

**NEUROANATOMICAL CORRELATES OF PSYCHOSTIMULANT-ASSOCIATED PSYCHOSIS**

by

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## **ABSTRACT**

After prolonged psychostimulant abuse, some individuals develop transient psychotic symptoms referred to as “substance induced psychosis” (SIP), which closely resemble the symptoms observed in schizophrenia spectrum disorders. The comparability in psychotic presentation between SIP and the schizophrénias suggests that similar underlying neural deficits may contribute to the emergence of psychosis across these disorders. Anatomically, only a small number of studies have attempted to characterize the structural alterations in SIP – all of which solely focus on methamphetamine associated psychosis.

To further characterize the nature of psychostimulant-associated psychosis, three investigations were performed to identify 1) gray matter abnormalities, 2) white matter abnormalities, and 3) environmental risk factors of current symptom severity in psychostimulant dependent individuals with and without a DSM-IV diagnosis of substance-induced psychosis.

To investigate gray matter abnormalities in study 1, a voxel-based analysis of magnetic resonance images (MRI) was performed between a group of 74 cocaine dependent nonpsychotic (CDN) individuals and a group of 29 individuals with cocaine-associated psychosis (CAP). The CAP group had significantly smaller volumes of the thalamus and left hippocampus, controlling for age, total brain volume, current methamphetamine dependence, and current marijuana dependence.

To investigate white matter abnormalities in study 2, diffusion tensor imaging was employed in a group of individuals with cocaine-associated psychosis (CAP; n=24) and a cocaine dependent nonpsychotic group (CDN; n=43). Tract based spatial statistics (TBSS) was used to investigate group-differences in white matter diffusion parameters. The cocaine-associated psychosis group showed significantly lower fractional anisotropy values than the cocaine dependent nonpsychotic group ( $p < 0.05$ ) in voxels within white matter tracts of fronto-temporal, fronto-thalamic, and interhemispheric pathways.

In study 3, environmental risk factors were used to predict current positive and negative psychotic symptom severity in a sample of 171 individuals meeting DSM-IV-TR criteria for psychostimulant dependence. Increased severity of current positive psychotic symptoms was significantly related to increased frequency of methamphetamine and marijuana use in the past 28 days, and methadone-abstinence.

Collectively, these results begin to characterize structural alterations in the expression of psychostimulant associated psychosis – the nature of which suggests there may be shared neuroanatomical correlates in the expression of different forms of psychosis.

## PREFACE

This work I describe in this thesis was made possible due to the Hotel Study, overseen by Dr. William Honer, at the University of British Columbia. The hardworking volunteers and staff of the Hotel study therefore collected all of the raw data utilized in this thesis. Mr Wayne Su spearheaded extensive work in the processing of magnetic resonance imaging data and provided supervision on analyzing the structural data. I formulated and performed all of the statistical analysis presented here, with guidance from Drs. Allen Thornton, Geoff Smith, and Donna Lang. I am the sole writer of this thesis, including figures and tables, incorporating feedback and revisions from my supervisor, Dr. Alasdair Barr.

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# TABLE OF CONTENTS

<b>Abstract .....</b>	<b>ii</b>
<b>Preface.....</b>	<b>iii</b>
<b>Table of Contents.....</b>	<b>iv</b>
<b>List of Tables .....</b>	<b>vii</b>
<b>List of Figures .....</b>	<b>viii</b>
<b>List of Abbreviations.....</b>	<b>ix</b>
<b>Acknowledgements .....</b>	<b>xi</b>
<b>Chapter 1: General Introduction .....</b>	<b>1</b>
1.1 Substance-Induced Psychosis .....	1
1.2 DSM Diagnostic Criteria .....	2
1.3 Symptoms.....	3
1.4 Neurobiology of Psychosis.....	3
1.5 Genetics .....	6
1.6 Risk Factors .....	7
1.7 Neuroanatomical Studies of SIP .....	8
1.8 Neuroimaging.....	9
1.8.1 Structural MRI .....	9
1.8.2 Diffusion Tensor Imaging (DTI) .....	10
1.9 Thesis Hypothesis.....	11
<b>Chapter 2: Subcortical gray matter alterations in cocaine dependent individuals with substance-induced psychosis compared to non- psychotic cocaine users .....</b>	<b>13</b>
2.1 Introduction .....	13
2.2 Materials and Methods .....	15
2.2.1 Participants .....	15
2.2.2 Demographics .....	16
2.2.3 MRI Acquisition.....	16
2.2.4 Image Processing .....	16
2.2.5 Statistical Analysis .....	17
2.3. Results .....	18
2.3.1 Demographic Variables.....	18
2.3.2 Volumes of Subcortical ROIs.....	19

2.3.3 Associations Between Clinical Information and Brain Volumes.....	21
2.4 Discussion .....	22
2.5 Conclusions .....	25
<b>Chapter 3: Characterization of white matter integrity deficits in cocaine-dependent individuals with substance-induced psychosis compared to non-psychotic cocaine users... 27</b>	
3.1 Introduction .....	27
3.2 Materials and Methods .....	29
3.2.1 Participants .....	29
3.2.2 Demographics .....	30
3.2.3 Cognition .....	30
3.2.4 MRI Acquisition .....	30
3.2.5 Image Processing .....	31
3.2.6 Tract-Based Spatial Statistics (TBSS) .....	31
3.2.7 Statistical Analysis .....	32
3.3 Results .....	32
3.3.1 Demographics .....	32
3.3.2 Drug Use .....	33
3.3.3 Cognition .....	33
3.3.4 TBSS – Global White Matter .....	34
3.3.5 Association with Symptom Severity.....	36
3.3.6 WM Tract Volume .....	36
3.4 Discussion .....	39
3.5 Conclusion .....	43
<b>Chapter 4: Factors affecting severity of positive and negative symptoms of psychosis in a polysubstance using population with psychostimulant dependence ..... 44</b>	
4.1 Introduction .....	44
4.2 Materials and Methods .....	46
4.2.1 Participants .....	46
4.2.2 Measures.....	46
4.2.3 Statistical Analysis .....	47
4.3 Results .....	48
4.3.1 Demographic Variables.....	48
4.3.2 Symptom Severity Bivariate Analysis.....	49
4.3.3 Positive Symptom Severity Multivariable Analysis .....	50

4.3.4 Negative Symptom Severity Multivariate Analysis .....	52
4.3.5 Supplementary Analysis .....	53
4.3.5.1 Specific Symptom Supplementary Analysis.....	53
4.3.5.2 Cocaine Frequency Supplementary Analysis.....	54
4.4 Discussion .....	54
4.5 Conclusion .....	58
<b>Chapter 5: Overall Conclusion .....</b>	<b>60</b>
5.1 Gray Matter.....	60
5.2 White Matter .....	60
5.3 Symptom Severity.....	61
5.4 Integrated Discussion.....	61
5.5 Strengths and Limitations.....	62
5.6 Implications for Future Studies .....	63
<b>References .....</b>	<b>65</b>

## LIST OF TABLES

Table 1.1 DSM-IV-TR Diagnostic Criteria for Substance-Induced Psychosis (SIP) .....	2
Table 2.1 Demographic and Substance Use.....	19
Table 2.2 ANCOVA analysis .....	21
Table 3.1 Mean demographic and drug use data .....	34
Table 3.2 Mean Clinical and Cognitive data .....	36
Table 4.1 Demographics .....	51
Table 4.2 Multivariate Analysis for Positive and Negative Symptom Severity Models .....	53

## LIST OF FIGURES

Figure 1.1 Dopaminergic pathways of cortical activation .....	5
Figure 1.2 Water diffusion properties .....	11
Figure 2.1. Hemisphere x group interaction in the hippocampus .....	20
Figure 2.2. Hippocampal and Thalamic Gray Matter Volumes .....	22
Figure 3.1 TBSS between-group FA differences .....	37
Figure 3.2 TBSS between-group RD differences .....	38

## LIST OF ABBREVIATIONS

AD	Axial Diffusivity
ANCOVA	analysis of covariance
BECED	Best Estimate Clinical Evaluation and Diagnosis
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAP	Cocaine-associated psychosis
CDN	cocaine dependent nonpsychotic
CSF	cerebrospinal fluid
CTX	Cortex
DAOA	D-amino acid oxidase activator
DRD4	dopamine receptor D4
DSM	Diagnostic and Statistical Manual of Mental Disorders
DTES	Downtown Eastside
DTI	Diffusion Tensor Imaging
DTNBP1	Dystrobrevin-binding protein 1
FA	Fractional Anisotropy
FWE	Family-Wise-Error
GABA	Gamma-Aminobutyric acid
GPI	Globus Pallidus Interna
GRM2	Metabotropic glutamate receptor 2
HVLT	Hopkins Verbal Learning Test
IGT	Iowa Gambling Task
JHU-ICBM	John Hopkins University International Consortium Brain Mapping
MAP	methamphetamine associated psychosis
MRI	magnetic resonance imaging

NaC	nucleus accumbens
NMDAR	N-methyl-D-aspartate receptor
NRG1	Neuregulin 1
PANSS	Positive and Negative Symptom Scale
PET	positron emission tomography
ROI	Region of Interest
RD	Radial Diffusivity
SIP	Substance-induced psychosis
SLC6A9	Glycine transporter 1
SNr	substantia nigra pars reticulata
SPSS	Statistical Package for the Social Sciences
STR	Striatum
TBSS	Tract based spatial statistics
TBV	Total Brain Volume
TFCE	Threshold-Free Cluster Enhancement
TH	Thalamus
TLFB	Time Line Follow Back
VIF	Variance inflation factor
VTA	Ventral Tegmental Area
WTAR	Wechsler Test of Adult Reading

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This thesis is dedicated to all those in the world who are doing their darnedest to figure out this whole reality thing. A potential whirlwind of a never-ending loop, but questions worth asking and thoughts worth thinking.

\*~Keep digging deep, brothers and sisters of the intellectual keep

Though answers may not be found, the process will surely abound

Invaluable reflections of the self, insights helping us come to terms with our inner elf

Dedicated from me to all that chew, the most gratuitous of thanks to you~\*

~\*Heart feel, Minds think, In the end, all so the Soul can link\*~

## **CHAPTER 1: GENERAL INTRODUCTION**

### **1.1 SUBSTANCE-INDUCED PSYCHOSIS**

Psychostimulants, including amphetamines and cocaine, are the second most commonly used illicit substances worldwide, with an estimated 28 to 75 million users (World Drug Report, 2014). These substances produce a range of acute psychological effects in humans, with lower doses generating feelings of increased energy, mood and confidence, while frequent exposure and higher doses can lead to a host of adverse effects – including physical (e.g. strokes, seizures, arrhythmias) and psychiatric (e.g. dependency, depression, anxiety, psychosis) complications (Barr et al., 2006). With sufficient drug exposure, some individuals develop symptoms that result in a syndrome referred to as “substance induced psychosis” (SIP), which symptomatically resembles the schizophrenia spectrum disorders (Medhus, Mordal, Holm, Morland, & Bramness, 2013). These SIP episodes are characterized by both positive (hallucinations, delusions, disorganized thinking) and negative (flattened affect, emotional withdrawal, lack of spontaneity) symptoms. Unlike psychoses of the schizophrenia spectrum disorders, SIP is defined as a transient psychotic episode enduring up to one month after the drug is metabolized and cleared from the body (Association, 2000; Oriake et al., 2011). SIP is typically associated with exposure to high doses of psychostimulants over an extended duration, with an average latency of 3-5 years between first drug exposure and the initial psychotic episode (Ujike & Sato, 2004) – although psychosis within 1 month of initial use has been reported as well (Harris and Batki, 2000). Individuals that have had a SIP episode are highly susceptible to trigger a relapse, whether from resumption of psychostimulant use, heavy alcohol consumption, or severe insomnia (Sato et al., 1992; Grant et al., 2012).

## 1.2 DSM DIAGNOSTIC CRITERIA

The American Psychiatric Association bases the Diagnostic and Statistical Manual of Mental Disorders (DSM) on a multiaxial system involving assessment on five major axes, including: Axis I (clinical disorders), Axis II (personality disorders), Axis III (general medical conditions), Axis IV (psychosocial and environmental problems), and Axis V (global assessment of functioning). SIP is considered an Axis I disorder, whereby the psychotic symptoms are judged to be a physiological consequence of a drug of abuse and cease after removal of the agent (APA). Specific criteria required for a diagnosis of SIP can be found in Table 1.1. Currently, the DSM is in its 5<sup>th</sup> edition, however as the study from which this thesis is based began in 2008, all diagnoses referred to in this thesis indicate DSM-IV-TR criteria. While the DSM V no longer categorizes disorders into a multiaxial system, the specific criteria for SIP remain unchanged.

**Table 1.1** DSM-IV-TR Diagnostic Criteria for Substance-Induced Psychosis (SIP)

---

<b>A</b>	Presence of one or both: <ul style="list-style-type: none"><li>• Delusions</li><li>• Hallucinations</li></ul>
<b>B</b>	Evidence from history, physical examination, or laboratory findings of <u>both</u> <ul style="list-style-type: none"><li>• The symptoms of 'A' develop during or soon after substance intoxication or withdrawal</li><li>• The involved substance is capable of producing the symptoms in 'A'</li></ul>
<b>C</b>	The disturbance is not better explained by a psychotic disorder that is not substance induced. <ul style="list-style-type: none"><li>• Symptoms don't precede the onset of substance use</li><li>• Symptoms recede within approximately 1 month <u>after</u> the cessation of withdrawal / intoxication</li><li>• The disturbance does not occur exclusively during the course of a delirium</li><li>• The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning</li></ul>

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### **1.3 SYMPTOMS**

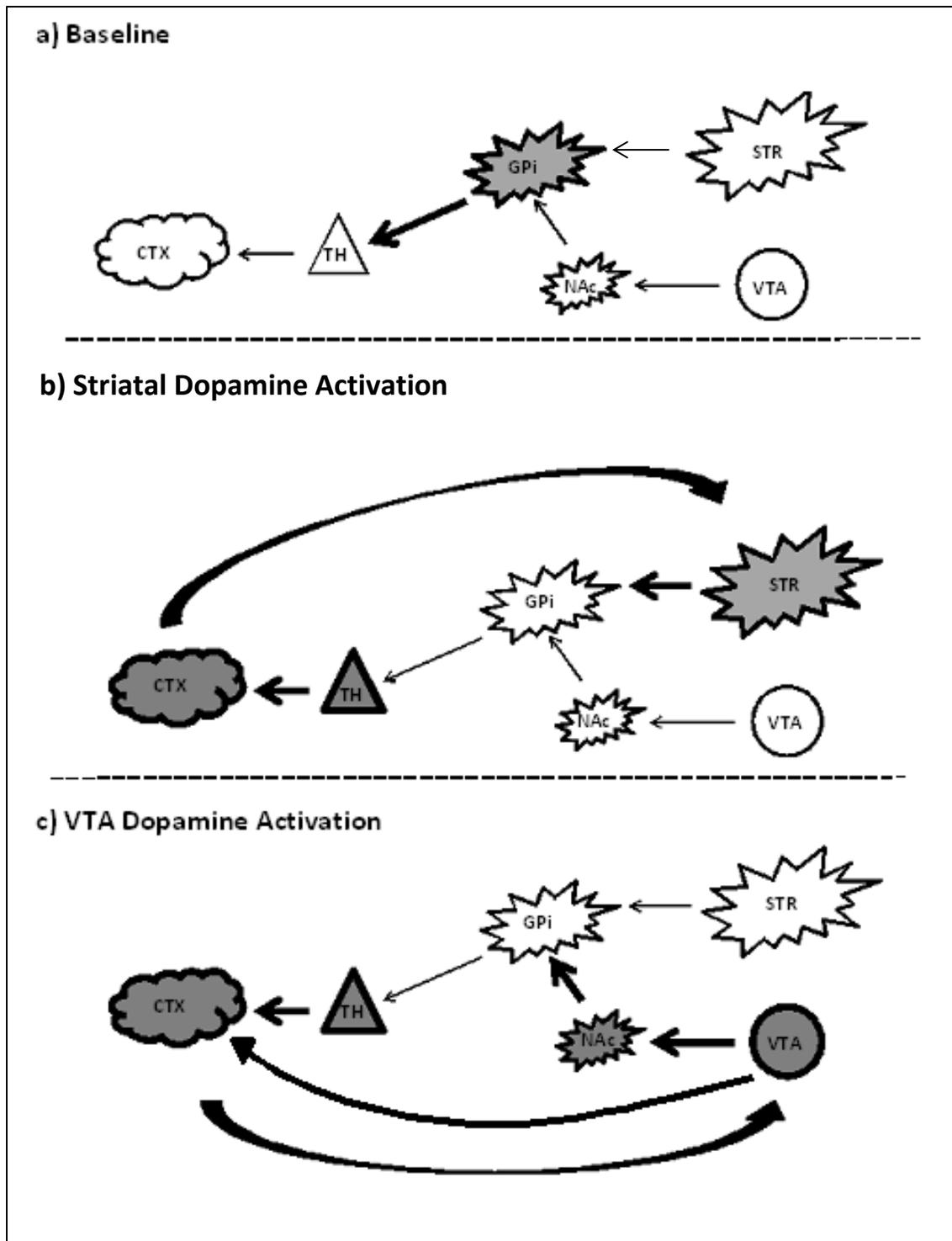
While heavy psychostimulant use may predispose individuals to SIP, many psychostimulant users will never experience a SIP episode. Approximately 50-75% of cocaine users (Brady 1991; Mooney et al., 2006; Satel and Edell 1991; Smith et al., 2009; Vorspan et al., 2012) and 50-60% of methamphetamine users (Grant et al., 2012; Hall et al., 1996; McKetin et al., 2006; Smith et al., 2009) experience psychotic symptoms during consumption, including paranoia, delusions, and vivid sensory hallucinations (Barr et al., 2013). While positive symptoms remain the hallmark of psychostimulant associated psychosis, negative symptoms have been noted, though the prevalence and severity of these symptoms is equivocal (Panenka et al., 2013; Srisurapanont et al., 2011; Zorick et al., 2008). Though most studies fail to mention negative symptoms, Srisurapanont et al. (2003) reported negative symptoms including poverty of speech, psychomotor retardation, and flattened affect in over 20% of patients with methamphetamine associated psychosis. The presence of negative symptoms may be a key differentiating feature between SIP and schizophreniform disorders, and critical to our understanding of how psychostimulant abuse may lead to certain clinical manifestations but not others.

### **1.4 NEUROBIOLOGY OF PSYCHOSIS**

Though the neurobiological mechanism of psychosis is not fully elucidated, several theories posit that a dopaminergic positive feedback loop can trigger the system of the brain into a psychotic break (Lisman et al., 2010; Hsieh et al., 2014). In a healthy system, dopamine acts through several pathways to enhance glutamate signalling in the cortex. Normally, the thalamus receives continuous GABA-ergic (gamma-aminobutyric acid) inhibition from the substantia nigra pars reticulata (SNr) and globus pallidus interna (GPI) (Figure 1.1a). When dopamine is released into the striatum, this GABA-ergic block of the thalamus is discontinued, allowing the thalamus to glutamatergically activate neurons of the cortex (Figure 1.1b). Separate dopaminergic innervation occurs from the ventral tegmental area (VTA) to directly activate neurons of the cortex, as well as the nucleus accumbens (NAc) (Figure 1.1c). Similarly to

the striatum, the NAc also inhibits the GABA-ergic block of the thalamus – yielding more glutamatergic innervation to the cortex. In a normal system, these effects lead to behavioral learning (striatal innervation; Yin and Knowlton, 2006), the experience of reward (NAc innervation; Volkow et al., 1996), and enhanced cognitive performance (VTA innervation; Silber et al., 2006).

Various models of psychosis direct attention to different components of these dopaminergic systems. The dopamine hyperfunction theory of schizophrenia suggests that hyperactive dopamine responses are responsible for psychosis, as patients with schizophrenia have a stronger baseline dopamine release than controls (Laruelle et al., 2003). The GABA hypofunction theory of schizophrenia suggests that psychosis is a result of damage to cortical GABAergic interneurons, which in turn create dysregulated glutamate signaling in the cortex to be transmitted through cortico-striatal feedback loops (Benes, 1995; Hsieh et al., 2014). Evidence from post-mortem tissue studies in schizophrenia have reported widespread decreases in the enzymes that synthesize GABA in interneurons (Benes, 1995; Lewis et al., 2005). In combination of these theories, it has also been suggested that major changes in both the dopamine and GABA system may be downstream effects of *N*-methyl-D-aspartate receptor (NMDAR) hypofunction (Lisman et al., 2010). NMDA antagonists have been shown to produce dopamine release (dopamine hyperfunction), as well as decrease the enzymes that synthesize GABA (GABA hypofunction). The NMDA receptor hypofunction model of schizophrenia posits that an external stressor triggers a sustained positive feedback loop between the hippocampus, VTA, and NAc, producing and sustaining a ‘psychotic break’ (Lisman et al., 2010).



**Figure 1.1 Dopaminergic pathways of cortical activation**

Dopaminergic pathways of cortical activation. a) Baseline inhibition of thalamus b) dopamine activating striatum c) dopamine activating VTA. Darkened structures correlated with activity of structure. Star-shaped structures send GABAergic (inhibitory) projections, all other projections are excitatory. CTX=cortex, TH=thalamus, GPI=globus pallidus interna, NAc=nucleus accumbens, STR=striatum, VTA=ventral tegmental area

Psychostimulant abuse represents one such external stressor (Lisman et al., 2010). Psychostimulants simultaneously affect various dopaminergic pathways by precipitating the release of dopamine stores into the VTA and striatum. This leads to concurrent activation of several pathways to the cortex, releasing excessive glutamate and dopamine in cortical regions. Chronically, this exposure can be neurotoxic, decreasing concentrations of dopamine transporter in the dorsal striatum, nucleus accumbens, and prefrontal cortex (Grant et al., 2012; Wilson et al., 1996; Volkow et al., 2001). Decreases in DAT concentration have been correlated with increases in the clinical severity of psychotic symptoms (Iyo et al., 2004). Chronic exposure to psychostimulants may also damage cortical GABAergic interneurons (Hsieh et al., 2014; Kuczenski et al., 2007). Damage to these neurons may dysregulate glutamate signaling in the cortex, which may theoretically precipitate aberrant glutamate signals resulting in psychosis (Hsieh et al., 2014).

Though there are many theories as to the neurobiological mechanisms and pathways of psychosis, more pre-clinical research is required to understand how these cellular changes may result in the symptomatic presentations seen in clinical populations.

## **1.5 GENETICS**

SIP is a complex disorder in which several environmental exposures interact with many polymorphic genes to influence an individual's susceptibility. As the neurobiology of SIP likely involves a feedback loop of which thousands of proteins and genes contribute, a single abnormality responsible for precipitating psychosis is unlikely. Many susceptibility genes have been correlated with SIP, though findings have been inconsistent. Genetic variations including single nucleotide polymorphisms, variable number tandem repeats, insertions, and deletions have all been implicated in SIP. A high proportion of these variations are linked to glutamatergic neurotransmission, including DAOA (D-amino acid oxidase activator), DTNBP1 (Dystrobrevin-binding protein 1), GRM2 (Metabotropic glutamate receptor 2) and

SLC6A9 (Glycine transporter 1) (Grant et al., 2012). Additionally, many of the identified genes have also been implicated in schizophrenia (Grant et al., 2012; Bousman et al., 2011). This overlap with schizophrenia, glutamatergic neurotransmission, and SIP supports a common underlying genetic mechanism for multiple forms of psychosis. However, many genes typically associated with schizophrenia, such as NRG1 (neuregulin 1) and DRD4 (dopamine receptor D4), have not been associated with SIP susceptibility when they have been directly investigated (Bousman et al., 2011). Additionally, nearly all investigations of genetic associations with SIP have been performed in Asian (primarily Japanese) populations. Future studies incorporating more ethnically diverse populations are needed to shed further light on the genetic foundations of SIP. Though promising, research continues to suggest that causes of SIP are more than genetic in etiology.

## **1.6 RISK FACTORS**

While genetic and neurobiological factors are likely an important part of the etiology of SIP, interactions with environmental exposures certainly play a critical role in the precipitation of psychosis. Several parameters of substance use statistically increase the likelihood of an individual to later develop SIP. When SIP is investigated as a categorical outcome (i.e. present or not), many environmental exposures have been identified as risk factors. Specifically for experiencing cocaine induced psychotic symptoms, risk factors for psychosis have included an earlier age of exposure to cocaine (Chen et al., 2003; Farrell et al., 2002; Kalayasiri et al., 2006), intravenous route of administration (Kalayasiri et al., 2006), and the severity of dependence (Farrell et al., 2002; Kalayasiri et al., 2006).

Marijuana exposure has also been reported to increase the risk of experiencing psychosis following cocaine use. Kalayasiri et al. (2010) reported that adolescent-onset of marijuana use ( $\leq 15$  years old) increased the risk of psychosis in cocaine dependent individuals, while Roncero et al. (2013) reported that lifetime cannabis dependence was a significant risk factor in predicting the presence of cocaine

psychosis in cocaine dependent-patients. Farrell et al. (2002) reported that marijuana dependency in the year prior to assessment was associated with over three times the odds of psychosis at the time of assessment. Although several parameters of marijuana exposure have been associated with cocaine-induced psychotic symptoms, the specific findings associated with marijuana have been poorly replicated.

## **1.7 NEUROANATOMICAL STUDIES OF SIP**

The biological basis that confers a predisposition to SIP is still undetermined, as only a small number of neuroanatomical investigations of SIP have been performed. Past reports have included investigations utilizing various imaging modalities, including magnetic resonance imaging (MRI), positron emission tomography (PET), and spectroscopy. To date, studies have exclusively focused on methamphetamine associated psychosis (MAP). These studies have reported that MAP is associated with decreases in dopamine transporter density of the basal ganglia and prefrontal cortex (Sekine et al., 2002), subcortical gray matter reductions of the hippocampus and amygdala (Orikabe et al., 2011), and cortical gray matter reductions of the left frontal and temporal areas (Aoki et al., 2013). One spectroscopy study has performed a direct neuroanatomical comparison of schizophrenia to MAP (Okada et al. 2015). Brain dysfunction was investigated as a measure of prefrontal cortical activity utilizing near-infrared spectroscopy to show cortical activation accompanying an inhibitory task. Both MAP and schizophrenia subjects had reduced hemodynamic changes in the bilateral ventrolateral prefrontal cortex when compared to age and gender matched healthy controls. Only the MAP group showed reduced activation in the frontopolar prefrontal cortex, an effect that may be specific to methamphetamine abuse.

Unfortunately, all of these studies have compared patients with MAP to healthy controls, which fails to control for the potential neurotoxic effects of chronic methamphetamine exposure (Thompson et al., 2004). A recent spectroscopy study controlled for chronic psychostimulant exposure by comparing 10

methamphetamine dependent participants with psychosis to 16 methamphetamine dependent participants without psychosis (Howells et al., 2014). While the methamphetamine dependent groups collectively differed from a healthy control group, there were no differences between the methamphetamine subgroups – possibly the result of an underpowered study. In a recent gray matter investigation, differences in subcortical gray matter volumes and cortical thickness were compared in methamphetamine dependent participants with and without psychosis (Uhlman et al., 2016). MAP patients showed thinner cortices in the fronto-temporal areas as well as smaller hippocampal volumes than methamphetamine dependent participants without psychosis. These findings in MAP are the first differences reported without the confound of chronic psychostimulant exposure and are consistent with neuroimaging findings in other psychotic disorders (Shenton et al., 2001; Fusar-Poli et al., 2011). Though these similarities to other psychoses were concluded through an indirect comparison, this supports a hypothesis of shared neuroanatomic phenotype underlying the emergence of different forms of psychosis.

## **1.8 NEUROIMAGING**

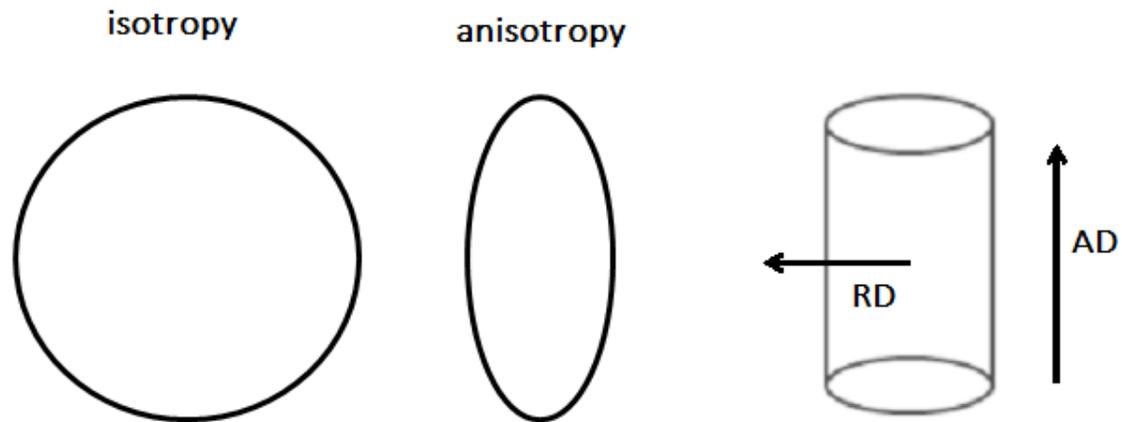
### **1.8.1 STRUCTURAL MRI**

Conventional modalities such as anatomical/structural MRI provide information to qualitatively and quantitatively describe the size and shape of gray and white matter structures in the brain based on signal density and intensity from groups of pixels within a voxel of interest. A voxel is defined as a three-dimensional rectangular cuboid, whose dimensions are set by the slice thickness, the area of a slice, and the grid imposed on the slice by the scanning process (Huettel et al., 2009). A voxel typically contains millions of neurons, with the actual number depending on voxel size and the area of the brain being imaged. Differing cell densities between grey and white matter allows the brain to be segmented separately into gray matter, white matter, and cerebrospinal fluid (CSF). From these distinctions, volumes of interest can be calculated by summing the appropriate voxels. MRI was one of the first

imaging modalities to provide an in-vivo investigation of brain, confirming theories of brain abnormalities in schizophrenia (Shenton et al., 2001). Since the first MRI investigation of schizophrenia in 1984 (Smith et al., 1984), a multitude of MRI studies have identified core phenotypic features associated with schizophrenia.

### **1.8.2 DIFFUSION TENSOR IMAGING (DTI)**

In schizophrenia spectrum disorders, symptoms are posited to result from aberrant anatomic connectivity, either globally or via specific white matter tracts (Konrad & Winterer, 2008; Melicher et al., 2015). White matter microstructural organization can be estimated using DTI. DTI is a non-invasive MRI technique that utilizes the diffusion properties of water molecules to reveal microscopic tissue architecture in-vivo (Le Bihan et al., 1986). Patterns of water diffusion within tissue are used to infer structural characteristics and integrity in white matter pathways (Ellison-Wright & Bullmore, 2009). In white matter, water diffuses more easily along – rather than across – the fibre tract axis, resulting in anisotropic diffusion. The most common index for quantifying anisotropy is with fractional anisotropy (FA), which averages both the axial (longitudinal) and radial (transverse) diffusivity measurements (Basser et al., 1994). As pictured in Figure 1.2, other indices of diffusion include axial diffusion (AD; diffusion along the fibre tract axis) and radial diffusion (RD; diffusion perpendicular to the fibre tract axis). Reductions in FA have been interpreted as a disruption in the organization of tracts / white matter integrity (Madler et al., 2008). DTI has been used extensively to characterize white matter alterations in schizophrenia, with alterations observed predominantly in interhemispheric, fronto-temporal, and fronto-thalamic tracts (Ellison-Wright & Bullmore, 2009; Kanaan et al., 2005).



**Figure 1.2 Water diffusion properties**

Isotropy refers to equal diffusion in all directions. Anisotropy is when diffusion doesn't occur equally in all directions. RD=radial diffusion, diffusion across axon. AD=axial diffusion, diffusion along axon.

## **1.9 THESIS HYPOTHESIS**

The phenotypic characteristics differentiating psychostimulant dependent individuals who don't develop psychosis from individuals who do remains unidentified. To date, all neurobiological investigations of this question have exclusively focused on the psychostimulant methamphetamine, and no investigations of white matter integrity have been performed. Of the MAP studies performed, inadequate sample size and absent psychostimulant-dependent control groups have prevented confident conclusions of what structural alterations differentiate psychostimulant associated psychosis from psychostimulant dependence.

The purpose of this thesis was to examine what components differentiate cocaine dependent individuals who have not developed psychosis from cocaine dependent individuals with substance-induced psychosis. The specific components investigated were:

- 1) Subcortical gray matter structures (Chapter 2)

2) Whole brain white matter diffusion properties (Chapter 3)

3) Environmental risk factors of clinical severity of current psychotic symptoms (Chapter 4)

It was hypothesized that patients with cocaine associated psychosis (CAP) would show structural abnormalities compared to cocaine dependent nonpsychotic subjects in ways consistent with schizophrenia spectrum disorders.

## **CHAPTER 2: SUBCORTICAL GRAY MATTER ALTERATIONS IN COCAINE DEPENDENT INDIVIDUALS WITH SUBSTANCE-INDUCED PSYCHOSIS COMPARED TO NON-PSYCHOTIC COCAINE USERS**

### **2.1 INTRODUCTION**

There are an estimated 14 to 21 million cocaine users worldwide, with particularly high rates of use in North America, Europe, and South America (World Drug Report, 2015). Approximately 50-75% of cocaine users experience acute psychotic symptoms during consumption, including paranoia, delusions, and vivid sensory hallucinations (Brady 1991; Barr et al., 2006; Mooney et al., 2006; Satel and Edell 1991; Smith et al., 2009; Vorspan et al., 2012). In a subset of 5-40% of cocaine dependent individuals, psychotic symptoms can persist beyond intoxication and drug elimination as a syndrome referred to as “substance induced psychosis” (SIP) (Herrero et al., 2008; Roncero et al., 2014; Vergara-Moragues 2012). SIP resembles schizophrenia spectrum disorders, with the presentation of both positive (hallucinations, delusions, disorganized thinking) and negative (flattened affect, emotional withdrawal, lack of spontaneity) symptoms. Clinical presentation of these psychotic symptoms, especially the positive symptoms, is frequently indistinguishable from those presented in idiopathic psychosis (Panenka et al, 2013; Shaner et al., 1998; Srisurapanont et al., 2011).

While genetic studies have provided preliminary evidence to suggest that genes associated with schizophrenia may be involved in the etiology of SIP (Grant et al., 2012), the neuroanatomical basis of SIP has been scarcely investigated. Only a small number of neuroimaging studies have addressed characterization of the structural abnormalities that may be associated with SIP. We previously reported white matter integrity deficits in cocaine-associated psychosis compared to cocaine-dependent nonpsychotic controls (Willi et al., 2016). In individuals with related methamphetamine-associated psychosis, gray matter volumetric reductions have been reported in frontal and temporal cortical areas (Aoki et al., 2013), as well as in the amygdala and hippocampus (Orikabe et al., 2011). However, these

gray matter investigations compared patients with methamphetamine-associated psychosis to drug-naive controls, making it difficult to determine which structural characteristics reflect the toxic effects of psychostimulant exposure, and which are unique to psychosis.

Chronic exposure to psychostimulants has been reported to cause neuroanatomical alterations, with differences established in both active and long-term abstinent users (Mackey and Paulus, 2013); meta-analyses have highlighted both cortical and subcortical changes. The prefrontal cortex exhibits gray matter reductions (Ersche et al., 2013), while subcortically, basal ganglia enlargement (Churchwell et al., 2012; Ersche et al., 2011) and thalamic reduction (Ersche et al., 2013; Sim et al., 2007) have been observed with prolonged psychostimulant use. Results from volumetric studies of the hippocampus have been equivocal. Most studies report no difference in comparison to healthy controls (Bartzokis et al., 2002; Jacobsen et al., 2001; Jernigan et al., 2005), while a few studies report a decrease in hippocampal volume (Alia-Klein et al., 2011; Mackey and Paulus, 2013; Thompson et al., 2004).

Idiopathic psychoses, such as schizophrenia, have been associated with subtle-to-moderate sized regional alterations in brain volume, which may reflect effects of the illness and/or chronic antipsychotic medication (Shenton et al., 2001, van Erp et al., 2015). A recent meta-analysis of 35 studies comparing antipsychotic-naïve schizophrenia patients to controls found changes primarily in subcortical nuclei, with decreased volumes of the hippocampus, thalamus, and caudate (Haijma et al., 2013) – indicating that psychosis in the absence of antipsychotic drugs may be most strongly associated with subcortical changes. To date, the only gray matter subcortical structures that have specifically been investigated in SIP are the hippocampus and amygdala (Orikabe et al., 2011), and this study did not control for psychostimulant effects with a drug-taking, non-psychotic group.

The goal of the current study was to investigate subcortical gray matter volumes in cocaine users with SIP, independent of the effects of antipsychotic medication or chronic psychostimulant exposure. A

voxel-based analysis was performed between a group of cocaine-dependent nonpsychotic subjects and a group with cocaine-associated psychosis, where antipsychotic medication was not common. Based on the previous literature on the effects of psychosis and psychostimulant use, three hypotheses were made. First, because smaller hippocampi are frequently reported in psychosis, but rarely in psychostimulant use, we hypothesized smaller hippocampal volumes in cocaine associated psychosis (CAP) than in nonpsychotic cocaine users. Second, because smaller thalami are reported in both psychosis and psychostimulant use, we hypothesized the CAP group would have modestly smaller thalami as a result of additive exposures. Lastly, we hypothesized smaller caudate volumes in CAP, psychosis in antipsychotic-naïve individuals is associated with reduced volumes.

## **2.2 MATERIALS AND METHODS**

### **2.2.1 PARTICIPANTS**

Participants were recruited as part of a larger study of 370 subjects living in single room occupancy hotels with a history of mental illness and/or substance abuse in the Downtown Eastside of Vancouver, B.C. (Honer WG, CBG-101827, MOP-137103). Subjects were evaluated by a qualified psychiatrist and received a brain MRI as part of the study. For the current investigation, exclusionary criteria were a history of a DSM-IV-TR diagnosis of schizophrenia, schizoaffective disorder, psychosis not-otherwise-specified, or bipolar disorder. Additional exclusionary criteria included past stroke/hemorrhage, significant MRI artifacts (motion, major distortion) and other gross morphometric brain abnormalities (i.e. encephalomalacia, chronic trauma). Of the remaining 138 participants, only participants meeting DSM-IV criteria for current cocaine dependence were retained (including any 3 of the following patterns of a 12 month time: tolerance, withdrawal, increased use, unsuccessful efforts to cut down on use, large amounts of time spent obtaining and using, use continued despite understanding of associated problems). Dependence was additionally confirmed by positive cocaine urine drug screen within 2 weeks of scan yielding 103 total subjects to be included in this analysis. Subjects were divided into two

groups: 1) 29 cocaine-associated psychosis subjects (CAP), and, 2) 74 cocaine-dependent nonpsychotic subjects (CDN). In accordance with Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All participants provided written informed consent.

### **2.2.2 DEMOGRAPHICS**

Demographic data including age, gender, and education were collected. The Mini-International Neuropsychiatric Interview was administered, and was supplemented by a clinical interview and mental status examination. Diagnoses of psychiatric disorders and substance dependency were made according to the DSM-IV by an experienced psychiatrist (WGH,OL or FV-R) through consensus evaluation with the Best Estimate Clinical Evaluation and Diagnosis (BECED; (Endicott, 1988)). Years of regular substance use and age of first use were provided by self-report for cocaine, marijuana, opioids, and alcohol. Psychosis severity at the time of MRI scan was assessed with the Positive and Negative Symptom Scale (PANSS, (Kay, Fiszbein, & Opler, 1987)).

### **2.2.3 MRI ACQUISITION**

All scanning was performed on a 3T MRI Scanner (Philips Achieva) at the University of British Columbia MRI Research Centre between 2008 and 2014 utilizing an 8-channel SENSE head coil. High resolution 3D T1-weighted FFE sagittal images were acquired with the following parameters: TE=3.7ms, TR=8.1ms, flip angle=8°, FOV=256mmx256mm, acquisition matrix=256x250, reconstruction matrix=256x256, voxel size=1.0x1.0x1.0mm<sup>3</sup>, 190 contiguous slices, thickness = 1mm, gap=0, scan duration=443 seconds, no partial parallel imaging acceleration.

### **2.2.4 IMAGE PROCESSING**

All images were visually screened for severe motion artifact / MRI abnormalities by a trained specialist (DL, WS). The high resolution T1-weighted images were converted to NIFTI format by using the dcm2ni tool (<http://www.sph.sc.edu/comd/rorden/mricron/>), and realigned to the axial plane. Intensity bias correction was used to adjust for non-uniformity using the MINC N3 tool (Sled et al., 1998). The bias-

corrected image was then segmented into gray matter, white matter, and CSF using the default configuration of SPM8 (Ashburner et al., 2003). A brain mask was then created by merging CSF, GM, and WM voxels, followed by morphological operations. Finally, scans underwent nonlinear registration to the MNI 152 template by using the FSL FNIRT tool (Andersson et al., 2007). Segmentation into deep gray matter structures of interest was performed with the Harvard-Oxford subcortical atlas.

### **2.2.5 STATISTICAL ANALYSIS**

Clinical and demographic differences between groups were analyzed by either a Chi-square test or independent t-tests. The Shapiro-Wilk's test of normality was used to assess the normality of the distribution of subcortical gray matter volumes of interest. When outliers (>3.3 SD from the mean) were present in gray matter volumes of interest (hippocampus, thalamus and caudate), the raw score was adjusted to the most inlying extreme score as recommended by Tabachnick and Fidell (2007).

For group comparisons of region of interest (ROI; hippocampus, thalamus, caudate) volumes, we employed a repeated measures analysis of covariance (ANCOVA) with 1 between-subject factor (group: CAP/CDN) and 1 within-subject factor (hemisphere: left/right). Volumes of the ROIs were used as the dependent variables, and total brain volume, age, methamphetamine dependence, and marijuana dependence were entered as covariates. In the case of a significant group-by-hemisphere interaction, post-hoc t-tests were performed separately for each hemisphere. Statistical significance was set at  $p < 0.05$ . Residual plots were used to check the assumptions of linear regression including linearity, normality, and variance of the residuals.

In an exploratory analysis, gray matter volumes were tested for associations with clinical indices. Associations between relative gray matter volumes (ROI/TBV) and clinical indices including total years of cocaine use, PANSS Positive Symptom subscale, PANSS Negative Symptom Subscale, and PANSS General Psychopathology subscale were tested with Spearman's rank correlation.

All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 22.

## **2.3. RESULTS**

### **2.3.1 DEMOGRAPHIC VARIABLES**

All participants were clinically dependent on cocaine, a majority of which were crack cocaine users (86.4%). Participants' had a mean age of (46.1±8.6) years, were mainly males (75%), and had a limited education (mean 10.1± 2.2 years). The group of individuals with cocaine-associated psychosis had significantly higher ( $p<0.05$ ) PANSS subscales than the cocaine-dependent nonpsychotic group on Positive and General Psychopathology subscales, but not in the Negative subscale. The psychosis group had higher frequencies of current methamphetamine and marijuana dependency. No typical antipsychotics were prescribed in the total sample, while the atypical antipsychotic quetiapine was prescribed for 5.4% (4/74) of the CDN and 6.9% (2/29) of the CAP group. See Table 2.1 for all demographic and substance use data.

**Table 2.1 Demographic and Substance Use**

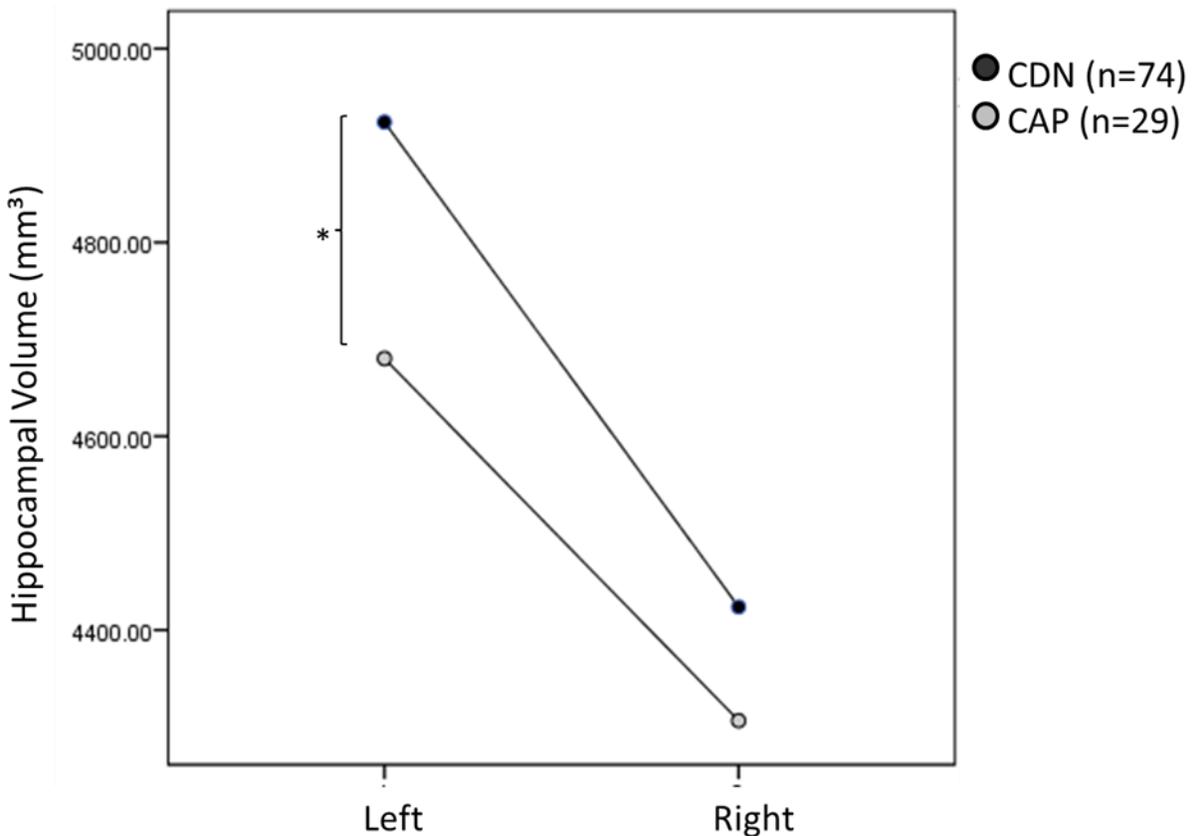
	CDN (n=74)		SIP (n=29)		<i>test statistic*</i>	<i>df</i>	<i>p</i>
	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)			
Gender (F)		21.6% (16/74)		31% (9/29)	0.099*	101	0.321
Age	46.1 (9.1)		46.0 (7.8)		0.050	101	0.961
Education	10.1 (2.4)		9.8 (1.4)		0.729	101	0.468
HIV positive		21.1% (15/71)		27.5% (8/29)	0.07*	98	0.491
PANSS Positive Symptomts	12.5 (3.2)		16.4 (4.5)		-4.717	101	0.001
PANSS Negative Symptoms	15.4 (5.4)		16.9 (5.2)		-1.259	101	0.211
PANSS General Psychopathology	33.9 (7.0)		37.2 (7.9)		-2.014	101	0.047
Total PANSS	61.9 (13.7)		70.5 (15.2)		-2.724	101	0.008
Cocaine Inject		65.3% (47/72)		72.4% (21/29)	0.069*	99	0.494
Cocaine Powder Dependence		38.4% (28/73)		44.8% (13/29)	0.06*	100	0.552
Crack Cocaine Dependence		86.3% (63/73)		86.2% (25/29)	-0.001*	100	0.99
Methamphetamine Dependence		9.4% (7/74)		31% (9/29)	0.268*	101	0.006
Marijuana Dependence		21.6% (16/74)		41.4% (12/29)	0.2*	101	0.043
Alcohol Dependence		17.6% (13/74)		13.8% (4/29)	-0.046*	101	0.646
Methadone Dependence		56.8% (42/74)		65.5% (19/29)	0.08*	101	0.421
Opioid Dependence		48.6% (36/74)		67.8% (19/28)	0.172*	100	0.084
Years Cocaine Use	13.8 (9.7)		13.3 (9.8)		0.236	96	0.814
Years Cannabis Use	13.0 (13.0)		15.1 (11.9)		-0.743	96	0.459
Years Opiate Use	11.6 (11.4)		14.5 (11.4)		-1.082	96	0.282
Years Alcohol Use	12.4 (11.4)		12.7 (9.2)		-0.115	96	0.909

\*test statistic either refers to either a t-value, or a chi-square value (\*).

### 2.3.2 VOLUMES OF SUBCORTICAL ROIS

Repeated measures ANCOVA revealed a significant main effect of group on thalamic volume ( $F[1, 97]=4.008, p=0.048$ ), with no significant group x side interaction ( $F(1, 97)=0.231, p=0.632$ ). In the hippocampus, there was a significant effect of group ( $F[1, 97]=4.901, p=0.029$ ) and a group x side

interaction ( $F[1, 97]=4.662, p=0.033$ ), as shown in Figure 2.1. Since a significant group x side interaction was found, post-hoc t-tests were performed separately for each hippocampal side. A significant effect of group was found for the left hippocampus ( $F[1, 102]=7.410, p=0.008$ ), while the right hippocampus failed to achieve conventional significance ( $F[1, 102]=1.965, p=0.164$ ). See Table 2.2 for volumetric ANCOVA results. There were no significant interactions between drug dependency covariates and group.



**Figure 2.1. Hemisphere x group interaction in the hippocampus.**

Hippocampal volumes corrected for age, TBV, methamphetamine dependence, and marijuana dependence.

\*indicates a significant ( $p<0.05$ ) between group difference in the left, but not right, hemisphere.

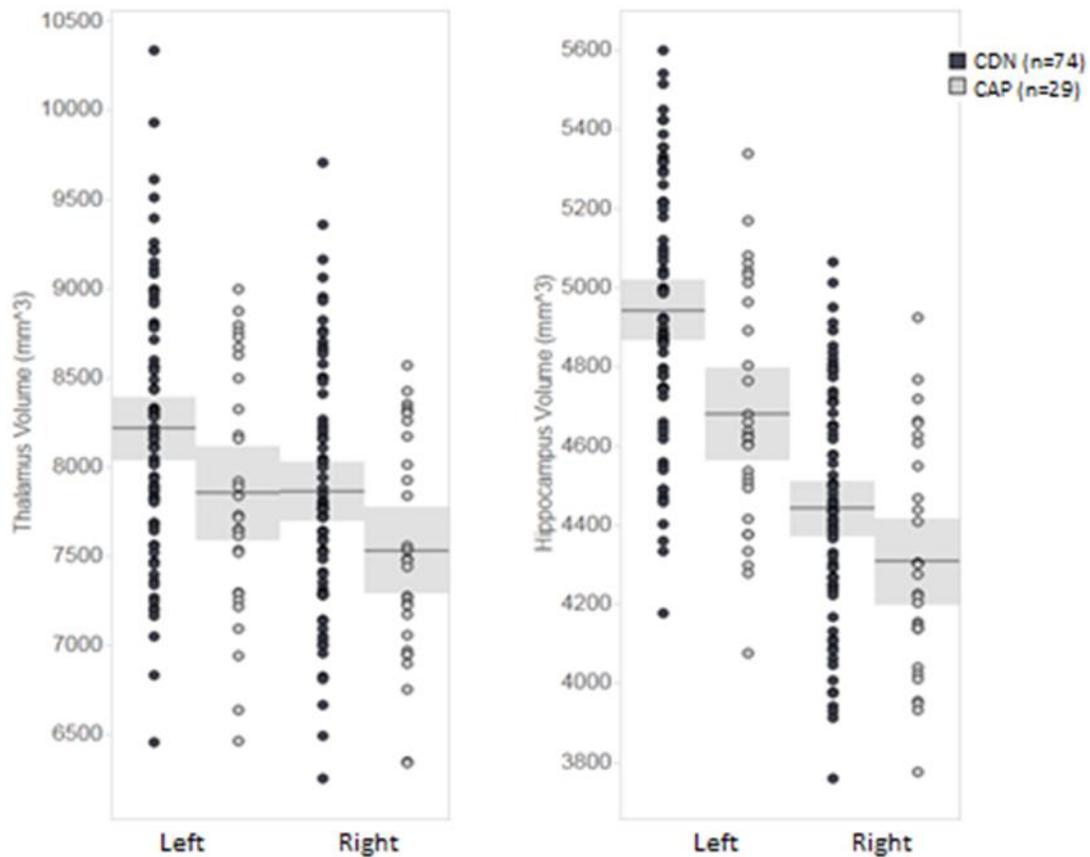
**Table 2.2 ANCOVA analysis**

	CDN (n=74)		CAP (n=29)		Repeated Measures ANCOVA Group		Repeated Measures ANCOVA Side*Group		Post-Hoc Analysis (Left)		Post-Hoc Analysis (Right)	
	Mean (mm <sup>3</sup> )	SD (mm <sup>3</sup> )	Mean (mm <sup>3</sup> )	SD (mm <sup>3</sup> )	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Thalamus	16006.3	236.82	15386.3	287.9	4.008	0.048	0.231	0.632	--	--	--	--
Hippocampus	9354.7	125.5	8961.4	140.9	4.901	0.029	4.662	0.033	7.41	0.008	1.965	0.164
Caudate	7557.4	246.2	7142.0	307.4	0.595	0.442	0.025	0.874	--	--	--	--

Gray matter volumes refer to raw volumes. Repeated Measures ANCOVA results refer to analysis controlling for age, TBV, methamphetamine dependence, and marijuana dependence. Post Hoc analysis performed when a significant Side\*Group interaction was present.

### 2.3.3 ASSOCIATIONS BETWEEN CLINICAL INFORMATION AND BRAIN VOLUMES

In exploratory analyses, no significant associations were found between clinical indices of symptom severity (PANSS positive, negative, general symptoms) or cocaine use (total years use) with bilateral thalamus, hippocampus, or caudate volumes when controlling for age, TBV, methamphetamine dependence and marijuana dependence.



**Figure 2.2. Hippocampal and Thalamic Gray Matter Volumes**

Plots of gray matter volume corrected for age, TBV, methamphetamine dependence, and marijuana dependence. Scatter plots show mean volumes and 95% confidence intervals for each structure in cocaine dependent nonpsychotic (CDN, n=74) and cocaine associated psychosis (CAP, n=29) groups.

## 2.4 DISCUSSION

To our knowledge, the present study is the first to demonstrate gray matter volume reduction in the hippocampus and thalamus of cocaine dependent individuals with psychosis compared to those without psychosis (Figure 2.2). In the hippocampus, these findings were specific to the left hemisphere, similar to left-sided asymmetry reported in the schizophrenia literature (Seidman et al., 2002). There was a higher prevalence of methamphetamine and marijuana dependence in those with psychosis, though controlling

for these possible confounds did not eliminate the statistical findings observed in gray matter difference.

Gray matter structural abnormalities in SIP have been previously investigated, but only for the pharmacologically similar psychostimulant drug methamphetamine. Previous investigations of methamphetamine associated psychosis reported volumetric reductions in frontopolar cortical areas (Aoki et al., 2013), bilateral hippocampus and bilateral amygdala (Orikabe et al., 2011). Here, we similarly report volumetric reductions in the hippocampus – though only on the left side. Structural abnormalities specific to left temporal lobe structures are commonly reported in psychosis, a pattern that has been proposed as a neurodevelopmental vulnerability for schizophrenia (Crow et al., 1989; Seidman et al., 2002; Shenton et al., 1992).

Hippocampal volumetric reduction has been consistently observed in meta-analyses of schizophrenia (Haijma et al., 2013; Shenton et al., 2001; van Erp et al., 2015). Additionally, smaller hippocampal volumes have been reported in groups with a high risk, either clinically (Pantelis et al., 2003) or genetically (Keshavan et al., 2002), for developing schizophrenia. Similarly, thalamic volume reduction has been reported in subjects with chronic schizophrenia and first episode psychosis (Adriano et al., 2010; Haijma et al., 2013), as well as in those at high risk for developing schizophrenia (Lawrie et al., 2001). Combined with our findings presented here, this suggests that hippocampal and thalamic abnormalities are associated with psychosis. A combined hippocampal/thalamic deficit is consistent with the N-methyl-D-aspartate receptor (NMDAR) hypofunction model of schizophrenia (Lisman et al., 2010), which posits that inhibition of NMDA receptors of the thalamus can lead to a positive feedback loop circulating from thalamus to hippocampus to activation of the dopaminergic system, thereby leading to increased dopamine release in the thalamus. Whether the structural reductions seen in the thalamus

and hippocampus result from a neurodevelopmental vulnerability or as a result of a heightened susceptibility to the toxic effects of psychostimulants remains unknown.

Typical antipsychotic drugs have been confirmed to cause volumetric enlargements in the basal ganglia (Chakos et al., 1995). However, meta-analysis of antipsychotic naïve patients with schizophrenia has recently reported that psychosis is associated with a volumetric reduction of the caudate (Haijma et al., 2013). Contrary to this effect of psychosis in an antipsychotic-naïve population, chronic cocaine use can cause volumetric increases of the caudate (Ersche et al., 2011). As these two factors have seemingly opposing effects, the volumetric result of the combination of exposures is of interest. Data are limited, but comparison between schizophrenia subjects with or without a concurrent substance use disorder (mostly alcohol and cannabis) found increased gray matter volumes in the basal ganglia of the dual diagnosis group (Koenders et al., 2015; Potvin et al., 2007), suggesting that exposure to non-psychostimulant substance abuse results in a measurable difference in basal ganglia volume. The present study, with no participants treated with typical antipsychotic drugs, noted no differences in caudate volume between cocaine users with or without concurrent psychosis. This may indicate that the caudate is not affected in SIP, or that smaller basal ganglia volumes in the SIP group were reversed by chronic cocaine exposure. Future studies will be required to clarify these potential phenomena.

Though the findings of reduced thalamic and hippocampal volumes are consistent with reports in the schizophrenia literature (Adriano et al., 2010; Haijma et al., 2013; Shenton et al., 2001), the relationship between psychostimulant use, gray matter volume and psychosis remains a complex issue. The gray matter volume reductions reported here could represent neurodevelopmental substrates for psychosis that exist prior to drug use, as suggested by the neurodevelopmental hypothesis of schizophrenia (Weinberger, Berman, Zec, 1986). Alternatively, volumetric reductions could reflect a heightened susceptibility to the neurotoxic effects of chronic psychostimulant exposure, supporting the

neurotoxicity model (Hsieh et al., 2014; Robinson and Becker, 1986). The hypothesis that some degree of drug-induced damage is necessary to precipitate an episode of SIP is supported by an average latency from first use of methamphetamine to onset of psychosis as 3-5 years (Ujike and Sato, 2004). Psychosis relapse in SIP subjects has been shown to follow subsequent stressors including continued usage of methamphetamine or insomnia, suggesting an underlying neurological change has occurred between pre and post SIP (Sato et al., 1992; Ujike and Sato, 2004). Additional longitudinal studies will be required to address this issue, especially in the context of sustained abstinence.

A limitation of this study is the absence of a cocaine-naïve control group. Though this would not change the observation that SIP is associated with decreased hippocampal and thalamic volumes compared to non-psychotic cocaine users, it would provide insight into the nature of potential additive effects of comorbid psychosis and substance abuse. However, a cocaine-naïve control group would likely not be matched on the multitude of other environmental factors inherent to being part of a marginalized population (high infection rates, homelessness, limited formal education, other substances of abuse, etc.). Separation of drug versus other environmental effects on the brain is not be feasible in the current cohort. Additionally, acute substance use (previous 48 hours) was not controlled for, as the urine drug screen did not occur on the date of the MRI scan for most subjects. However, the hypothesis that subcortical gray matter volumes are susceptible to acute drug exposure is not supported by the literature.

## **2.5 CONCLUSIONS**

This is the first study to investigate gray matter structural differences associated with psychosis in cocaine dependent individuals, and one of the first gray matter investigations of SIP to control for the effects of the substance precipitating psychosis. As in schizophrenia, gray matter volumetric reductions were observed in the thalamus and left hippocampus in individuals with cocaine associated psychosis

compared to cocaine dependent nonpsychotic individuals. Caution must be taken in interpreting these findings as a direct comparison to schizophrenia subjects was not performed. In summary, the present study provides empirical evidence that gray matter volume reductions in specific subcortical nuclei may be common to multiple forms of psychosis.

## **CHAPTER 3: CHARACTERIZATION OF WHITE MATTER INTEGRITY DEFICITS IN COCAINE-DEPENDENT INDIVIDUALS WITH SUBSTANCE-INDUCED PSYCHOSIS COMPARED TO NON-PSYCHOTIC COCAINE USERS**

### **3.1 INTRODUCTION**

Psychostimulant drugs produce a range of acute psychological effects, with lower doses generating feelings of increased energy, mood and confidence, while higher doses can result in additional, dysphoric effects. With sufficient drug exposure, some individuals develop symptoms that result in a syndrome referred to as “substance induced psychosis” (SIP), which symptomatically resembles schizophrenia spectrum disorders (Medhus, Mordal, Holm, Morland, & Bramness, 2013). These SIP episodes are characterized by both positive (hallucinations, delusions, disorganized thinking) and negative (flattened affect, emotional withdrawal, lack of spontaneity) symptoms. Cognitive deficits in SIP similar to those noted in schizophrenia have also been reported (Jacobs, Fujii, Schiffman, & Bello, 2008). Unlike idiopathic psychoses, SIP is defined as a transient psychotic episode enduring up to one month after the drug is metabolized and cleared from the body (Association, 2000; Orikabe et al., 2011). SIP is typically associated with exposure to high doses of psychostimulants over an extended duration, with an average latency of 3-5 years between first drug exposure and the initial psychotic episode (Ujike & Sato, 2004).

While heavy psychostimulant use may predispose individuals to SIP, many psychostimulant users will never experience an episode of SIP. Approximately 25-45% of methamphetamine-dependent individuals, most of whom consumed large quantities of the drug, developed psychosis at some point (McKetin, McLaren, Lubman, & Hides, 2006) – implying that only a minority of users are vulnerable. The biological basis that confers a predisposition to SIP is unknown. While genetic studies have provided preliminary evidence that particular variants in genes commonly associated with schizophrenia may be involved (Grant et al., 2012), it is also likely that differences in brain structure or function may

contribute to individual susceptibility to SIP. This has been addressed empirically in only a small number of neuroimaging studies, and only for the psychostimulant drug methamphetamine. Frontal and temporal volume loss (Aoki et al., 2013) and smaller hippocampal and amygdala volumes (Orikabe et al., 2011) were observed in methamphetamine users with SIP compared to healthy controls. However, the effects of methamphetamine on the brain are an ongoing area of study (reviewed in (Panenka et al., 2013; Thompson et al., 2004)). Without inclusion of drug-using non psychotic subjects, it is difficult to determine which structural changes are unique to psychosis, and which reflect the toxic effects of chronic exposure to the psychostimulant.

In idiopathic psychosis such as schizophrenia, symptoms are posited to result from aberrant anatomic connectivity, either globally or via specific white matter tracts (Konrad & Winterer, 2008; Melicher et al., 2015). White matter microstructural organization can be quantified using Diffusion Tensor Imaging (DTI), which measures the directionality of water diffusion within tissue to infer structural characteristics and integrity in white matter pathways (Alexander et al., 2007). In white matter, water diffuses more easily along, rather than across, the fibre tract axis, resulting in anisotropic diffusion. The most common index for quantifying anisotropy is with fractional anisotropy (FA). Other indices of diffusion include axial diffusion (AD; diffusion along the fibre tract axis) and radial diffusion (RD; diffusion perpendicular to the fibre tract axis). Reductions in FA have been interpreted as a disruption in the organization of tracts / white matter integrity (Madler et al., 2008). DTI has been used extensively to characterize white matter alterations in schizophrenia, with alterations observed predominantly in interhemispheric, fronto-temporal, and fronto-thalamic tracts (Ellison-Wright & Bullmore, 2009; Kanaan et al., 2005).

The goal of the current study was to investigate white matter integrity in psychostimulant users with SIP. Subjects were recruited as part of the Hotel Study (Honer WG, CBG-101827, MOP-137103), in which subjects underwent detailed psychiatric and neurocognitive assessment, as well as a MRI brain scan, at

entry into the study. For the current investigation, we compared a group of cocaine dependent nonpsychotic subjects to a group with cocaine-associated psychosis – to control for general effects of cocaine on the brain. We used a whole brain tract-based spatial statistics (TBSS) approach (Smith et al., 2006) to compare changes in white matter diffusion properties between groups. We hypothesized that patients with cocaine-associated psychosis (CAP) would show reduced white matter integrity compared to cocaine dependent nonpsychotic (CDN) subjects in fronto-temporal and interhemispheric pathways.

## **3.2 MATERIALS AND METHODS**

### **3.2.1 PARTICIPANTS**

Participants were recruited as part of a larger study of 370 subjects living in single room occupancy hotels with a history of mental illness and/or substance abuse in the Downtown Eastside of Vancouver, B.C. (see Vila-Rodriguez et al., 2013). For the current investigation, exclusionary criteria were history of DSM-IV diagnosis of schizophrenia, schizoaffective disorder, psychosis not-otherwise-specified, or bipolar disorder. Additional exclusionary criteria included past moderate or severe traumatic brain injury (loss of consciousness > 30 minutes or confusion > 24 hours after injury), stroke, significant MRI artifacts (motion, major distortion) and other gross morphometric brain abnormalities (i.e. encephalomalacia). All participants met DSM-IV criteria for cocaine dependence, verified by urine toxicology (mean (SD) of 8.4 (6.8) days from imaging acquisition). When a urine drug screen was unavailable, recent cocaine use was verified according to self-report via the Time Line Follow Back method (TLFB; n=4) (Sobell, Sobell, Klajner, Pavan, & Basian, 1986). Subjects were divided into two groups: 1) 24 cocaine-associated psychosis subjects (CAP), and, 2) 47 cocaine-dependent nonpsychotic subjects (CDN). The maximum inclusion age was set at 58 to ensure equal age distribution across groups, resulting in the exclusion of 4 CDN subjects for a final CDN sample size of 43. In accordance to Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All participants provided written informed consent.

### **3.2.2 DEMOGRAPHICS**

Data including age, gender, and education were collected. The Mini-International Neuropsychiatric Interview was administered, and it was supplemented by a clinical interview and mental status examination carried out by a psychiatrist. Diagnoses of psychiatric disorders and substance dependence were made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (Association, 2000) by an experienced psychiatrist (WGH, OL or FVR) through consensus evaluation with the Best Estimate Clinical Evaluation and Diagnosis (BECED; (Endicott, 1988)). The TLFB (Sobell, Sobell, Klajner, Pavan, & Basian, 1986)) was employed by a trained research assistant to quantify recent drug use. Years of regular psychostimulant use and age of first use were provided by self-report. Psychosis severity at time of MRI scan was assessed with the Positive and Negative Symptom Scale (PANSS, (Kay, Fiszbein, & Opler, 1987)).

### **3.2.3 COGNITION**

Neuropsychological tests were administered by trained researchers proximal to the time of imaging acquisition. Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; (Wechsler, 2001)). Verbal learning was measured with the immediate recall score of the Hopkins Verbal Learning Test-Revised (HVLT; (Brandt & Benedict, 2001)). The Cambridge Neuropsychological Test Automated Battery (CANTAB; (Fray, Robbins, & Sahakian, 1996)) was used to index sustained attention with the Rapid Visual Information Processing Subtest, and mental flexibility with the Intra-dimensional Extra-dimensional Subtest. Cognitive Inhibition was measured using the Color-word Trial from the Stroop Color-Word Test. Affective decision-making was assessed using the Total Net Score from the Iowa Gambling Task (IGT; (Bechara, Damasio, Damasio, & Anderson, 1994)).

### **3.2.4 MRI ACQUISITION**

All participants were scanned on a 3T MRI Scanner (Philips Achieva) at the University of British Columbia MRI Research Centre using an 8-channel SENSE head coil between 2008 and 2014. Subjects were scanned twice within the session using the same protocols (total scan time=7:32 mins). Standard

orthogonal localizers were performed. Diffusion Imaging was performed with the following parameters: 32 diffusion gradient directions were used with  $b=700\text{s/mm}^2$ ,  $TE=60\text{ms}$ ,  $TR=6451\text{ms}$ , flip angle= $90^\circ$ ,  $FOV=224\text{mm}\times 224\text{mm}$ , acquisition matrix= $100\times 100$ , reconstruction matrix= $112\times 112$ , voxel dimensions= $2.0\times 2.0\text{mm}$ , 70 contiguous slices, thickness= $2.2\text{mm}$ , gap=0, SENSE=2.1.

### **3.2.5 IMAGE PROCESSING**

Diffusion weighted data were corrected for eddy current and head motion using affine registration of all gradient volumes with the first  $b=0$  volume (FLIRT; FMRIB Software Library, Oxford, UK). Slices with extreme intensities were re-estimated from the average of adjacent slices. The two DTI scans were then averaged. A brain mask was created by running Brain Extraction Tool with a fractional intensity threshold of 0.3 (Smith, 2002). DTI fitting was performed with Slicer 3 using nonlinear least-square fitting with shifted negative eigenvalues.

### **3.2.6 TRACT-BASED SPATIAL STATISTICS (TBSS)**

TBSS (Smith et al., 2006) and Randomise (Nichols & Holmes, 2002) of the FMRIB Software Library (FSL, Analysis Group, FMRIB, Oxford, UK) was used for comparisons of FA, MD, AD and RD. Individual FA maps were then non-linearly registered via FSL-FNIRT to the John Hopkins University International Consortium Brain Mapping (JHU-ICBM) FA template provided by FSL, followed by creation of a study-specific mean FA skeleton. Individual FA values were then projected onto this mean skeleton. MD, AD, and RD values were projected onto the skeleton using the previously created FA transformation. FA threshold was set to 0.20 and voxel-based comparisons of FA, MD, AD, and RD were performed on the mean FA skeleton using Randomise (Nichols & Holmes, 2002) from FSL Version 4.1.9, including age and methamphetamine dependence as covariates, as these variables affect FA (Bendlin et al., 2010; Salo et al., 2009). The analysis performs 5,000 random permutations, using threshold-free cluster enhancement (TFCE)(Smith et al., 2006) to threshold the statistical data, and Family-Wise-Error (FWE) to correct for multiple

comparisons before creating a  $p < .05$  T-contrast map. The JHU-ICBM-DTI-81 white matter label atlas was used to identify specific anatomical areas implicated by TBSS (Hua et al., 2008).

The JHU-ICBM-DTI-81 white matter label atlas was transformed back onto individual DTI space by reversing the previous non-linear registration for each subject to calculate white matter tract volumes.

### **3.2.7 STATISTICAL ANALYSIS**

Demographic and clinical variables were analyzed with Chi-square tests or independent Student t-tests as appropriate.

To further investigate intergroup FA and RD differences, mean FA or RD was extracted from the clusters where the highest statistical group difference was identified using a p-value cut-off threshold of  $p < 0.05$ .

The anatomical regions to which these clusters belonged were determined using the JHU-ICBM-DTI-81 white matter label atlas. A partial correlation was performed to assess relationships between the mean clusters of FA/RD and PANSS positive subscale, controlling for age and methamphetamine dependence

White matter tract volume was compared by partial correlation controlling for age, methamphetamine dependence, and total brain volume (Jancke et al., 1997).

Statistical analysis was performed with SPSS Vs22.

## **3.3 RESULTS**

### **3.3.1 DEMOGRAPHICS**

The mean age of the CAP group was 40.4 ( $\pm 8.2$ ) years, and 43.3 ( $\pm 7.3$ ) years for the CDN group. The CAP group included 15 males and 9 females, while the CDN group included 30 males and 13 females. Age, gender distribution, and mean years of completed education were similar across groups ( $p > 0.05$ ; Table 3.1). Additionally, there was no difference in HIV status between groups (20.8% positive in CAP and 18.6% in CDN). Scores on all PANSS subscales were higher in the CAP than CDN group, including Positive

(CAP: 15.3 ( $\pm 4.1$ ), CDN: 11.9 ( $\pm 3.1$ )), Negative (CAP: 18.3 ( $\pm 5.4$ ), CDN: 15.2 ( $\pm 4.9$ ), and General Psychopathology Subscales (CAP: 37.1 ( $\pm 7.5$ ), CDN: 33.7 ( $\pm 6.4$ )) (Table 3.2).

The atypical antipsychotic quetiapine was prescribed for 20% of the CAP and 9% of the CDN group, mostly for hypnotic effects.

### **3.3.2 DRUG USE**

DSM-IV TR substance dependence was diagnosed by a qualified psychiatrist. Aside from cocaine use, the tobacco dependence rate was 93% of the pooled sample. Methamphetamine (CAP=24%, CDN=14%) and marijuana (CAP=42%, CDN=26%) use were non-significantly greater in the CAP group. Heroin, methadone, and alcohol dependence were approximately even between groups (Table 3.1).

### **3.3.3 COGNITION**

For cognitive analyses, sample sizes vary due to invalid performances by some participants on select tests (Table 3.2). No significant group differences or trends were observed for any of the cognitive measures (all  $p > 0.10$ ), including estimated premorbid IQ, verbal learning, inhibition, sustained attention, mental flexibility and decision making. For descriptive purposes, demographically corrected (age and/or education) T-scores were calculated for the group-pooled neurocognitive measures using available normative data (mean of 50, SD of 10; Table 3.2). Briefly, the sample exhibited greatest impairments in verbal learning ( $> 1.5$  SDs below the mean), with milder impairment for sustained attention and mental flexibility ( $> 1$  SD below the mean). In contrast, estimated premorbid IQ, inhibitory control and decision-making ability fell within normal limits.

**Table 3.1 Mean demographic and drug use data.**

	CDN (n=43)		CAP (n=24)		Statistic*	p value
	Mean	SD	Mean	SD	t	p
<b>Age</b>	43.3	7.3	40.4	8.2	1.606	.110
<b>Education</b>	10.4	2.5	10.1	1.3	.601	.550
<b>Years Regular Meth Use</b>	4.1	10	2.6	3.6	.647	.520
<b>Age first meth use</b>	23.5	9.8	24.4	13.1	-.275	.784
<b>Days Cocaine Use in Past Month</b>	17.1	10.0	19.3	10.9	-.714	.480
<b>Years Regular Cocaine Use</b>	12.4	9.0	11.8	8.4	.472	.640
<b>Age Cocaine First Use</b>	17.7	18.8	19.2	5.8	.752	.460
<b>Cigarette Pack Years</b>	13.2	14.800	12.600	11.800	.122	.900
	N	%	N	%	X <sup>2</sup>	p
<b>Gender (F)</b>	13	30.2	9	37.5	.449	.510
<b>Meth Dependency</b>	6	14.0	6	24.0	1.380	.250
<b>Alcohol Dependency</b>	8	18.6	5	20.8	.071	.790
<b>Heroin Dependency</b>	21	48.8	12	50.0	.000	1.000
<b>Methadone Dependency</b>	24	55.8	16	66.7	.629	.440
<b>Marijuana Dependency</b>	11	25.5	10	41.7	2.021	.160

\*based on 65 degrees of freedom

### 3.3.4 TBSS – GLOBAL WHITE MATTER

The CAP group had lower FA than the CDN group ( $p < 0.05$ , FWE) in (i) fronto-temporal, (ii) fronto-thalamic, and (iii) interhemispheric white matter tracts (Voxel-based differences shown in Figure 3.1). Specifically, deficits were present in: (i) bilateral inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus (ii) right anterior limb of the internal capsule, right posterior limb of the internal

capsule, bilateral posterior corona radiata, left superior corona radiata, left minor forceps, and (iii) splenium and body of the corpus callosum. There were no areas of increased FA in the CAP group compared to the CDN group.

Radial diffusivity (RD) was significantly higher in the CAP group compared with the CDN group in white matter tracts of the: (i) bilateral superior longitudinal fasciculus, (ii) left anterior, superior, and posterior corona radiata, and (iii) splenium and body of corpus callosum (Figure 3.2). There were no areas of significantly decreased RD in the CAP group.

No differences were present between groups comparing either mean diffusivity or axial diffusivity.

**Table 3.2.** Mean Clinical and Cognitive data

	CDN			CAP			<i>p value</i>	<i>Mean T-score (df)</i>
	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>n</i>	<i>Mean</i>	<i>SD</i>		
WTAR (premorbid IQ)	43	97.4	9.0	24	94.3	9.6	0.19	50.0 (65)
Stroop (inhibition)	42	37.5	9.9	21	34.5	7.7	0.22	49.9 (61)
HVLT (verbal learning)	42	20.4	5.5	22	18.5	5.4	0.21	31.7 (62)
RVP A' (attention)	37	0.869	0.052	20	0.86	0.058	0.55	39 (55)
IED (mental flexibility)	36	128.4	40.9	20	142.5	51.5	0.27	38.5 (54)
IGT Net Score (decision making)	38	1.6	30.4	22	-13.0	43.6	0.17	44.8 (58)
Positive PANSS	43	11.9	3.1	24	15.3	4.1	0.000	N/A (65)
Negative PANSS	43	15.2	4.9	24	18.3	5.4	0.025	N/A (65)
General PANSS	43	33.7	6.4	24	37.1	7.5	0.057	N/A (65)
Total PANSS	43	60.8	12.0	24	70.8	14.4	0.004	N/A (65)

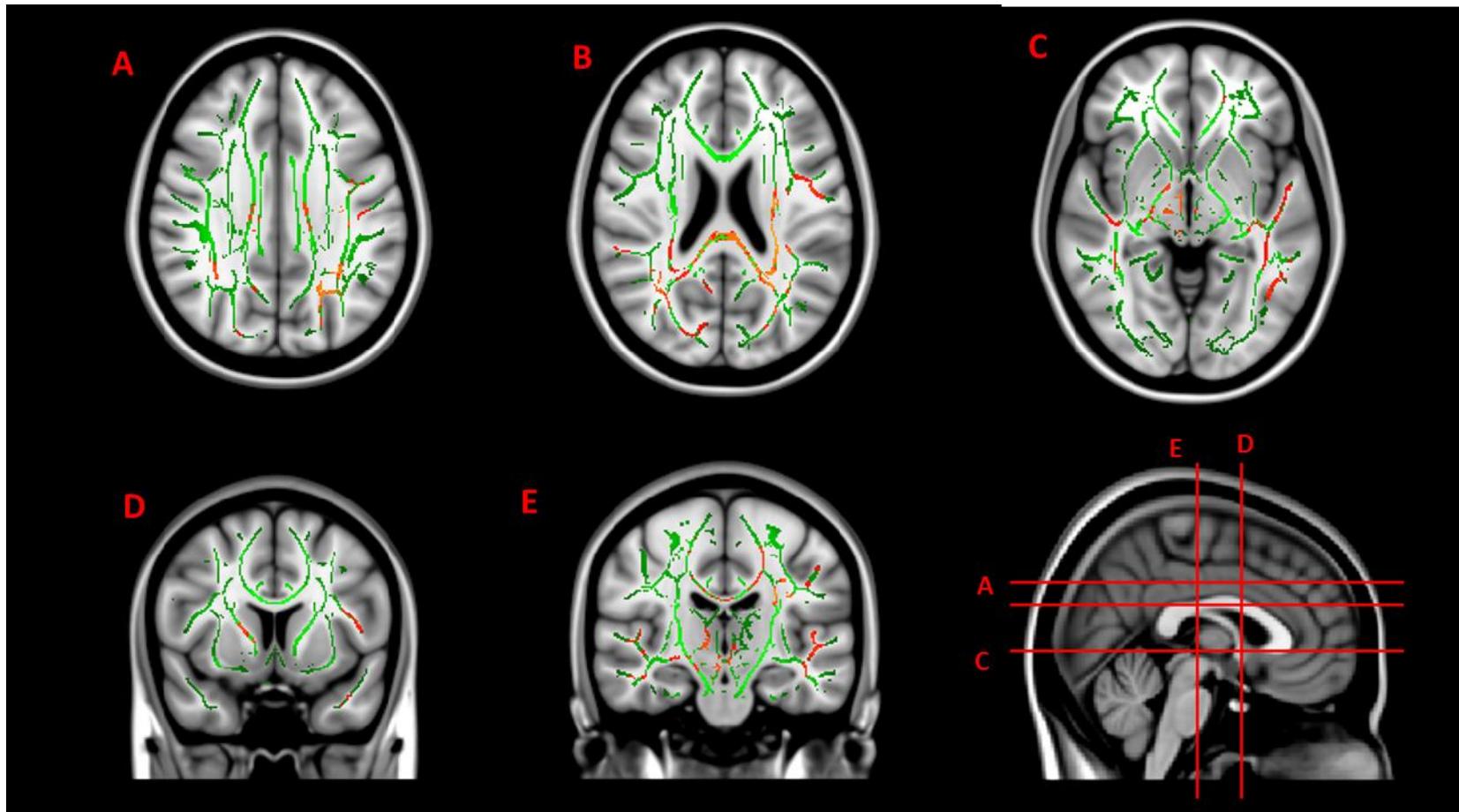
\* Due to invalid tests, sample sizes of cognitive tests were diminished in a case by case basis.

### 3.3.5 ASSOCIATION WITH SYMPTOM SEVERITY

Mean FA/RD was extracted from the clusters where the highest statistical group difference was identified using a p-value cutoff threshold of  $p < 0.05$ . PANSS Positive Subscale was related to 1) splenium (FA:  $r = -0.251$ ,  $p = 0.044$ ) and 2) body of the corpus callosum (FA:  $r = -0.304$ ,  $p = 0.014$ ; RD:  $r = 0.333$ ,  $p = 0.007$ ). FA correlations were negative, with greater symptom severity associated with lower FA values. RD correlations were positive, with higher RD values associated with greater symptom severity. No findings were statistically significant after applying Bonferroni correction for multiple comparisons.

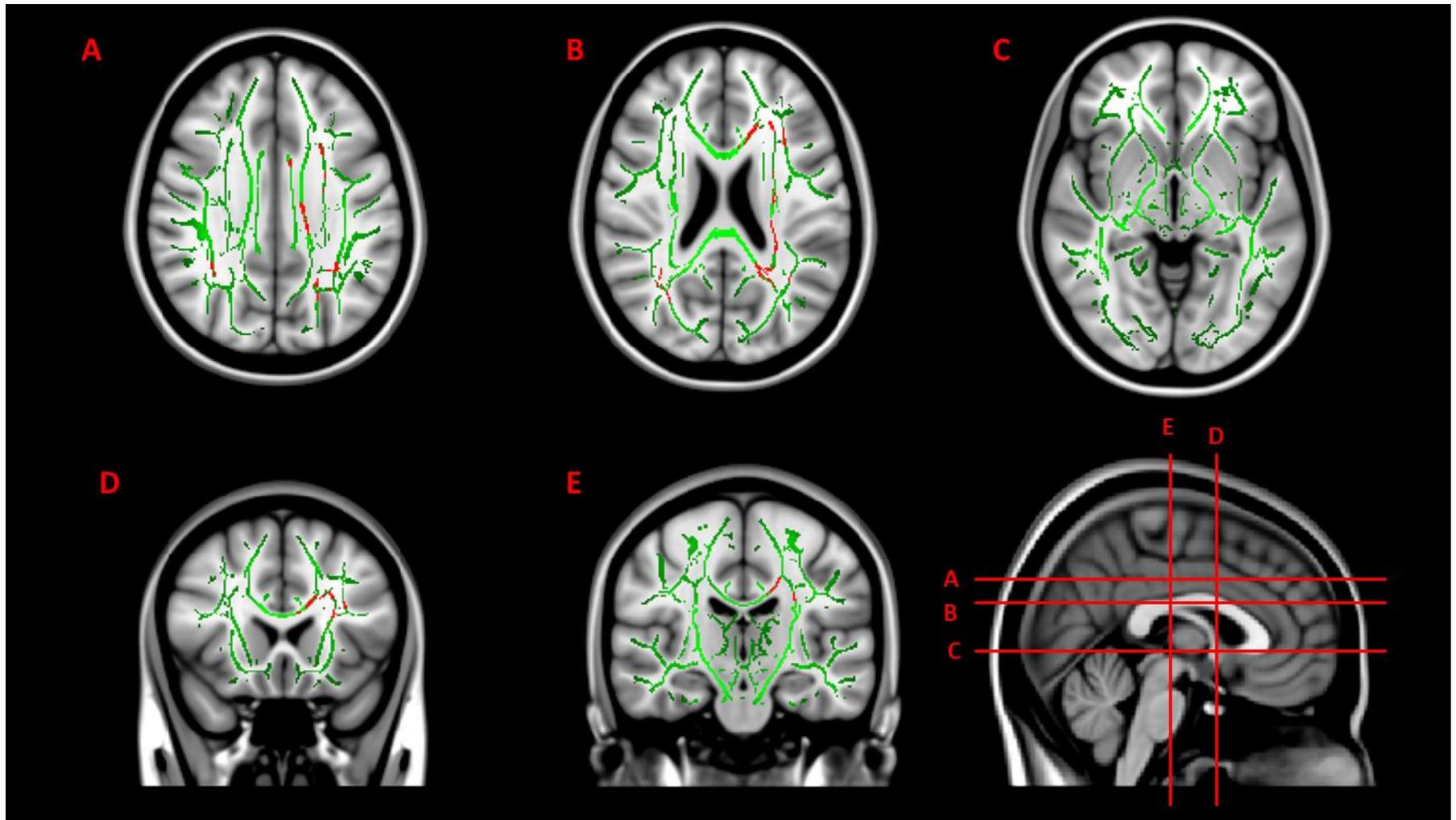
### 3.3.6 WM TRACT VOLUME

There were no WM tract volume differences between groups in any of the tracts identified to have FA differences after correcting for multiple comparisons (all p-values  $> 0.05$ ).



**Figure 3.1 TBSS between-group FA differences**

Areas of decreased FA in CAP vs CDN groups (green=skeleton; red=decreased FA in CAP at  $p \leq 0.05$ ). A-C: A series of axial slices highlighting differences within A) Left superior longitudinal fasciculus, bilateral superior corona radiata, B) splenium of corpus callosum, bilateral posterior corona radiata, left superior corona radiata, C) left inferior longitudinal fasciculus. D-E: A series of coronal slices highlighting differences in: D) right anterior limb of internal capsule, left superior longitudinal fasciculus, E) splenium of corpus callosum, left superior corona radiata, bilateral inferior longitudinal fasciculi



**Figure 3.2 TBSS between-group RD differences**

Areas of increased RD in CAP vs CDN groups (green=skeleton; red=increased RD in CAP at  $p \leq 0.05$ ). A-C: A series of axial slices highlighting differences within A) left cingulum, left superior corona radiata, B) left splenium of corpus callosum, left genu of corpus callosum, left posterior corona radiata, left anterior corona radiata. D-E: A series of coronal slices highlighting differences in: D) left genu of corpus callosum, left anterior corona radiata, E) left anterior corona radiata

### **3.4 DISCUSSION**

The present study showed decreased FA and increased RD values in cocaine dependent subjects with psychosis compared to those without psychosis, in the body and splenium of the corpus callosum, bilateral superior longitudinal fasciculi, left posterior corona radiata, left superior corona radiata, and right anterior limb of the internal capsule. There were no group differences in mean or axial diffusivity. The alterations in radial, but not axial, diffusivity may reflect deficits in white matter microstructural integrity, including damage to myelin or the cellular membrane (Song et al., 2003; Song et al., 2005). These changes were inversely correlated with symptom severity in the splenium and body of the corpus callosum, though this finding did not withstand correction for multiple comparisons. Cognitively, the combined sample exhibited substantial impairment in the domains of verbal learning, mental flexibility, and sustained attention compared to normative data, although no significant group differences were observed.

To date, neuroanatomical characterization of SIP has been limited to a small number of structural MRI studies that have investigated gray matter abnormalities in methamphetamine associated psychosis (MAP; (Aoki et al., 2013; Orikabe et al., 2011; Sekine et al., 2002)), with a paucity of data on cocaine-associated psychosis. One study observed reduced amygdala and hippocampal volumes in MAP subjects compared to healthy controls (Orikabe et al., 2011), while another reported gray matter volume reductions within frontal, and temporal regions (Aoki et al., 2013) – reflecting prior reports of idiopathic psychosis (Shenton, Dickey, Frumin, & McCarley, 2001). The observation of decreased white matter FA values in chronic cocaine users with SIP compared to cocaine users without psychosis adds a novel and important dimension to the SIP literature. Of considerable interest, these white matter alterations closely resemble those observed in schizophrenia. Numerous DTI studies have reported lower FA values in schizophrenia. Meta-analysis has demonstrated the most consistent deficits are in left frontal and left temporal deep white matter regions – specifically within the genu/splenium of the corpus callosum,

cingulum bundle, left inferior fronto-occipital fasciculus, left anterior thalamic radiation, and left inferior longitudinal fasciculus (Ellison-Wright & Bullmore, 2009). In the current study, we identified FA reductions in a subset of these tracts, including the splenium of the corpus callosum, inferior longitudinal fasciculus, and anterior limb of the internal capsule (Ellison-Wright & Bullmore, 2009). Interestingly, though FA reductions were seen bilaterally, RD increases were notably more prevalent on the left than the right side – with group differences present in left but not right splenium, genu, cingulum, anterior corona radiata, superior corona radiata, and posterior corona radiata. This left-sided lateralization of abnormalities has also been observed in studies of schizophrenia (Ellison-Wright & Bullmore, 2009; Shenton et al., 2001). Of note, a recent DTI study of white matter pathways in a relatively large sample of first episode psychosis patients (Melicher et al., 2015) observed that changes in schizophrenia were diffuse rather than regionally specific in nature. Caution should be exercised with respect to the expectation for localized white matter FA changes in the expression of psychosis, especially when group sizes are modest.

The different indices of diffusion provide an expanded insight into the observed white matter differences. FA is a composite measure, calculated from the sum of the radial and axial diffusivity. Increased radial diffusivity is thought to reflect deficits in myelin integrity (Song et al., 2003), whereas decreased axial diffusivity is thought to reflect axonal damage (Song et al., 2005). Our finding of reduced FA concomitant with increased radial diffusivity, and no differences in axial diffusivity or white matter volume, may implicate aberrant myelination without axonal damage.

This pattern of altered diffusion parallels those observed in schizophrenia (Levitt et al., 2012; Seal et al., 2008), and is consistent with findings suggestive of myelin pathology in post mortem tissue (Flynn et al., 2003). The overlap between the present findings in SIP and those of schizophrenia suggest that reduced structural integrity of white matter tracts within fronto-temporal, fronto-thalamic, and interhemispheric

pathways may be a common neuroanatomical substrate for the development and expression of psychosis. However, whether the white matter deficits reported presently are of a similar magnitude to those seen in schizophrenia remains unknown.

Direct comparisons between SIP and schizophrenia have been performed in measures of symptomology and cognitive dysfunction (Jacobs et al., 2008; Medhus et al., 2013). It is generally agreed that psychostimulant-induced positive symptoms are almost indistinguishable from the positive symptoms of schizophrenia (Medhus et al., 2013; Panenka et al., 2013). Similarly, both MAP and paranoid schizophrenia subjects show comparable neurocognitive deficits across similar cognitive domains (Jacobs et al., 2008). Given that cocaine abuse is associated with cognitive impairment, it was expected that comorbid cocaine use and psychosis would have additive negative effects on cognition (Potvin, Joyal, Pelletier, & Stip, 2008). In the current study, differences in cognition between groups were not seen, though both groups showed impairments compared to population norms. Studies of schizophrenia and comorbid substance abuse have generated contrary findings, as many describe no between schizophrenia with or without comorbid drug use, while it has even been reported that there is an increase in cognition with dual-diagnosis (Potvin et al., 2008). Our present findings suggest that comorbidity is not associated with additive cognitive deficits.

Understanding the nature of the relationship between chronic cocaine use, white matter integrity and psychosis remains a complex challenge. As noted, heavy and sustained use of psychostimulants may lead to SIP, but only 25-45% of methamphetamine-dependent users will later experience drug-induced psychosis (McKetin et al., 2006), indicating that the etiology of SIP is not entirely dependent on substance abuse. The present findings suggest that white matter deficits may play a role in the expression of SIP, although the nature of that association could take several forms. Firstly, the lower white matter integrity in the CAP group may reflect a difference between groups existing prior to drug

exposure. White matter structural deficits in the CAP group may be the result of earlier abnormal neurodevelopment, resulting in a weakened network left vulnerable to environmental stressors, akin to the neurodevelopmental hypothesis of schizophrenia (Weinberger, Berman, & Zec, 1986). This hypothesis is consistent with research reporting fronto-temporal dysconnectivity in subjects at ultra-high risk for developing schizophrenia (Karlsgodt, Niendam, Bearden, & Cannon, 2009). Secondly, lower white matter integrity may be the result of differential sensitivity to the neurotoxic effects of drugs of abuse (Hsieh et al., 2014). Psychostimulant abuse can damage white matter tracts, including the corpus callosum, internal capsule, association fibres, and frontal white matter regions (Lim et al., 2008; Thompson et al., 2004), all of which have been implicated in idiopathic psychosis. The CAP group may reflect a population that is more vulnerable to the neurotoxic effects of cocaine, in which chronic and sustained use of cocaine results in greater damage to white matter tracts that subserve psychosis. After a critical threshold, damage may become sufficient to sustain psychosis in the absence of the drug. The hypothesis that some minimum degree of drug-induced damage must occur before onset of psychosis is supported by studies of MAP that have reported the average latency from first use of methamphetamine to onset of psychosis is 3-5 years (Ujike & Sato, 2004). After remission, psychosis relapse occurred promptly after subsequent doses of methamphetamine, with 60% of subjects relapsing within one week, and 80% relapsing within one month of drug use (Ujike & Sato, 2004). Spontaneous MAP relapse has also been reported after significant stressors, such as severe insomnia (Sato, Numachi, & Hamamura, 1992; Ujike & Sato, 2004), suggesting that following a certain threshold of damage or sensitization of neural substrates, subjects remain prone to future relapse. Finally, white matter deficits may also be a consequence of psychosis, or the effects of a third factor responsible for both presentation of psychotic symptoms and white matter alterations. With the current cross-sectional study design, the temporal order of drug use, white matter changes and emergent psychosis cannot be definitively determined, and future longitudinal studies will be required to address this issue.

A potential limitation of this study is the absence of a cocaine-naïve control group. Though this would not change the observation that SIP is associated with lower white matter integrity compared to non-psychotic cocaine users, it would be useful in revealing how large these deficits are compared to drug naïve subjects. However, it is highly likely that a cocaine-naïve control group would not be matched on the multitude of factors that are inherent to being part of a marginalized population (high infection rates, homelessness, limited formal education, other substances of abuse, etc.), and thus separation of drug versus other environmental effects on the brain would not be feasible. A second potential limitation is that acute substance use (previous 48 hours) was not controlled for, as the urine drug screen did not occur on the date of the scan for most subjects. However, the authors are not aware of a literature suggesting white matter FA values are susceptible to acute drug exposure. In this vein, information regarding dosage consumed, route of administration, or pattern of ingestion (e.g. “bingeing”) was not available, which may play a role in the development of SIP.

### **3.5 CONCLUSION**

The present study is the first to suggest a structural white matter biomarker in SIP, controlling for the effect of substance abuse. We detected reductions in white matter integrity in cocaine dependent subjects with SIP, manifest as decreases in FA characterize by increases in radial diffusivity in fronto-temporal, fronto-thalamic, and interhemispheric white matter pathways, compared to cocaine-dependent subjects without psychosis. These pathways parallel those implicated in schizophrenia, suggesting that damage to these pathways may be a shared factor in the expression of different forms of psychosis. Longitudinal studies will help address whether such white matter abnormalities are pre-existing and reflect a natural diathesis, or reflect individual differences in the vulnerability to the neurotoxic effects of psychostimulant drugs.

## **CHAPTER 4: FACTORS AFFECTING SEVERITY OF POSITIVE AND NEGATIVE SYMPTOMS OF PSYCHOSIS IN A POLYSUBSTANCE USING POPULATION WITH PSYCHOSTIMULANT DEPENDENCE**

### **4.1 INTRODUCTION**

Psychostimulants, including amphetamines and cocaine, are the second most commonly used illicit substances worldwide, with an estimated 28 to 75 million users (World Drug Report, 2014). In urban communities, the rates and heterogeneity of psychostimulant use become even more prevalent (Fischer et al., 2006; Kuramoto et al., 2011). At low doses these drugs generate feelings of increased energy and mood, while frequent exposure and higher doses can lead to a host of adverse effects, including physical (e.g. strokes, seizures, arrhythmias) and psychiatric complications (e.g. dependency, depression, anxiety, psychosis) (Barr et al., 2006).

Approximately 50-75% of cocaine users (Brady 1991; Mooney et al., 2006; Satel and Edell, 1991; Smith et al., 2009; Vergara-Moragues et al., 2014; Vorspan et al., 2012) and 50-60% of methamphetamine users (Grant et al., 2012; Hall et al., 1996; McKetin et al., 2006; Smith et al., 2009) experience psychotic symptoms during consumption, including paranoia, delusions, and vivid sensory hallucinations (Barr et al., 2013; Mahoney et al., 2008). Though high frequencies of psychotic symptoms have been reported in both methamphetamine and cocaine users, direct comparison has shown that methamphetamine users more commonly exhibit psychotic symptoms than cocaine users (Mahoney et al., 2008).

Due to their high prevalence and severity, positive symptoms have been the hallmark of characterizing psychostimulant-associated psychosis (Panenka et al., 2013; Zorick et al., 2008). These positive symptoms are frequently indistinguishable from the positive symptoms of schizophrenia spectrum disorders (Shaner et al., 1998; Zorick et al., 2008). While there is some evidence that negative symptoms are also present in psychostimulant-associated psychosis (Srisurapanont et al., 2011), others have theorized that the absence of negative symptoms in psychostimulant-associated psychosis may be a key

differentiating factor from schizophrenia spectrum disorders (Zorick et al., 2008). The prevalence and severity of negative symptoms in psychostimulant-associated psychosis remains equivocal (Panenka et al., 2013; Srisurapanont et al., 2011; Zorick et al., 2008).

The presentation of psychotic symptoms ranges in severity from subclinical psychotic experiences, to clinically significant psychotic disorders (Binbay et al., 2012; van Os, 2014). Even though psychostimulant use causes psychosis across a spectrum of severity, most studies report psychosis as a dichotomous categorical occurrence. Only a small number of studies have investigated the severity of current positive symptoms, noted that chronic use (greater than 5 years), weekly use pattern, and injection administration were significant predictors of greater symptom severity (Lichlyter et al., 2011; Vorspan et al., 2012). However, Vorspan et al. was limited to studying only cocaine users, while Lichlyter et al. performed their study in a 30-day stimulant-abstinent sample. Data on the effect of recent psychostimulant use on psychotic symptom severity is lacking, and has never been evaluated in the context of negative symptoms. When investigated as a categorical outcome (i.e. present or not), identified risk factors for psychostimulant associated psychosis have included earlier age of first use (Chen et al., 2003; Farrell et al., 2002; Kalayasiri et al., 2006a; Roncero et al., 2014), severity of dependence (Farrell et al., 2002; Kalayasiri et al., 2006a; Vergara-Moragues et al., 2014), marijuana dependence (Farrell et al., 2002; Kalayasiri et al., 2010; Roncero et al., 2013; Roncero et al., 2014), route of administration (Hall et al., 1996), and recent frequency of use (McKetin et al., 2013). However, categorically defining psychostimulant-induced psychosis may not capture important information when psychosis occurs on a continuum of severity (Binbay et al., 2012; van Os, 2014). Simplifying psychosis to a binary outcome requires the establishment of a threshold, which varies among studies. Some studies define psychostimulant associated psychosis as any lifetime occurrence of a symptom, which may be too broad of an inclusion parameter (Kalayasiri et al., 2006a; Roncero et al., 2014). Other studies require a diagnosis according to standardized criteria (Farrell et al., 2002; Willi et al., 2016), excluding moderately

symptomatic states, which may overlook risk factors pertinent to progression through the continuum of psychosis (Yung et al., 2003). Utilization of different thresholds for definitions of psychosis impedes replication and direct study-to-study comparisons.

The aim of the current study was to identify risk factors that contribute to the spectrum of psychotic severity presenting concurrently with psychostimulant abuse, in both positive and negative dimensions. We hypothesized that variables regarding recent frequency of use would be the strongest predictors of current symptom severity, with greater use associated with greater symptom severity. Here, we describe the results of regression models to help explain the variance of psychosis symptom severity in a psychostimulant dependent population.

## **4.2 MATERIALS AND METHODS**

### **4.2.1 PARTICIPANTS**

Participants were selected from the ongoing Hotel Study, an observational longitudinal cohort study of multimorbidity in the Downtown Eastside (DTES) of Vancouver, British Columbia (Honer WG, CBG-101827, MOP-137103). In this cohort of 370 individuals, all cases of past or present psychosis not related to substance abuse were excluded, including schizophrenia, schizoaffective disorder, bipolar with psychosis, major depressive disorder with psychosis, or psychosis not otherwise specified according to DSM-IV-TR criteria. From the remaining 243 participants, inclusion criteria were current psychostimulant dependence at study entry (DSM-IV-TR criteria) and an available Positive and Negative Symptom Syndrome (PANSS) baseline assessment, resulting in the retention of 179 participants. In accordance to Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All participants provided written informed consent.

### **4.2.2 MEASURES**

Demographic information including age, gender, and education were collected. Psychiatric health and substance use disorders were assessed according to DSM-IV-TR diagnostic criteria through consensus

with the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988) by an experienced psychiatrist (WGH, OL, or FVR).

Frequency of drug use was retrospectively collected for the 28 days prior to psychiatric assessment with the Time Line Follow Back method (TLFB; Sobell et al., 1986). Drug use frequency was divided by 7 to obtain weeks of use per month. Methadone status was recorded as either positive or abstinent. A urine drug screen was collected at time of psychiatric assessment to validate self-reported data. In instances where no psychostimulant use was reported in the past 28 days, and a urine drug screen was positive, data were omitted from analysis (8 cases, final  $n=171$ ). Years of regular substance usage and age of first usage were provided via self-report.

Severity of psychotic symptoms were assessed using the PANSS (Kay et al., 1987). For the positive dimension, PANSS items P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness), G9 (unusual thought content), and G12 (insight) were summed, as previously described using a 5-dimensional factor (potential range: 6-42) (Emsley et al., 2003). For the negative dimension, PANSS items N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (social withdrawal), N6 (lack of spontaneity), G7 (motor retardation), G13 (disturbance of volition), and G16 (social avoidance) were summed, as previously described (potential range: 7-49) (Emsley et al., 2003).

#### **4.2.3 STATISTICAL ANALYSIS**

Data were analyzed using SPSS software version 22 (SPSS Inc., IBM Corp., Armonk, USA). Descriptive statistics were calculated for all variables.

To pre-screen variables of interest before entry into a statistical model, bivariate analyses between variables of interest and the sum of positive symptoms (P1, P3, P5, P6, G9, and G12) or negative symptoms (N1, N2, N3, N4, N6, G7, G13, G16) were performed using a Pearson Correlation.

Pre-screened variables with at least a weak association with the symptom severity outcome ( $p < 0.20$ ) were entered into a multiple linear regression model. Model optimization was performed by utilizing a backward elimination model selection approach, where the least significant variable (if  $p > 0.10$ ) was dropped from the model. This process was repeated until all variables in the model met criteria ( $p < 0.10$ ). Potential interaction effects were explored between the independent variables, and tested for significance at  $p < 0.05$ . Collinearity between independent variables was tested for with the variance inflation factor (VIF).

To investigate possible associations with specific psychotic symptoms, Pearson correlations were performed in a secondary exploratory analysis between significant independent variables from the regression models and the individual PANSS items. Positive symptom PANSS items P1, P3, P5, P6, G9, and G12 were checked for correlations with independent variables of the positive symptom regression, while negative symptom PANSS items N1, N2, N3, N4, N6, G7, G13, G16 were checked for correlations with independent variables of the negative symptom regression.

Potential effects of cocaine use frequency on psychotic symptoms were further investigated in two ways: first, by analyzing individuals with cocaine dependency and concurrent cocaine and methamphetamine dependency ( $n$  analyzed=144) and second, by excluding all participants dependent on methamphetamine, leaving only cocaine dependent participants ( $n=122$ ). Differences in symptom severity based on type of cocaine (powder or crack) were investigated with a Student's  $t$ -test.

## **4.3 RESULTS**

### **4.3.1 DEMOGRAPHIC VARIABLES**

A total of 171 participants were investigated in this analysis. Table 1 describes the socio-demographic characteristics of the sample. Concurrent mood disorders were present in a small subset of the sample: 11.6% had a DSM-IV TR diagnosis of major depressive disorder, while 3.5% of the sample had a diagnosis

of bipolar disorder. Of the total sample, 92.7% of the participants were currently unemployed, 59.6% had at least one previous incarceration, and 47.2% had received medication or treatment for mental illness at some point in their lives.

All participants were clinically dependent on a psychostimulant (cocaine (85%) or methamphetamine (28.1%)). In the month prior to assessment, other drug use in the sample included marijuana (42.7%), opioid (54.4%), alcohol (43.35), and methadone (52.3%). In the 28 days prior to psychiatric assessment, cocaine was the most frequently used drug in the sample, with an average (SD) of 14.9 (11.6) days of use. There was an average of 8.5 (11.3) days of opioid use, 7.6 (11.4) days of marijuana use, and 4.0 (8.1) days of methamphetamine use.

The mean age of first psychostimulant use (SD) was 21.6 (8.9). The average duration of regular psychostimulant use was 14.7 years (10.0). The mean age of first marijuana use was 13.7 (3.2), with an average duration of regular use of 14.2 years (12.5). See Table 1 for all substance use data.

The mean positive factor PANSS score was 13.0 (4.0) with an observed range of 6 to 28. The mean negative factor PANSS score was 16.3 (5.6) with an observed range of 8 to 35. The mean total PANSS score was 64.1 (13.8) with an observed range of 37 to 111.

#### **4.3.2 SYMPTOM SEVERITY BIVARIATE ANALYSIS**

Increases in positive symptom severity were significantly associated ( $p < 0.05$ ) with an increased frequency of methamphetamine (Pearson's  $r = 0.193$ ) and marijuana (Pearson's  $r = 0.227$ ) use. Methadone-positive status was associated with decreases in positive symptom severity. Increases in positive symptom severity showed a weak association ( $p < 0.20$ ) with male gender, injection route of psychostimulant and years of regular marijuana use. No significant associations were observed with cocaine frequency (Pearson's  $r = -0.066$ ,  $p = 0.394$ ).

Increases in negative symptom severity were significantly associated ( $p < 0.05$ ) with an increased frequency of opioid use (Pearson's  $r = 0.163$ ) and alcohol use (Pearson's  $r = -0.159$ ) in the past 28 days, and years of regular alcohol use (Pearson's  $r = -0.156$ ). Increases in negative symptom severity showed a weak association ( $p < 0.20$ ) with younger age, female gender, less education, an increased frequency of cocaine use, and less years of injecting psychostimulants.

Concurrent mood disorders (major depressive disorder or bipolar disorder), were not associated with PANSS positive or negative subscale severity, all  $p > 0.40$ .

See Table 1 for all associations tested.

#### **4.3.3 POSITIVE SYMPTOM SEVERITY MULTIVARIABLE ANALYSIS**

In a multiple linear regression model, positive symptom severity was the dependent variable with the pre-screened variables (Section 3.2) entered as independent variables including weeks of methamphetamine use in the last 28 days, weeks of marijuana use in the last 28 days, methadone status, gender, injection of psychostimulants in the last 28 days, and years of marijuana use. Methamphetamine frequency, marijuana frequency, and methadone status all explained a significant amount of the variance in the regression model ( $p < 0.05$ ).

For each week increase of methamphetamine use in the past 28 days, the Positive PANSS severity increased by 0.52 points. For each week increase of marijuana use in the past 28 days, Positive PANSS severity increased by 0.38 points. Methadone positive status resulted in a decrease of 1.33 Positive points, relative to methadone-abstinent participants.

The final model was found to explain 10.0% of the variation in positive symptoms as measured with the PANSS ( $R = 0.317$   $R^2 = 0.100$  ANOVA  $F(5, df) = 6.219$ ,  $p < 0.001$ ). Individual regression coefficients can be found in Table 2. No significant interaction effects were present between any of the predictor variables (all  $p > 0.10$ ), and all VIF  $< 1.2$ .

**Table 4.1 Demographics**

	Total (n=171; df=169)	Positive Symptoms <sup>+</sup>		Negative Symptoms <sup>++</sup>	
		Pearson's r	p-value	Pearson's r	p-value
<b>Age in years (SD)</b>	45.5 (8.8)	-0.070	0.360	-0.103	0.178
<b>Female (%)</b>	27.5%	-0.108	0.161	0.122	0.111
<b>Education in years (SD)</b>	10.1 (2.1)	-0.071	0.362	-0.123	0.112
<b>Methadone Status (%)</b>	50.90%	-0.210 <sup>**</sup>	0.006	0.091	0.236
<b>Marijuana Frequency (Days/Last Month)</b>	7.6 (11.4)	0.227 <sup>**</sup>	0.003	-0.030	0.698
<b>Meth Frequency (Days/Last Month)</b>	4.0 (8.1)	0.193 <sup>+</sup>	0.011	0.075	0.330
<b>Cocaine Frequency (Days/Last Month)</b>	14.9 (11.6)	-0.066	0.394	0.136	0.077
<b>Opioid Frequency (Days/Last Month)</b>	8.6 (11.3)	0.024	0.755	0.163 <sup>+</sup>	0.033
<b>Alcohol Frequency (Days/Last Month)</b>	2.6 (6.2)	0.056	0.464	-0.159 <sup>+</sup>	0.038
<b>Psychostimulant IV in Last Month (%)</b>	44.40%	0.101	0.188	-0.010	0.896
<b>Years Psychostimulants (SD)</b>	14.7 (10.0)	0.050	0.519	-0.042	0.591
<b>Years Cocaine (SD)</b>	13.8 (10.0)	0.034	0.663	-0.045	0.562
<b>Years Amphetamines (SD)</b>	3.5 (6.6)	0.013	0.877	0.024	0.771
<b>Years Alcohol (SD)</b>	12.7 (11.3)	0.090	0.247	-0.156 <sup>+</sup>	0.044
<b>Years Marijuana (SD)</b>	14.2 (12.5)	0.104	0.182	0.024	0.761
<b>Years Hallucinogens (SD)</b>	2.8 (6.6)	0.077	0.370	-0.018	0.831
<b>Years Injecting (SD)</b>	15.4 (12.3)	-0.076	0.373	-0.114	0.180

	Total (n=171; df=169)	Positive Symptoms <sup>+</sup>		Negative Symptoms <sup>++</sup>	
		Pearson's r	p-value	Pearson's r	p-value
Age First Use Marijuana (SD)	18.5 (5.4)	-0.054	0.481	-0.095	0.217
Age First Use Cocaine (SD)	21.2 (9.0)	0.017	0.833	-0.002	0.978
Age First Use Psychostimulants (SD)	21.6 (8.9)	0.009	0.911	0.002	0.977
Age First Use Hallucinogens (SD)	16.7 (3.9)	0.061	0.459	-0.076	0.355
Age First Use Opioids (SD)	23.7 (9.4)	-0.044	0.587	0.044	0.580
Age First Injection (SD)	22.8 (9.0)	-0.023	0.785	0.095	0.258

<sup>+</sup>Positive Symptoms = Sum of PANSS items P1, P3, P5, P6, G9, and G12

<sup>++</sup>Negative Symptoms = Sum of PANSS items N1, N2, N3, N4, N6, G7, G13, G16

#### 4.3.4 NEGATIVE SYMPTOM SEVERITY MULTIVARIATE ANALYSIS

In a multiple regression model, negative symptom severity was treated as the dependent variable with the pre-screened variables opioid frequency of use in the past 28 days, alcohol frequency of use in the past 28 days, total years of regular alcohol use, age, gender, education, frequency of cocaine used in the past 28 days, and years of injecting psychostimulants were entered as independent variables. Frequency of opioid use in the past 28 days was the only independent variable that explained a significant amount of the variance in the regression model ( $p=0.002$ ).

For each week of opioid use in the past 28 days, negative symptom severity increased by 0.91 points.

The model explained 8.2% of the variation in negative symptoms as measured with the PANSS ( $R=0.286$ ,  $R^2=0.082$ , ANOVA  $F(3, df)=6.014$ ,  $p=0.003$ ). Individual regression coefficients can be found in Table 2. No significant interaction effects were present between any of the predictor variables (all  $p>0.08$ ).

**Table 4.2 Multivariate Analysis for Positive and Negative Symptom Severity Models**

		<b>Multivariable</b>		
		$\beta$ -Unstandardized (Std Error)	$\beta$ -Standardized	p-value
<b>Positive Regression</b>	MA Frequency (weeks/previous month)	0.518 (0.259)	0.152	0.045
	MJ Frequency (weeks/previous month)	0.378 (0.189)	0.157	0.043
	Methadone Status (0=abstinent, 1=positive)	-1.331 (0.594)	-0.169	0.026
<b>Negative Regression</b>	Opioid Frequency (weeks/previous month)	0.910 (0.287)	0.267	0.002
	Regular Years Injecting Psychostimulants	-0.073 (0.038)	-0.159	0.059

#### **4.3.5 SUPPLEMENTARY ANALYSIS**

##### *4.3.5.1 SPECIFIC SYMPTOM SUPPLEMENTARY ANALYSIS*

In an exploratory analysis, increased delusions (P1), grandiose thoughts (P5), and unusual thought content (G9) were all significantly associated with both increased methamphetamine frequency and marijuana frequency, while methadone-positive status was associated with diminished delusions (P1). Increased opioid frequency was specifically associated with increased negative symptoms of emotional

withdrawal (N2), social withdrawal (N4), and motor retardation (G7). As a secondary analysis exploring specific components of results from the primary analysis, a Bonferroni correction was not applied to the multiple correlations tested.

#### *4.3.5.2 COCAINE FREQUENCY SUPPLEMENTARY ANALYSIS*

Cocaine frequency was not correlated with current positive symptom severity when all methamphetamine users were excluded ( $n=112$ ;  $df=110$ ; Pearson's  $r=-0.025$ ,  $p=0.793$ ), or when analyzing cocaine and concurrent cocaine/methamphetamine users ( $n=145$ ;  $df=143$ ; Pearson's  $r=-0.005$ ,  $p=0.954$ ). When cocaine powder users were compared to cocaine crack users, no statistical difference in symptom severity was present in either cocaine sub-group ( $n=122$ ;  $df=120$ ;  $t=0.602$ ,  $p=0.549$  //  $n=144$ ;  $df=142$ ;  $t=1.308$ ,  $p=0.193$ ).

## **4.4 DISCUSSION**

In a sample of polysubstance using individuals with psychostimulant dependence, we report that the severity of current positive psychotic symptoms – primarily the severity of delusions – is significantly related to methadone-abstinent status and an increased frequency of methamphetamine and marijuana use in the past 28 days. Current negative psychotic symptoms were not associated with any of the predictors of positive symptom severity, though they were significantly related to the frequency of opioid use in the past 28 days. Cocaine frequency of use was unrelated to symptom severity.

The largest contributor to current positive symptom severity was the frequency of methamphetamine use in the past 28 days. The relationship between methamphetamine and psychosis severity is supported by a literature describing frequency of methamphetamine use as a major predictor of categorically defined psychosis (Farrell et al., 2002; Hall et al., 1996). McKetin et al. (2013) followed methamphetamine users longitudinally to demonstrate a strong dose-dependent relationship between frequency of methamphetamine use and the presence of a clinically significant psychotic symptom.

Increased lifetime duration of psychostimulant use (Lecomte et al., 2013; Lichlyter et al., 2010) and earlier age of first psychostimulant use (Farrell et al., 2002; Lichlyter et al., 2010; Power et al., 2014; Roncero et al., 2014; Vorspan et al., 2012) have also been associated with the presence of psychotic symptoms.

The frequency of marijuana use in the past 28 days was also a significant contributor to the variance seen in current positive symptom severity. Thus increased use of marijuana in psychostimulant dependent individuals was associated with more severe psychosis. The hypothesized link between marijuana and the development of organic psychoses has long been recognized, with leading theories suggesting that marijuana can precipitate psychosis in otherwise vulnerable individuals (Caspi et al., 2005; Degenhardt et al., 2003; Henquet et al., 2005; Murray et al., 2007). Studies exclusively investigating cocaine users found that early marijuana exposure was a risk factor for cocaine-dependent individuals to develop cocaine-induced psychosis (Kalayasiri et al., 2010). Additionally, meta-analysis has shown that continued marijuana use after psychosis onset predicts higher relapse rates and more severe positive symptoms than individuals who discontinue marijuana use (Schoeler et al., 2016). However, a common alternative explanation for the marijuana / psychosis correlation is one of “self-medication”, whereby persons experiencing prodromal symptoms use marijuana to self-medicate their distress (Hambrecht et al., 2000; Henquet et al., 2005). Bianconi et al (2016) have suggested that the association between marijuana and psychosis may be due to a hypersensitivity in individuals with past psychotic experiences, leading to greater substance-induced euphoria, while also exacerbating psychotic symptoms. Conclusions regarding marijuana in the current study should be tempered by the fact that all participants were concurrently dependent on psychostimulants.

A relationship between positive symptoms and methamphetamine or marijuana frequency of use is consistent with existing literature on risk factors for psychostimulant associated psychosis (Farrell et al.,

2002; Kalayasiri et al., 2010; Lichlyter et al., 2010; McKetin et al., 2006). In contrast to expectation, no association between frequency of cocaine use and positive or negative symptom severity was observed. This may reflect the relatively more severe physiological effects of methamphetamine when compared to cocaine (Cook, 1991; Mahoney et al., 2008). Mahoney et al. (2008) showed that in a direct comparison of methamphetamine dependent to cocaine dependent individuals, psychotic symptoms were observed more frequently in the methamphetamine group, in both abstinent and intoxicated states. Furthermore, the longer half-life of methamphetamine may result in greater sleep deprivation which could contribute to psychosis (Ciccarone et al., 2011; Mahoney et al., 2014; Ujike and Sato, 2004). In the present study, when methamphetamine users were excluded in supplementary analysis, the frequency of cocaine use was still not related to positive symptom severity. The absence of a relationship between the severity of positive symptoms and cocaine use was not expected. It can be suggested that one factor involved may be related to recorded patterns of cocaine ingestion. The Time Line Follow Back questionnaire is not able to determine if subjects consumed cocaine as part of a binge, which could increase the likelihood of positive symptoms (Kalayasiri et al., 2006b), compared to a pattern of “chipping”, a frequent use of small amounts, which is a consumption pattern common in cocaine users.

The final contributor to current positive symptom severity was methadone status, whereby methadone use was associated with decreased symptom severity. In the context of organic psychoses, dual-diagnosis schizophrenia patients with opioid dependency exhibited decreases in psychiatric symptom severity over the course of methadone treatment (Cacciola et al., 2001; Maremmani et al., 2007; Pani et al., 2003). Additionally, case studies have reported reduced psychotic symptoms with methadone treatment in schizophrenia patients with concurrent opioid dependency (Brizer et al., 1985; Pacini et al., 2005; Walby et al., 2000). While the biological mechanisms underlying this effect remain unknown, a preclinical investigation reported that methadone exposure causes long-term reductions in striatal

dopamine D2 receptor density (Allouche et al., 2015). This indicates that methadone may directly affect dopaminergic signalling, potentially modifying the same neural substrates implicated in psychosis (Crayton et al., 1968). Farrell et al. (2002) have suggested that reductions of arousal levels from opioid use may be a proxy for the observation of an ‘antipsychotic effect’ of opioids. The current findings suggest a specific association between methadone and delusions, a hallmark symptom of psychosis unrelated to arousal levels.

In addition to the novel findings for positive symptoms, the present study is one of the few to address predictors of the negative symptoms presented in psychostimulant-associated psychosis. Negative symptoms are often thought of as less severe and/or prevalent in psychostimulant-associated psychosis than schizophrenia (Srisurapanont et al., 2003; Zorick et al., 2008). In contrast, a more recent factor analysis found that the severity of negative symptoms of methamphetamine-associated psychosis did not differ to those present in schizophrenia (Srisurapanont et al., 2011). The current results suggest that while negative symptoms may appear to be present in psychostimulant users, the severity of these symptoms are associated not with psychostimulant abuse, but rather with opioid drug effects. Future studies investigating negative symptoms in polysubstance users should ensure that the effects of opioids are carefully controlled for. This may help in differentiating idiopathic psychosis and psychostimulant-associated psychosis, when prominent negative symptoms are present. The current data also suggest that the two conditions are not necessarily part of the same continuum, which has been suggested (Bramness et al., 2012).

The approach of investigating psychosis as a continuous variable allowed us to identify risk factors pertaining to the variation within psychosis severity (van Os et al., 2014b). While an approach of viewing psychosis as a categorical outcome is clinically useful for diagnostic purposes, valuable information is sacrificed with the establishment of this dichotomy. If the defined cut-off is set too low, important

variation within the context of psychotic experiences will be ignored. If the cut-off is set too high, individuals presenting with mild symptoms will be unrealistically grouped with individuals experiencing no symptoms (Royston et al., 2006). Additionally, by using a continuous approach, investigations are better equipped to capture temporally pertinent relationships between variables of interest and psychosis. This approach does not explain why many psychostimulant users never experience a psychotic episode, but it does identify the major predicting variables of the current severity of psychosis. This may provide clinicians tangible targets for therapeutic intervention of acutely-ill individuals – instead of reporting vague risk factors.

The final linear regression model significantly predicted positive symptom severity in a psychostimulant dependent sample, but the model accounted for only a modest proportion of the variation seen in symptom severity. This highlights the complexity of clinical presentation where comorbidities and multiple mediating factors may be contributing to symptom severity. In this regard, many predisposing factors beyond the scope of the study were not included here, such as genetic vulnerabilities, stress exposure, trait impulsivity, past psychotic experiences (number and duration), and sleep (Taylor et al., 2013). Additionally, self-report was a major source of the substance use data used for this study. Though general use was confirmed by a urine drug screen, current psychostimulant users may not be fully reliable sources of information for past histories of use. Also, the degree of polysubstance abuse in this population was likely a source of complex interactions and variability – though we believe that the prevalent comorbidities dealt with here are an accurate representation of the reality of living in a marginalized, urban population.

#### **4.5 CONCLUSION**

The results suggest that the frequency of methamphetamine and marijuana use is associated with the severity of positive symptoms experienced by psychostimulant dependent individuals. In contrast, the

severity of negative symptoms may be related to independent factors, such as opioid use. Additionally, an “antipsychotic”-like effect of methadone warrants further study. These findings may have direct and translational clinical implications, suggesting the frequency of methamphetamine and marijuana use as a tangible target for reducing current psychotic symptoms in individuals with comorbid polysubstance abuse and psychosis.

## **CHAPTER 5: OVERALL CONCLUSION**

The goal of this thesis was to examine what components differentiate cocaine dependent individuals who haven't developed psychosis from cocaine dependent individuals with substance-induced psychosis. These differences were characterized neuroanatomically in both subcortical gray matter structures and in white matter pathways. Additionally, factors related to the severity of psychotic symptoms were investigated for their respective effects. Overall, the identified differences largely encompassed components that have been previously identified as abnormal in the schizophrenia literature.

### **5.1 GRAY MATTER**

Smaller gray matter volumes of the thalamus and left hippocampus were present in cocaine dependent individuals with psychosis compared to those without psychosis. There was a higher prevalence of methamphetamine and marijuana dependence in those with psychosis, though accounting for these factors did not eliminate the statistical findings observed in gray matter difference. This was the first investigation of subcortical gray matter volumes in cocaine dependent individuals with concurrent psychosis. This suggests that gray matter volume reductions in specific subcortical nuclei may be common to multiple forms of psychosis.

### **5.2 WHITE MATTER**

Reductions in white matter integrity in cocaine dependent subjects with SIP were observed as measured by reduced fractional anisotropy (FA) and increased radial diffusivity (RD) in fronto-temporal, fronto-thalamic, and interhemispheric white matter pathways, compared to cocaine-dependent subjects without psychosis. Alterations in radial, but not axial, diffusivity may reflect deficits in white matter microstructural integrity, including damage to either myelin or the cellular membrane. The present

study is the first to suggest a structural white matter biomarker in SIP. These pathways parallel those implicated in schizophrenia, suggesting that damage to these pathways may be a shared factor in the expression of different forms of psychosis.

### **5.3 SYMPTOM SEVERITY**

Increased frequency of methamphetamine use and marijuana use in the past 28 days and methadone abstinence were significantly related to an increased severity of positive clinical symptoms of psychosis, primarily in the severity of delusions. These parameters of substance use did not concurrently explain the severity of negative clinical symptoms of psychosis. These findings suggest a tangible target for reducing current psychotic symptoms in individuals with comorbid polysubstance abuse and psychosis.

### **5.4 INTEGRATED DISCUSSION**

In summary, this thesis identified several factors that differentiate psychostimulant users who develop psychosis from those who do not. These differences were found to be multimodal, present in both gray and white matter structures, and similar to differences previously identified as abnormal in the schizophrenia literature. These data suggest that many of the same risk factors and deficits associated with schizophrenia spectrum disorders are also relevant to SIP.

Collectively, the results presented suggest that parameters of methamphetamine use and marijuana use are related to psychosis. In neuroanatomical investigation, there was a significantly higher prevalence of methamphetamine dependence and marijuana dependence in the SIP group (Chapter 3). Regression analysis showed that recent frequency of both methamphetamine and marijuana use was associated with increased positive symptom severity, but not negative symptom severity (Chapter 4). There is a dearth of literature in regards to the prevalence and severity of negative symptoms in SIP, leaving the issue and ongoing item of debate (Panenka et al., 2013; Srisurapanont et al., 2011; Zorick et al., 2008). In our studies, negative symptoms continue to yield unanswered conclusions. In the gray matter

investigation there were no statistical differences between psychotic and nonpsychotic groups (Chapter 2.3.1), while there were significantly more severe negative symptoms associated with SIP in the white matter investigation (Chapter 3.3.1). When investigated directly in regression analysis, negative symptoms were associated with the frequency of recent opioid use (Chapter 4.3.4), but showed no associations with substances related to the positive symptoms of psychosis. Collectively, the data suggests that though negative symptoms may be present in SIP, they are of less magnitude than positive symptoms and likely arise through different mechanisms.

## **5.5 STRENGTHS AND LIMITATIONS**

The research presented in this thesis collectively represents many novel additions to the current literature of substance-induced psychosis. Here, the first ever structural investigations of SIP related to cocaine use, as well as the first ever diffusion tensor imaging investigation of SIP was reported. Additionally, this was the first study to describe the association between substance use and the severity of negative symptoms. All of the analyses exclusively investigated individuals with current psychostimulant dependence, eliminating the common confound of psychostimulant exposure in past investigations of SIP. Additionally, all diagnoses were made according to DSM-IV-TR guidelines by qualified psychiatrists, addressing inconsistencies in the research literature regarding how SIP is defined.

Conclusions from the investigations are limited due to restraints of study design. The absence of a cocaine-naïve control group leaves unanswered questions regarding the magnitude of the differences observed. It may be that the individuals without psychosis show no differences when compared to a healthy control group. Similarly, the absence of a schizophrenia group prevents a direct comparison between psychoses, again leaving unanswered questions relating to the magnitude of differences observed. Another potential limitation is that the diagnostic certainty of substance-induced psychosis as opposed to a primary psychotic disorder with concurrent substance use cannot be completely certain, as

diagnoses of SIP are sometimes later diagnosed as a schizophrenia spectrum disorder (Caton et al., 2007). The effects of acute substance abuse, though balanced in the models investigated in this thesis, may have led to varying individual acute 'states of mind' at the time of the clinical interview, which may or may not have had an effect of self-report data. And finally, the data values utilized in the neuroimaging studies (Chapters 2 and 3) may have been influenced by imaging quality issues (i.e. motion, field inhomogeneity). However, in the current studies images were collected at high field to optimize signal-to-noise ratios, carefully screened for motion and susceptibility artifacts and appropriate eddy current corrections were employed in the imaging pipeline.

## **5.6 IMPLICATIONS FOR FUTURE STUDIES**

In this thesis, data from cross sectional analysis has suggested that there are structural correlates that differentiate psychostimulant dependent individuals who develop psychosis compared to those who do not. Due to cross sectional study design, whether these structural correlates represent pre-psychosis neurodevelopmental abnormalities or hypersensitive responses to the neurotoxic effects of chronic psychostimulant exposure remains unknown.

As the Hotel Study is an ongoing longitudinal study with annual MRI scans, structures of interest can be tracked over time. Through this approach, it will be possible to investigate if identified differences are neurodevelopmental in nature or reflect an accumulation of environmental stressors. As SIP is theoretically a transient psychosis, sustained only with continued substance abuse, there will be subgroups of individuals who continue to present psychotic symptoms, while the symptoms of others will recede. This scenario presents an opportunity to investigate the relationship between the clinical state of mind and the structural state of brain. As viable structural targets have been identified in this thesis, it is now possible to track individual differences over time. Whether differences arise between

the structural trajectories of individuals with continuous psychosis versus those that attain psychosis abstinence, informative insights regarding the nature of psychosis are now investigable.

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