. *Biological Psychiatry, 66*, 533-539.

Stroop, JR. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643 - 662.

Sung, Y. H., Cho, S. C., Hwang, J., Kim, S. J., Kim, H., Bae, S., . . . Lyoo, I. K. (2007). Relationship between N-acetyl-aspartate in gray and white matter of abstinent methamphetamine abusers and their history of drug abuse: A proton magnetic resonance spectroscopy study. *Drug and Alcohol Dependence, 88*(1), 28-35.

Suslow, T., Junghanns, K., Weitzsch, C., & Arolt, V. (1998). Relations between neuropsychological vulnerability markers and negative symptoms in schizophrenia. *Psychopathology, 31*(4), 178-187.

Sutton, M. A., Schmidt, E. F., Choi, K. H., Schad, C. A., Whisler, K., Simmons, D., . . . Self, D. W. (2003). Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. *Nature, 421*(6918), 70-75.

Suzuki, A., Nakamura, K., Sekine, Y., Minabe, Y., Takei, N., Suzuki, K., . . . Mori, N. (2006). An association study between catechol-O-methyl transferase gene polymorphism and methamphetamine psychotic disorder. *Psychiatric Genetics, 16*(4), 133-138.

Sweeting, M., & Farrell, M. (2005). Methamphetamine psychosis: How is it related to schizophrenia? A review of the literature. *Current Psychiatry Reviews, 1*(2), 115-122.

Szoke, A., Trandafir, A., Dupont, M. E., Meary, A., Schurhoff, F., & Leboyer, M. (2008). Longitudinal studies of cognition in schizophrenia: Meta-analysis. *The British Journal of Psychiatry, 192*(4), 248-257.

Szulc, A., Galinska, B., Tarasow, E., Dzienis, W., Kubas, B., Konarzewska, B., . . . Czernikiewicz, A. (2005). The effect of risperidone on metabolite measures in the frontal lobe, temporal lobe, and thalamus in schizophrenic patients. A proton magnetic resonance spectroscopy (1H MRS). *Pharmacopsychiatry, 38*(5), 214-219.

Szulc, A., Galinska, B., Tarasow, E., Kubas, B., Dzienis, W., Konarzewska, B., . . . Walecki, J. (2007). N-acetylaspartate (NAA) levels in selected areas of the brain in patients with chronic schizophrenia treated with typical and atypical neuroleptics: A proton magnetic resonance spectroscopy (1H MRS) study. *Medical Science Monitor, 13 Suppl 1*, 17-22.

Tamminga, C. A. (2006). The neurobiology of cognition in schizophrenia. *Journal of Clinical Psychiatry, 67*(9), e11.

Tanaka, Y., Obata, T., Sassa, T., Yoshitome, E., Asai, Y., Ikehira, H., . . . Nishikawa, T. (2006). Quantitative magnetic resonance spectroscopy of schizophrenia: Relationship between decreased N-acetylaspartate and frontal lobe dysfunction. *Psychiatry and Clinical Neurosciences, 60*(3), 365-372.

Taylor, M. J., Schweinsburg, B. C., Alhassoon, O. M., Gongvatana, A., Brown, G. G., Young-Casey, C., . . . Grant, I. (2007). Effects of human immunodeficiency virus and methamphetamine on cerebral metabolites measured with magnetic resonance spectroscopy. *Journal of Neurovirology, 13*(2), 150-159.

Tayoshi, S., Sumitani, S., Taniguchi, K., Shibuya-Tayoshi, S., Numata, S., Iga, J., . . . Ohmori, T. (2009). Metabolite changes and gender differences in schizophrenia using 3-Tesla proton magnetic resonance spectroscopy (1H-MRS). *Schizophrenia Research, 108*, 69-77.

Tebartz van Elst, L., Valerius, G., Buchert, M., Thiel, T., Rusch, N., Bubl, E., . . . Olbrich, H. M. (2005). Increased prefrontal and hippocampal glutamate concentration in schizophrenia: Evidence from a magnetic resonance spectroscopy study. *Biological Psychiatry, 58*(9), 724-730.

Theberge, J., Al-Semaan, Y., Drost, D. J., Malla, A. K., Neufeld, R. W., Bartha, R., . . . Williamson, P. C. (2004). Duration of untreated psychosis vs. N-acetylaspartate and choline in first episode schizophrenia: A 1H magnetic

resonance spectroscopy study at 4.0 Tesla. *Psychiatry Research, 131*, 107-114.

Theberge, J., Al-Semaan, Y., Williamson, P. C., Menon, R. S., Neufeld, R. W., Rajakumar, N., . . . Drost, D. J. (2003). Glutamate and glutamine in the anterior cingulate and thalamus of medicated patients with chronic schizophrenia and healthy comparison subjects measured with 4.0-T proton MRS. *American Journal of Psychiatry, 160*(12), 2231-2233.

Theberge, J., Bartha, R., Drost, D. J., Menon, R. S., Malla, A., Takhar, J., . . . Williamson, P. C. (2002). Glutamate and glutamine measured with 4.0 T proton MRS in never-treated patients with schizophrenia and healthy volunteers. *American Journal of Psychiatry, 159*(11), 1944-1946.

Theberge, J., Williamson, K. E., Aoyama, N., Drost, D. J., Manchanda, R., Malla, A. K., . . . Williamson, P. C. (2007a). Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *The British Journal of Psychiatry, 191*, 325-334.

Theberge, J., Williamson, K. E., Aoyama, N., Drost, D. J., Manchanda, R., Malla, A. K., . . . Williamson, P. C. (2007b). Longitudinal grey-matter and glutamatergic losses in first-episode schizophrenia. *British Journal of Psychiatry, 191*, 325-334.

Thirthalli, J., & Benegal, V. (2006). Psychosis among substance users. *Current Opinion in Psychiatry, 19*(3), 239-245.

Thoma, P., Wiebel, B., & Daum, I. (2007). Response inhibition and cognitive flexibility in schizophrenia with and without comorbid substance use disorder. *Schizophrenia Research, 92*(1-3), 168-180.

Thompson, P. M., Hayashi, K. M., Simon, S. L., Geaga, J. A., Hong, M. S., Sui, Y., . . . London, E. D. (2004). Structural abnormalities in the brains of human subjects who use methamphetamine. *The Journal of Neuroscience, 24*(26), 6028-6036.

Tibbo, P., Hanstock, C., Valiakalayil, A., & Allen, P. (2004). 3-T proton MRS investigation of glutamate and glutamine in adolescents at high genetic risk for schizophrenia. *American Journal of Psychiatry, 161*(6), 1116-1118.

Tiwari, A. K., Zai, C. C., Muller, D. J., & Kennedy, J. L. (2010). Genetics in schizophrenia: Where are we and what next? *Dialogues in Clinical Neuroscience, 12*(3), 289-303.

Tomiyama, G. (1990). Chronic schizophrenia-like states in methamphetamine psychosis. *Japanese Journal of Psychiatry and Neurology, 44*(3), 531-539.

Townsend, L. A., & Norman, R. M. (2004). Course of cognitive functioning in first episode schizophrenia spectrum disorders. *Expert Review of Neurotherapeutics, 4*(1), 61-68.

Tsai, G., & Coyle, J. T. (2002). Glutamatergic mechanisms in schizophrenia. *Annual Reviews of Pharmacology and Toxicology, 42*, 165-179.

Tucker, P. (2009). Substance misuse and early psychosis. *Australas Psychiatry, 17*(4), 291-294.

Uhl, I., Mavrogiorgou, P., Norra, C., Forstreuter, F., Scheel, M., Witthaus, H., . . . Juckel, G. (2011). (1)H-MR spectroscopy in ultra-high risk and first episode stages of schizophrenia. *Journal of Psychiatric Research, 45*(9), 1135-1139.

Ujike, H., Harano, M., Inada, T., Yamada, M., Komiyama, T., Sekine, Y., . . . Ozaki, N. (2003). Nine- or fewer repeat alleles in VNTR polymorphism of the dopamine transporter gene is a strong risk factor for prolonged methamphetamine psychosis. *Pharmacogenomics Journal, 3*(4), 242-247.

Ujike, H., & Sato, M. (2004). Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. *Annals of the New York Academy of Sciences, 1025*, 279-287.

United Nations Office on Drugs and Crime. (2009). World Drug Report 2009. New York, New York: United Nations Office on Drugs and Crime.

United Nations Office on Drugs and Crime. (2010). World Drug Report 2010. New York, New York: United Nations Office on Drugs and Crime.

Usui, N., Haji, T., Maruyama, M., Katsuyama, N., Uchida, S., Hozawa, A., . . . Taira, M. (2009). Cortical areas related to performance of WAIS Digit Symbol Test: A functional imaging study. *Neuroscience Letters, 463*(1), 1-5.

Valiakalayil, A. (2006). *Proton MRS investigation of glutamate and executive functioning in first episode psychosis.* Master of Science, University of Alberta, Edmonton.

Valli, I., Stone, J., Mechelli, A., Bhattacharyya, S., Raffin, M., Allen, P., . . . McGuire, P. (2011). Altered medial temporal activation related to local glutamate levels in subjects with prodromal signs of psychosis. *Biological Psychiatry, 69*(1), 97-99.

van der Knaap, M. S., van der Grond, J., van Rijen, P. C., Faber, J. A., Valk, J., & Willemse, K. (1990). Age-dependent changes in localized proton and phosphorus MR spectroscopy of the brain. *Radiology, 176*(2), 509-515.

van Holst, R. J., & Schilt, T. (2011). Drug-related decrease in neuropsychological functions of abstinent drug users. *Current Drug Abuse Reviews, 4*(1), 42-56.

Van Os, J. (2004). Does the urban environment cause psychosis? *The British Journal of Psychiatry, 184*(4), 287-288.

Ventura, J., Hellemann, G. S., Thames, A. D., Koellner, V., & Nuechterlein, K. H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophrenia Research, 113*(2-3), 189-199.

Verdejo-Garcia, A., Bechara, A., Recknor, E. C., & Perez-Garcia, M. (2006). Executive dysfunction in substance dependent individuals during drug use and abstinence: An examination of the behavioral, cognitive and emotional correlates of addiction. *Journal of the International Neuropsychological Society, 12*(3), 405-415.

Vik, P. W., Cellucci, T., Jarchow, A., & Hedt, J. (2004). Cognitive impairment in substance abuse. *Psychiatric Clinics of North America, 27*(1), 97-109, ix.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2003). The addicted human brain: Insights from imaging studies. *Journal of Clinical Investigation, 111*(10), 1444-1451.

Volkow, N. D., Fowler, J. S., & Wang, G. J. (2004). The addicted human brain viewed in the light of imaging studies: Brain circuits and treatment strategies. *Neuropharmacology, 47 Suppl 1*, 3-13.

Volkow, N. D., Fowler, J. S., Wang, G. J., & Swanson, J. M. (2004). Dopamine in drug abuse and addiction: Results from imaging studies and treatment implications. *Molecular Psychiatry, 9*(6), 557-569.

Volkow, N. D., & Li, T. K. (2004). Drug addiction: The neurobiology of behaviour gone awry. *Nature Reviews Neuroscience, 5*(12), 963-970.

Wallace, M., Hashim, Y.Z.H.-Y., Wingfield, M., Culliton, M., McAuliffe, F., Gibney, M.J., & Brennan, L. (2010). Effects of menstrual cycle phase on metabolomic profiles in premenopausal women. *Human Reproduction, 25*(4), 949-956.

War Department, & Adjutant General's Office (Eds.). (1944). *Army Individual Test*. Washington, D.C.

Wechsler, D. (1981). *Wechsler Adult Intelligence Scale - Revised*. San Antonio: The Psychological Corporation.

Weinberger, D. R., & Berman, K. F. (1996). Prefrontal function in schizophrenia: Confounds and controversies. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 351*(1346), 1495-1503.

Weinberger, D. R., Berman, K. F., & Zec, RF. (1986). Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. I Regional cerebral blood flow (rCBF) evidence. *Archives of General Psychiatry, 43*, 114-125.

Weinstein, A., & Cox, W. M. (2006). Cognitive processing of drug-related stimuli: The role of memory and attention. *Journal of Psychopharmacology, 20*(6), 850-859.

Westermeyer, J. (2006). Comorbid schizophrenia and substance abuse: A review of epidemiology and course. *American Journal on Addictions, 15*(5), 345-355.

White, F. J., & Kalivas, P. W. (1998). Neuroadaptations involved in amphetamine and cocaine addiction. *Drug and Alcohol Dependence, 51*(1-2), 141-153.

Wible, C. G., Anderson, J. E, Shenton, M. E., Kricun, A., Hirayasu, Y., Tanaka, S., . . . McCarley, R. W. (2001). Prefrontal cortex, negative symptoms, and schizophrenia: an MRI study. *Psychiatry Research: Neuroimaging, 108*(2), 65-78.

Williamson, P. C., Bartha, R., Drost, D. J., Menon, R. S., Malla, A., Carr, T. J., & Neufeld, R. W. (1999). Glutamate and glutamine on H MRS in never-treated schizophrenic patients. *Schizophrenia Research, 36*, 249.

Willner, P. (1997). The dopamine hypothesis of schizophrenia: Current status, future prospects. *International Clinical Psychopharmacology, 12*(6), 297-308.

Wilmsmeier, A., Ohrmann, P., Suslow, T., Siegmund, A., Koelkebeck, K., Rothermundt, M., . . . Pedersen, A. (2010). Neural correlates of set-

shifting: Decomposing executive functions in schizophrenia. *Journal of Psychiatry and Neuroscience, 35*(5), 321-329.

Winslow, B. T., Voorhees, K. I., & Pehl, K. A. (2007). Methamphetamine abuse. *American Family Physician, 76*(8), 1169-1174.

Wobrock, T., Sittinger, H., Behrendt, B., D'Amelio, R.o, Falkai, P., & Caspari, D. (2007). Comorbid substance abuse and neurocognitive function in recent-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience, 257*(4), 203-210.

Wood, S. J., Berger, G. E., Lambert, M., Conus, P., Velakoulis, D., Stuart, G. W., . . . Pantelis, C. (2006). Prediction of functional outcome 18 months after a first psychotic episode: A proton magnetic resonance spectroscopy study. *Archives of General Psychiatry, 63*, 969-976.

Wood, S. J., Berger, G. E., Wellard, R. M., Proffitt, T., McConchie, M., Velakoulis, D., . . . Pantelis, C. (2008). A 1H-MRS investigation of the medial temporal lobe in antipsychotic-naive and early-treated first episode psychosis. *Schizophrenia Research, 102*, 163-170.

Wood, S. J., Berger, G., Velakoulis, D., Phillips, L. J., McGorry, P. D., Yung, A. R., . . . Pantelis, C. (2003). Proton magnetic resonance spectroscopy in first episode psychosis and ultra high-risk individuals. *Schizophrenia Bulletin, 29*(4), 831-843.

Wood, S. J., Kennedy, D., Phillips, L. J., Seal, M. L., Yucel, M., Nelson, B., . . . Pantelis, C. (2010). Hippocampal pathology in individuals at ultra-high

risk for psychosis: A multi-modal magnetic resonance study. *Neuroimage, 52*(1), 62-68.

Wood, S. J., Yucel, M., Wellard, R. M., Harrison, B. J., Clarke, K., Fornito, A., . . . Pantelis, C. (2007). Evidence for neuronal dysfunction in the anterior cingulate of patients with schizophrenia: A proton magnetic resonance spectroscopy study at 3 T. *Schizophrenia Research, 94*, 328-331.

Woodberry, K. A., Giuliano, A. J., & Seidman, L. J. (2008). Premorbid IQ in schizophrenia: A meta-analytic review. *American Journal of Psychiatry, 165*(5), 579-587.

Woodward, N. D., Purdon, S. E., Meltzer, H. Y., & Zald, D. H. (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology, 8*(3), 457-472.

Xue, C. J., Ng, J. P., Li, Y., & Wolf, M. E. (1996). Acute and repeated systemic amphetamine administration: Effects on extracellular glutamate, aspartate, and serine levels in rat ventral tegmental area and nucleus accumbens. *Journal of Neurochemistry, 67*(1), 352-363.

Yamasue, H., Fukui, T., Fukuda, R., Yamada, H., Yamasaki, S., Kuroki, N., . . . Kato, T. (2002). 1H-MR spectroscopy and gray matter volume of the anterior cingulate cortex in schizophrenia. *Neuroreport, 13*(16), 2133-2137.

Yang, S., Salmeron, B. J., Ross, T. J., Xi, Z. X., Stein, E. A., & Yang, Y. (2009). Lower glutamate levels in rostral anterior cingulate of chronic cocaine

users - A (1)H-MRS study using TE-averaged PRESS at 3 T with an optimized quantification strategy. *Psychiatry Research, 174*, 171-176.

Yoo, S. Y., Yeon, S., Choi, C. H., Kang, D. H., Lee, J. M., Shin, N. Y., . . . Kwon, J. S. (2009). Proton magnetic resonance spectroscopy in subjects with high genetic risk of schizophrenia: Investigation of anterior cingulate, dorsolateral prefrontal cortex and thalamus. *Schizophrenia Research, 111*, 86-93.

Young, D., & Scoville, W. B. . (1938). Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. *Medical Clinics of North America, 22*, 637-646.

Yucel, M., & Lubman, D. I. (2007). Neurocognitive and neuroimaging evidence of behavioural dysregulation in human drug addiction: Implications for diagnosis, treatment and prevention. *Drug and Alcohol Review, 26*(1), 33-39.

Yucel, M., Lubman, D. I., Solowij, N., & Brewer, W. J. (2007). Understanding drug addiction: A neuropsychological perspective. *Australian and New Zealand Journal of Psychiatry, 41*(12), 957-968.

Yudko, E., Hall, H. V., & McPherson, S. B. (Eds.). (2003). *Methamphetamine Use: Clinical and Forensic Aspects*: CRC Press.

Yui, K., Goto, K., Ikemoto, S., & Ishiguro, T. (1995). Spontaneous recurrence of methamphetamine psychosis: Process and monoamine neurotransmitter function. *Nihon Shinkei Seishin Yakurigaku Zasshi, 15*(4), 363-374.

Yui, K., Goto, K., Ikemoto, S., & Ishiguro, T. (1997a). Methamphetamine psychosis: Spontaneous recurrence of paranoid-hallucinatory states and monoamine neurotransmitter function. *Journal of Clinical Psychopharmacology, 17*(1), 34-43.

Yui, K., Goto, K., Ikemoto, S., & Ishiguro, T. (1997b). Monoamine neurotransmitter metabolites and spontaneous recurrence of methamphetamine psychosis. *Brain Research Bulletin, 43*(1), 25-33.

Yui, K., Goto, K., Ikemoto, S., Nishijima, K., Yoshino, T., & Ishiguro, T. (2001). Susceptibility to subsequent episodes of spontaneous recurrence of methamphetamine psychosis. *Drug and Alcohol Dependence, 64*(2), 133-142.

Yui, K., Ikemoto, S., Goto, K., Nishijima, K., Yoshino, T., & Ishiguro, T. (2002). Spontaneous recurrence of methamphetamine-induced paranoid-hallucinatory states in female subjects: Susceptibility to psychotic states and implications for relapse of schizophrenia. *Pharmacopsychiatry, 35*(2), 62-71.

Yüksel, C., & Öngür, D. (2010). Magnetic resonance spectroscopy studies of glutamate-related abnormalities in mood disorders. *Biological Psychiatry, 68*(9), 785-794.

Zabala, A., Sanchez-Gonzalez, J., Parellada, M., Moreno, D. M., Reig, S., Burdalo, M. T., . . . Arango, C. (2007). Findings of proton magnetic resonance spectometry in the dorsolateral prefrontal cortex in adolescents with first episodes of psychosis. *Psychiatry Research, 156*, 33-42.

Zakzanis, Konstantine K., Mraz, Richard, & Graham, Simon J. (2005). An fMRI study of the Trail Making Test. *Neuropsychologia, 43*(13), 1878-1886.

Zhang, X. F., Hu, X. T., White, F. J., & Wolf, M. E. (1997). Increased responsiveness of ventral tegmental area dopamine neurons to glutamate after repeated administration of cocaine or amphetamine is transient and selectively involves AMPA receptors. *Journal of Pharmacology and Experimental Therapeutics, 281*(2), 699-706.

Zhang, Y., Loonam, T. M., Noailles, P. A. H., & Angulo, J. A. (2001). Comparison of cocaine- and methamphetamine-evoked dopamine and glutamate overflow in somatodendritic and terminal field regions of the rat brain during acute, chronic, and early withdrawal conditions. *Annals of the New York Academy of Sciences, 937*(1), 93-120.

Ziedonis, D., Williams, J. M., & Smelson, D. (2003). Serious mental illness and tobacco addiction: A model program to address this common but neglected issue. *American Journal of the Medical Sciences, 326*(4), 223-230.

Zorick, T. S., Rad, D., Rim, C., & Tsuang, J. (2008). An overview of methamphetamine-induced psychotic syndrome. *Addictive Disorders & Their Treatment, 7*(3), 143-155.

Zweben, J. E., Cohen, J. B., Christian, D., Galloway, G. P., Salinardi, M., Parent, D., & Iguchi, M. (2004). Psychiatric symptoms in methamphetamine users. *American Journal on Addictions, 13*(2), 181-190.