Structural Brain Markers are Differentially Associated with Neurocognitive Profiles in Socially Marginalized People with Multimorbid Illness

by

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Ethics Statement

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Abstract

Homeless and marginally housed individuals constitute a socially impoverished population characterized by high rates of multimorbid illness that includes polysubstance use, viral infection, and psychiatric illness. Their extensive exposure to risk factors is associated with numerous poor outcomes, yet little is known about structural brain integrity and its association with neurocognition in this population. In Study 1, we conducted a cluster analysis to re-construct three previously derived subgroups with distinct neurocognitive profiles in a large sample of socially marginalized persons (N = 299). Cluster 1 (n = 87) was characterized as highest functioning overall, whereas Cluster 3 (n = 103) was the lowest functioning neurocognitively, with a relative strength in decision-making. Cluster 2 (n = 109) fell intermediate to the other subgroups, with a relative weakness in decision-making. Next, we examined the association between complementary fronto-temporal cortical brain measures (gyrification, cortical thickness) and neurocognitive profiles using multinomial logistic regression. Chi-square tests and ANOVAs differentiated subgroups on proxy measures of neurodevelopment and acquired brain insult/risk exposure. We found that greater frontal and temporal gyrification and more proxies of aberrant neurodevelopment were associated with Cluster 3 (lowest functioning subgroup). Further, age moderated the association between orbitofrontal cortical thickness and neurocognition, with positive associations in older adults, and negative associations in younger adults. Finally, greater acquired brain insult/risk exposure was associated with the cluster characterized by selective decision-making impairment (Cluster 2), and the higher functioning cluster (Cluster 1). In Study 2, we examined the association between white matter integrity and neurocognitive profiles using multinomial logistic regression and Tract-based Spatial Statistics. We found significantly lower fractional anisotropy (FA), with corresponding increased axial and radial diffusivity (AD, RD) in widespread and bilateral brain regions of Cluster 3. Differences in RD were more prominent compared to AD. Altogether, our findings highlight the unique pathways to neurocognitive impairment in a heterogeneous population and help to clarify the vulnerabilities confronted by different subgroups.

Keywords: neurocognition; structural brain imaging; diffusion tensor imaging; cluster analysis; marginal housing; multimorbidity

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Finally, I would like to express gratitude for my dear family and friends. To my many friends near and far, you know who you are – thank you for always keeping my spirits uplifted. To my partner Tyler – the love and laughter you bring to my life is deeply cherished. Last, but certainly not least, I am very grateful for a lifetime of love, support, and nurturance from my family. To my parents, Diana and Todd, brothers Steven and Tyson, Auntie Jackie, and grandparents Omi and Papa – thank you from the bottom of my heart.

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List of Acronyms

ACC	Anterior cingulate cortex
AD	Axial diffusivity
CT	Cortical thickness
DTES	Downtown Eastside
DTI	Diffusion tensor imaging
EPS	Extrapyramidal symptoms
ERC	Entorhinal cortex
FDT	FMRIB Diffusion Toolbox
FMRIB	Functional Magnetic Resonance Imaging of the Brain
HIV	Human immunodeficiency virus
HVLT	Hopkins Verbal Learning Test
IDED	Intra-Dimensional Extra-Dimensional
IGT	Iowa Gambling Task
lGI	Local gyrification index
lOFC	Lateral orbitofrontal cortex
mOFC	Medial orbitofrontal cortex
MRI	Magnetic resonance imaging
NSS	Neurological soft signs
PANSS	Positive and Negative Syndrome Scale
RD	Radial diffusivity
ROI	Region of interest
RVIP	Rapid Visual Information Processing
SPSS	Statistics Package for the Social Sciences
SRO	Single-room occupancy
TBI	Traumatic brain injury
TBSS	Tract-based spatial statistics
WTAR	Wechsler Test of Adult Reading

Chapter 1. General Introduction

Individuals who are homeless or marginally housed comprise a heterogeneous, socially impoverished population. Marginal housing is a common solution in concentrated urban centers, providing basic shelter to people of low socioeconomic status who are on the brink of homelessness. These housing solutions, however, are often characterized by precarious, unstable, and substandard living conditions (Vlahov et al. 2007). Not surprisingly, the interface between marginal housing and homelessness is dynamic, whereby significant portions of marginally housed persons report previously being homeless, and many will transition to homelessness again (Hwang et al. 2011). Across these settings, co-occurring polysubstance use, infectious disease (e.g., HIV, Hepatitis C), and severe psychiatric illness are commonplace (Fazel et al., 2008; Robertson et al. 2004; Shannon et al. 2006; Vila-Rodriguez et al., 2013). Notably, the rate of reported comorbid substance use and psychiatric illness is upwards of 50% (Fazel et al., 2014; Krausz et al. 2013). These individuals also experience greater severity of psychiatric illness when compared to persons of low socioeconomic status with stable housing (Eyrich-Garg et al. 2008). The deleterious impact of multimorbidity is further compounded by significant barriers to accessing and engaging with health care, despite the fact that it is universally available in Canada (Argintaru et al., 2013).

Multimorbidity is an evolving, large-scale concern. Worldwide, comorbid mental and physical chronic disease has been linked with overall poorer health outcomes (Moussavi et al. 2007). A marked example of this comes from the Downtown Eastside (DTES) of Vancouver, BC – a neighborhood known as the poorest postal code in Canada. Our recent investigations of a large cohort dwelling in this region found that greater drug-related harm was associated with a 1.43-fold increase in multimorbidity (Jones et al., 2013). In the same sample, greater multimorbidity (physical and psychiatric illness) was found to be associated with poorer social and role functioning (The Hotel Study; Vila-Rodriguez et al., 2013). At present, the mortality rate in this

sample is 8.29 times what would be expected for an age- and sex-matched Canadian cohort (Jones et al., 2015). This finding is in keeping with a study using Canadian population data with similarly high rates of mortality reported for the homeless and marginally housed, compared to those with low-income alone (Hwang et al., 2009).

Multimorbidity has enormous social consequences that cannot be overlooked. Despite freely available health care in Canada, there continues to be increased use of the emergency room, ambulatory care, and hospitalizations in homeless and marginally housed persons. Estimated annual health care costs for homeless persons within in a major Canadian urban centre were reported to be far greater than the costs incurred by age- and sex-matched low income persons (6.67 million USD versus 1.5 million USD[1] annually; Hwang et al., 2013). These statistics do not include additional health care costs that come from longer hospital stays (Hwang, Weaver, Aubry, & Hoch, 2011), and use of other public services, such as the justice system, treatment programs, and housing supports (Stergiopolous et al., 2015). Even though established treatments exist for some of the most prevalent clinical conditions in this population, the current platforms for health service delivery are poor (Honer et al., 2016) and the reported rate of unmet health care needs continues to be high (Argintaru et al., 2013). This is most evident in our team's recent findings whereby increased mortality in persons below the age of 55 was linked with hepatic fibrosis and psychosis, both of which are treatable illnesses (Jones et al., 2015). The evolving interest in this significant public health issue has led to several intervention studies (Smith, Soubhi, Fortin, Hudon, & O'Dowd, 2012) and policy recommendations (Fazel, Geddes, & Kushel, 2014) that aim to challenge the traditional health care model that emphasizes treatment of single disorders, as oppose to comorbid conditions. However, determining the effectiveness of these approaches is precluded by existing gaps in the literature on the nature of multimorbid populations, especially within a socially marginalized context. Altogether, we are left with two major social challenges to address: 1) how to appropriately treat the epidemic of multimorbidity; and 2) how to prevent multimorbidity in the first place.

[1] Note that these statistics are derived from Canadian data but are reported in US dollars.

The current dissertation offers one potential avenue to address these outstanding issues by examining the association between distinct neurocognitive profiles and various structural brain measures in a sample of persons dwelling in the DTES. Characterizing neurocognition is an important starting point given that it plays a central role in facilitating successful execution of everyday real-world activities in healthy and clinical populations (Fett et al., 2011; Morgan & Heaton, 2009). It is instrumental to complex activities such as medication adherence, financial management, driving ability, and interpersonal communications (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009), all of which are especially relevant to a multimorbid population who already face numerous socioeconomic and psychosocial barriers that directly impact daily functioning. Indeed, neurocognition appears to have a unique contribution to real-world functioning even when other factors such as housing status and psychiatric symptoms are accounted for in marginalized persons (Stergiopoulos, Burra, Rourke, & Hwang, 2011). Schutt and colleagues (2007) identified executive functioning, memory, and sustained attention as key predictors of community functioning in persons with severe mental illness and a history of homelessness. Moreover, the associations between neurocognition and community functioning varied by social context (living independently versus in a group home environment). Recent efforts to develop more effective housing interventions for the homeless and unstably housed persons have been reasonably successful (Stergiopolous et al., 2015), but the findings from Schutt and others (2007) highlight the importance of delineating neurocognitive profiles and their potential to inform such interventions.

Strikingly, little is known about neurocognitive outcomes and the associated risk factors in marginally housed and homeless persons; yet, the prevalence of neurocognitive impairment appears to be remarkably high as demonstrated by only a handful of relevant reports. For example, in a large Canadian cohort of homeless adults, 72% were reportedly impaired, with the most prominent deficits in verbal learning and memory (Stergiopoulos et al., 2015). These findings correspond with our work investigating the marginally housed (Gicas et al., 2014), as well as with few additional existing studies suggesting the presence of broad impairments in the core domains of memory, attention, processing speed, and executive functioning (Burra, Stergiopoulos, & Rourke, 2009; Pluck, Lee, David, Spence, & Parks, 2012). However, the majority of the

existing literature is limited by the use of global or single measures of neurocognition and much of the variability in neurocognitive outcomes remains unexplained (Stergiopoulos et al., 2015).

Given the heterogeneity in this population, there are apt to be multiple pathways to neurocognitive impairment. Our previous work used cluster analysis to derive distinct neurocognitive profiles, enabling us to respect the inherent heterogeneity of this population while at the same time identifying more homogeneous subgroups defined on the basis of neurocognitive functioning (Gicas et al., 2014). This kind of neurocognitive subtyping is well suited to heterogeneous populations, such as schizophrenia and traumatic brain injury, and has demonstrated considerable clinical utility (Allen & Goldstein, 2013). For example, neurocognitive subtypes identified in schizophrenia were found to differentially predict functional outcomes and lifetime response to treatment (Gilbert et al., 2014). On the other hand, in healthy adults over 80 years old, distinct neurocognitive profiles were useful in validating theoretical models of neurocognitive aging thought to reflect various forms of brain pathology (Gawron et al., 2014). Developing a viable taxonomy of neurocognitive functioning in a population with varied exposure to risk factors for impairment is an ideal approach to characterizing the variability in neurocognition, which will enable us to identify subgroups at greatest risk for poor clinical and functional outcomes. However, the links between structural brain integrity and neurocognition have not been systematically investigated in marginalized persons despite the multimorbid burden that is apt to negatively impact brain structure. Indeed, in our initial investigations, nearly half of the Hotel sample met criteria for a neurological illness, with 28% evidencing pathological MRI findings (Vila-Rodriguez et al., 2013). Therefore, this presents as a fruitful investigative angle to better understand the neurobiological vulnerabilities of this population.

The extent to which the current neurocognitive profiles have different neuroanatomical underpinnings is of great interest for three primary reasons. First, by delineating the structure-function relationships, we can further establish the validity of the neurocognitive profiles as representing meaningful subgroups within a larger, heterogeneous population. Structural brain markers have a more direct association with neurocognition compared to external variables, such as substance use or psychiatric

illness, which were used previously to validate the profiles (see Gicas et al., 2014). Second, although structure-function associations are variable across the lifespan, they tend to be stronger in older adults (Burzynska et al., 2012; Raz & Rodrigue, 2006) and in the context of psychopathology (Premkumar, Kumari, Corr, Fannon, & Sharma, 2008). This highlights that brain health is especially critical to optimal functioning in a middle-aged, multimorbid population and thus may be a useful biological target for early interventions. Third of all, brain markers may provide us with a unique lens with which to study the putative broad-level etiologies of neurocognitive impairment, such as those arising from developmental, environmental, and biological factors. For instance, abnormal brain development is thought to lie at the core of schizophrenia (Marenco & Weinberger, 2000). Along the environmental dimension, distinct frontal-subcortical brain abnormalities have been linked with duration of substance dependence (Ersche, Williams, Robbins, & Bullmore, 2013). Additionally, subtle brain structure differences between neurocognitive profiles have demonstrated utility in discriminating normal aging versus dementia (Jacobson, McEvoy, Dale, & Fennema-Notestine, 2009). Altogether, knowledge of the neuroanatomical substrates of neurocognition could provide viable targets for clinical, pharmacological, and functional-based treatments to improve overall outcomes.

In an extension of our previous investigation (Gicas et al., 2014), the primary objective of this dissertation was to address a key gap in the literature by exploring the neuroanatomical underpinnings of neurocognition in a multimorbid, marginalized sample. We present two independent but complementary studies using advanced neuroimaging technologies to investigate the structural properties of gray and white matter in the brain and how they differentiate previously defined neurocognitive subgroups. This represents a novel and comprehensive investigation that provides a necessary foundational characterization of brain-behaviour associations in a marginalized population. Ultimately, this is of direct relevance to strategic health care delivery in which we can better address questions regarding who requires what kind of services and identify those who require the most intensive services in order to optimize lifetime health outcomes.

Chapter 2. Study 1: Introduction

In the first part of our investigation, we elected to focus on the link between cortical brain structure and neurocognition. Cortical gray matter is sensitive to change across the normal adult lifespan (Hogstrom, Westlye, Walhovd, & Fjell, 2013) and has been extensively studied in a vast number of clinical populations. Although gray and white matter are both vulnerable to the effects of neurotoxins and aging, degradation in cortical gray matter is reported to be more strongly associated with neurocognitive impairments (He et al., 2012). In the discussion to follow, we provide a rationale for examining individual and complementary cortical parameters, as well as a description of the neurocognitive profiles with which we aim to differentiate on the basis of cortical brain measures.

2.1. Cortical Parameters

Traditionally in imaging studies, cortical volume has been used as the primary means to index cortical changes and/or abnormalities. Volumetric measurements represent a composite measure of cortical thickness and surface area. However, this is problematic for several reasons. First, although cortical thickness and surface area are

both heritable features of cortical architecture, they have very distinct genetic contributions across the cortical mantle suggesting that they represent unrelated brain measures (Panizzon et al., 2009; Winkler et al., 2010). Second of all, cortical thickness and surface area follow different developmental trajectories (Wierenga, Langen, Oranje, & Durston, 2014). Further, across the adult lifespan, cortical thickness and surface area appear to be differentially affected by the aging process, with greater reductions in thickness relative to surface area and volume (Lemaitre et al., 2012; Storsve et al., 2014) and with varying predilections for brain regions across the frontal and temporal cortices (Hogstrom et al., 2013; Storsve et al., 2014). Finally, studies have demonstrated that cortical thickness may be more sensitive to changes associated with normal (Hutton, Draganski, Ashburner, & Weiskopf, 2009) and pathological (Burggren et al., 2008) aging, suggesting that volumetric measurements may not be the optimal choice when investigating cortical gray matter changes.

These measures can be contrasted with gyrification. Whereas cortical thickness and surface area are considered to be dynamic across the lifespan, the gross folding patterns of the cortex begin in utero during the last trimester of pregnancy, stabilize soon after birth, and subsequently undergo only subtle changes into adolescence (Armstrong, Schleicher, Omran, Curtis, & Zilles, 1995; White, Su, Schmidt, Kao, & Sapiro, 2010). Although small decreases in gyrification can be observed with increasing age, these are likely attributed to corollary reductions in surface area and opening of sulci rather than significant changes in the gyri themselves (Hogstrom et al., 2013).

For the current study, we used a surface-based method of imaging analysis, a gold-standard in the imaging field, to parse complementary aspects of cortical structure (Hogstrom, Westlye, Walhovd, & Fjell, 2013) as a means to provide insight into factors that may contribute to neurocognitive impairment. We specifically chose to examine thickness and gyrification as these can be considered to lie on a continuum of most dynamic to least dynamic, respectively, based on known developmental trajectories as noted above. Thus, this enables a differentiation of the neurobiological underpinnings of structural brain integrity by elucidating whether differences may be related to neurodevelopmental deviations versus lifetime environmental risk exposure. To illustrate, cortical folding is measured in 3-dimensional space using the local gyrification

index, which represents a ratio between the surface area buried within sulci to the surface area of the exposed cortex within a selected region of interest (Schaer et al., 2008). Given that gross gyrification of the brain is largely established at birth, deviations in basic neurodevelopmental processes in utero, as a result of genetic or environmental influences, can lead to hypo- or hyper-gyrification. Focal alterations in gyrification have been identified in neurodevelopmental disorders such as schizophrenia (Harris et al., 2007; Palaniyappan, Mallikarjun, Joseph, White, & Liddle, 2011), autism spectrum disorders (Libero, DeRamus, Deshpande, & Kana, 2014; Wallace et al., 2013), fetal alcohol spectrum disorders (Infante et al., 2015), and Williams syndrome (Fahim et al., 2012). However, gyrification represents a novel area of literature and findings are mixed, with reports of gyrification being increased, decreased, or variable by cortical subregion.

On the other hand, cortical thickness, which is measured as the distance (in millimeters) between the pial surface and the gray-white matter boundary (Fischl & Dale, 2000), is highly dynamic across the lifespan (Hogstrom et al., 2013; Schnack et al., 2015; Storsve et al., 2014). The frontal and temporal cortices are especially susceptible to thinning with normal age-related changes (Fjell et al., 2009; Lemaitre et al., 2012; McGinnis, Brickhouse, Pascual, & Dickerson, 2011; Raz and Rodrigue, 2006; Thambisetty et al., 2010) and with risk exposure, such as comorbid substance use disorders (Lawyer et al., 2010; Momenan et al., 2012), HIV infection (Holt, Kraft-Terry, & Chang, 2012), progression of psychiatric illness (Assunção Leme et al., 2013; Goldman et al., 2009; van Haren et al., 2011), and histories of concussion (Tremblay et al., 2013) or childhood abuse (Kelly et al., 2013). Together, gyrification and cortical thickness represent complementary cortical parameters that can be used to shed light on the extent to which structural brain integrity, with its presumed underpinnings, contributes to neurocognition in a very heterogeneous population.

2.2. Neurocognitive Profiles

In our prior report (Gicas et al., 2014), we statistically characterized three clusters with unique neurocognitive profiles across six domains – premorbid IQ, verbal memory, attention, inhibition, mental flexibility, and decision-making. The clusters were described

as follows: a) a higher functioning subgroup with generally intact abilities (Cluster 1); b) a lower functioning subgroup with generally impaired abilities, but with a relative strength in decision-making (Cluster 3); and c) a subgroup that fell intermediate to the others, with a selective and pronounced weakness in decision-making (Cluster 2). This statistical approach is ideally suited to managing the natural heterogeneity within our multimorbid sample by facilitating examination of within- and between-group patterns (Lange, Iverson, Senior & Chelune, 2002). These profiles are depicted in Figure 2.1. To provide further validation to the profiles, the clusters were meaningfully differentiated on numerous external variables, including sociodemographics, substance use, viral infection, negative symptoms, neurological soft signs, and risk-taking behaviour. A summary of these findings is presented in Table 2.1.

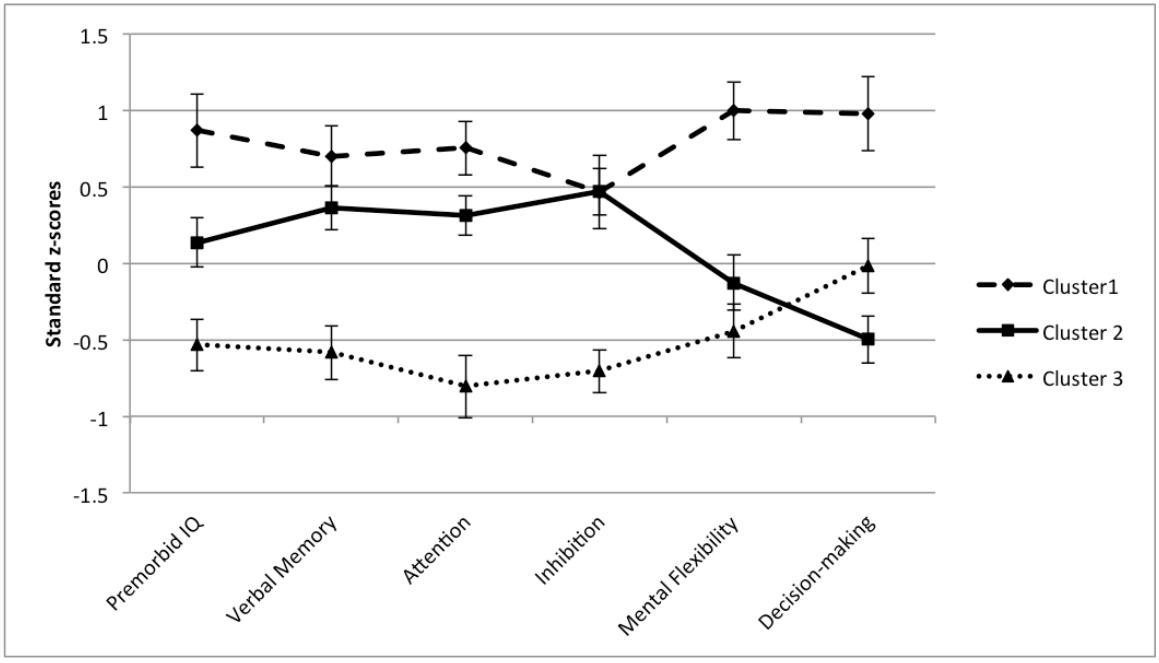

Figure 2.1 Profiles of mean neurocognitive scores for original clusters (N = 249). Errors bars represent 95% confidence intervals.

Note. Figure taken from Gicas et al. (2014).

Table 2.1 Descriptive Summaries of Neurocognitive Clusters

	Cluster 1	Cluster 2	Cluster 3
Neurocognition	Highest functioning group within the sample. Normatively, strong premorbid IQ, and average range attention and executive functions, with impaired memory.	Intermediate functioning group within the sample, with a relative weakness in decision-making skills. Normatively, average range premorbid IQ, attention, and inhibition, with impairments in memory, mental flexibility, and decision-making skills.	Lowest functioning group within the sample, with a relative strength in decision-making skills. Normatively, average range premorbid IQ, inhibition, and decision-making skills, with impairments in attention, memory, and mental flexibility.
External variables	More years of education, lower rate of HIV infection, lower total virus exposure, and less severe negative symptoms.	More heroin use, with trends towards more females, more injection drug use, less alcohol use, and more severe negative symptoms.	Less years of education, less heroin use, lower rate of heroin dependence, greater total virus exposure, more severe negative symptoms, and greater total neurological soft signs.

Note. Table taken from Gicas et al. (2014).

2.3. Objectives and Hypotheses

The primary objective of the current study was to further validate our previously derived neurocognitive profiles by differentiating them on cortical thickness and gyrification, which will ultimately shed light on the putative origins of structural brain differences and the associated neurocognitive impairments. To the best of our knowledge, these structural brain markers have never been examined in a multimorbid, marginally housed sample. Specifically, we linked neurocognition in marginalized persons to key cortical brain regions known to regulate inhibitory control, decision-making (anterior cingulate and orbitofrontal cortices; Miller & Cohen, 2001; Pujara & Koenigs, 2014), and memory (entorhinal cortex; Fjell et al., 2014; hippocampus; Van Petten, 2004). These regions of interest were selected *a priori* based on their known associations with neurocognitive functions that are represented in the previously derived neurocognitive profiles.

Based on the distinct neurocognitive patterns and their associated characteristics (see Figure 2.1 and Table 2.1), as well as literature suggesting differential sensitivity of cortical parameters (gyrification, cortical thickness) as described above, we formulated several hypotheses as follows:

1) *Decreased* regional fronto-temporal cortical thickness and *decreased* hippocampal volume will be associated with Cluster 3, the lowest functioning subgroup (compared to Clusters 1 and 2).

2) Regional fronto-temporal gyrification indices of Cluster 3 will significantly differ from Clusters 1 and 2, in alignment with a neurodevelopmental interpretation. This idea follows from the observation of lower premorbid functioning and greater psychiatric symptomatology in Cluster 3. However, the heterogeneity of findings within the gyrification literature precludes a directional hypothesis.

3) *Decreased* cortical thickness in the orbitofrontal cortex will be associated with Cluster 2 (compared to Clusters 1 and 3), given the circumscribed decision-making deficit in this subgroup.

4) Age will modulate the relationship between cortical thickness and neurocognitive clusters, with stronger associations in older individuals (Burzynska et al., 2012), given the malleability of cortical thickness across the lifespan.

5) A greater number of variables considered as proxy measures of developmental difficulties will be associated with Cluster 3, whereas a greater number of variables considered as proxies for acquired brain insult and risk exposure will be associated with Clusters 1 and 2. These will be considered as complementary analyses to the investigation of structural brain integrity.

Chapter 3. Methods

3.1. Participants

As part of a 10-year longitudinal investigation, a total of 371 participants were enrolled in the study between November 2008 and November 2014. Participants were recruited from four different single-room occupancy hotels (SROs; N = 306) located in the Downtown Eastside (DTES) of Vancouver, BC (see details in Vila-Rodriguez et al., 2013). To better capture the population of individuals living in this highly impoverished neighborhood, we recruited an additional 65 participants from outside the community courthouse, which is located in the DTES neighbourhood. All persons living in one of the four target SROs or persons dwelling in the DTES who had a community court date assigned within the previous six months were approached to participate in the study. Within the combined sample, the mean number of years spent on the DTES was 8.53 (Median = 6.87; SD = 7.53) with 71.6% of individuals reporting ever being homeless. The marginalization of this sample is further reflected in the high rates of unemployment (87%) and low mean monthly income in CAD (Mean = $859.13; Median = $825.00; SD = $396.98). A comparison of the sample characteristics of SRO and community court participants is presented in Table A1.

The inclusion criteria for the larger study were English fluency and either living in a SRO hotel or having contact with the community court within the previous 6 months. A flow diagram is presented in Figure 3.1 to outline participants retained for inclusion in the current study. To summarize, a total of 299 (of 371 recruited) had valid neurocognitive data and were included in our initial cluster analysis. Of the 299 clustered subjects, 211 had complete multivariate data and were included in our primary regression analysis. All participants provided written informed consent and received small honoraria for each assessment completed (clinical, neurocognitive, MRI). Ethics approvals were obtained from the Clinical Research Ethics Board of the University of

British Columbia in accordance with Tri-Council Policy, and the Simon Fraser University Office of Research Ethics. Additional details regarding study design and recruitment are provided in our previous work (Vila-Rodriguez et al., 2013; Jones et al., 2015). A description of the full clustered sample (N = 299) is provided in Table 3.1.

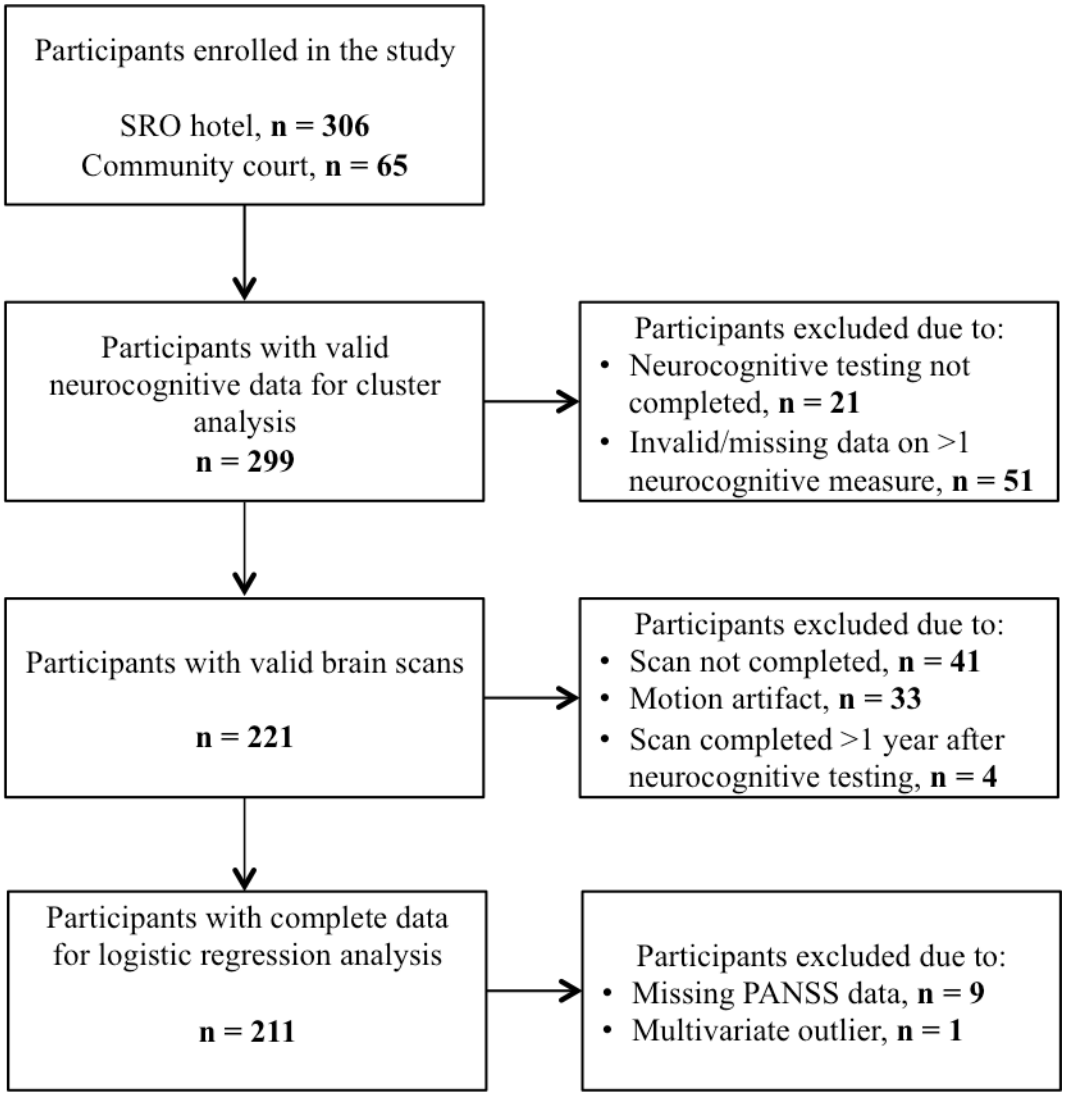

Figure 3.1 Flow diagram of participant inclusion.

Table 3.1 Sample Characteristics

Characteristic	%	*M* (*SD*)	*Mdn*	Range
Age (years)		43.3 (9.5)	44	23 - 68
Education (years)		10.4 (2.2)	10	3 - 16
Premorbid IQ (WTAR)		97.5 (8.8)	97	77 - 122
Symptoms of psychosis (PANSS)[a]				
Positive		15.3 (5.6)	14	7 - 36
Negative		16.2 (5.8)	15	7 - 39
General		36.0 (8.2)	35	19 - 59
Total		67.5 (16.6)	65	33 - 129
Gender (male)	78.6			
Ethnicity				
White	62.5			
First Nations	26.8			
Black	2.7			
Latino	0.7			
Other/Mixed/Unknown	7.3			
Psychiatric diagnosis				
Psychotic illness, any	46.2			
Mood disorder, any	28.1			
Anxiety disorder, any	26.8			
Substance Dependence Disorder				
Alcohol	15.7			
Cannabis	34.1			
Stimulant	83.9			
Opioid	43.5			
Viral infection				
HIV[c]	16.2			
Hepatitis C[d]	68.8			
Hepatitis B[e]	39.8			
Herpes simplex[c]	90.5			
Cytomegalovirus[e]	67.3			
Traumatic brain injury				
Possible	39.1			
Probable	14.7			
Definite	9.7			

Note. N = 299 unless otherwise specified. WTAR = Wechsler Test of Adult Reading; PANSS = Positive and Negative Syndrome Scale; BDI = Beck Depression Inventory; SOFAS = Social and Occupational Functioning Assessment Scale; RFS = Role Functioning Scale; NOS = Not otherwise specified.
[a]*N* = 283; [b]*N* = 285; [c]*N* = 296; [d]*N* = 295 [e]*N* = 294.

3.2. Materials and Procedures

3.2.1. Neurocognitive Assessment

Assessments were conducted by research assistants who were trained and supervised by a registered psychologist. Participants completed a battery of neurocognitive tests that included measures of premorbid IQ (Wechsler Test of Adult Reading (WTAR); Wechsler, 2001), verbal learning and memory (Hopkins Verbal Learning Test Revised (HVLT); Brandt & Benedict, 2001), color-word inhibition (Stroop Color-Word Test), sustained attention (Rapid Visual Information Processing subtest (RVIP); Fray, Robbins, & Sahakian, 1996), mental flexibility (Intra-Dimensional Extra-Dimensional subtest (IDED); Fray et al., 1996), and decision-making (Iowa Gambling Task (IGT); Bechara, Damasio, Damasio, & Anderson, 1994). These represent reliable and valid neuropsychological measures that are sensitive to impairments in a diverse range of clinical populations. Additional information on each of these measures, including psychometric properties, is reported in Appendix B.

Following completion of the neurocognitive assessment, the examiner subjectively rated the validity of each measure on the following scale: 1 = Clearly Invalid; 2 = Not Likely Valid; 3 = Questionably Valid; 4 = Most Likely Valid; 5 = Clearly Valid. These ratings were meant to provide an indication of whether the data obtained from tests reflected a reliable index of cognitive performance on the basis of observed adequate engagement in the testing process. Data rated as 4 or higher were retained for analyses, and all other ratings were individually inspected and cross-referenced against qualitative notes to verify rating accuracy. Reasons for invalid ratings could include, but are not limited to, participant intoxication, extreme fatigue, inability to adequately comply with test instructions, frustration, or equipment failures. Approximately 93% of the total sample that completed at least some of the neurocognitive battery had overall validity ratings of 4 or higher.

To assure English language fluency, we administered the English Language Acculturation Questionnaire. This measure includes 12 items which uses a 5-point scale to assess the degree to which an individual prefers to speak, think, read, and write

primarily in English. Scores range from 12 (very fluent in English) to 60 (not at all fluent in English). A score of 12 was automatically assigned to participants who reported being born in Canada and having learned English as their first language. We used a cut-off of 24 for the current study, which means participants were, on average, "much fluent in English". Only two cases exceeded the cut-off (scores of 26 and 28), but upon further inspection they were deemed appropriate for inclusion. In the current sample (N = 299), 92.6% reported being born in Canada and having learned English as their first language. Of the remaining participants, mean length of time residing in North America was 30.94 years (SD = 11.21), and mean age at immigration to North America was 14.41 years (SD = 10.45).

3.2.2. Clinical Assessment

Trained research assistants, psychiatrists, and/or neurologists conducted the clinical assessments. These sessions were scheduled at times independent from the neurocognitive assessments. Full details of the assessments are reported by Vila-Rodriguez et al. (2013). Details relevant to the current study are reported below with additional information regarding each measure included in Appendix C.

Developmental variables. Diagnosis of schizophrenia (and other psychiatric diagnoses, see Table 3.1) were rendered via consensus using the Best Estimate Clinical Evaluation and Diagnosis (Endicott, 1988), the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998), and a mental status examination, in accordance with criteria in the Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed., text revision, American Psychiatric Association, 2000). A history of special education or a modified curriculum in school was self-reported during a structured baseline interview. To assess neurological soft signs (NSS), a selection of items from the Cambridge Neurological Inventory was administered (Chen et al., 1995; see Table C1). All ratings were summed to yield a total NSS score, with higher scores representing worse neurological status. To assess extrapyramidal symptoms (EPS), the Extrapyramidal Symptom Rating Scale was administered (Chouinard & Margolese 2005). A total EPS score was derived by summing scores across the dimensions of dystonia, dyskinetic movements, and parkinsonism, with higher scores reflecting worse neurological status.

Acquired brain insult. Diagnoses of MRI pathology (stroke, hemorrhage, aneurysm) were made by a neuroradiologist according to definitions provided by Vernooij and colleagues (2007). Further, traumatic brain injury (TBI) was defined as follows: *none* (no reported history of a head injury); *possible* (reported loss of consciousness less than 5 minutes AND confusion less than one day); *probable* (loss of consciousness at least 5 minutes or greater OR confusion for at least one day or greater); and *definite* (visible signs on MRI OR classified as *probable* with persistent symptoms attributable to TBI).

Risk exposure. Diagnoses of substance dependence (see Table 3.1) were made following the consensus procedure used for psychiatric diagnoses summarized above. To index a history of childhood physical and/or sexual abuse (up to age 12), the Trauma History Questionnaire was administered (Hooper, Stockton, Krupnick, & Green, 2011). To measure virus exposure, blood samples were drawn and submitted to the BC Centre for Disease Control for serological assays of five viruses – HIV, hepatitis B, hepatitis C, herpes simplex virus, and cytomegalovirus. Seropositivity indicates having ever been exposed to a virus, except for HIV in which it indicates active infection. A sum of all positive results was computed and used to operationalize total virus exposure.

Other variables. Demographic variables, including age, years of education, gender, and ethnicity were self-reported during a structured baseline interview. Total years of education was determined using guidelines offered by Heaton, Miller, Taylor, and Grant (2004). To assess psychiatric symptoms, the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987) was administered. The total scores, as well as positive, negative, and general subscale scores were computed, with higher scores indicating more severe psychiatric symptoms.

3.2.3. Neuroimaging Acquisition and Processing

Structural imaging was conducted proximal to the neurocognitive testing session (89% within one day, 10% within one month, 1% within one year). Whole brain MRIs were acquired on a Philips Achieva 3.0T scanner equipped with an 8-channel SENSE-Head coil and using a 3D FFE T1 weighted structural sequence applied in the sagittal

plane with 190 1-mm thick slices (TR/TE = 7.6/3.5 ms; acquisition matrix = 256 x 250; field of view = 256 mm; flip angle = 8°; total acquisition time = 7:23 minutes). Images were visually inspected for significant motion artifact by trained raters. Additionally, all pial and white matter surfaces were visually inspected for segmentation failures and manually corrected where necessary.

Automatic cortical parcellation was performed using the publically available FreeSurfer 5.1 software (available for download at https://www.nmr.mgh.harvard.edu/) to generate values for local gyrification index (lGI) and cortical thickness (CT; details in Fischl et al., 2004) using the Desikan-Killiany atlas (Desikan et al., 2006). Left and right hemisphere cortical parameters were generated from the parcellation procedure and summed to create a bilateral index for the following regions: medial orbitofrontal cortex (mOFC), lateral orbitofrontal cortex (lOFC), anterior cingulate cortex (ACC; average of rostral and caudal subregions), and entorhinal cortex (ERC). The correlations between hemispheres for each region were .48 < *r*s < .81, suggesting these measures could be reasonably combined for the purpose of conducting more parsimonious statistical models. Whole brain averages for gyrification and cortical thickness were also computed.

To segment the hippocampus, we implemented an alternative approach to the automatic procedure offered by FreeSurfer due to the high rates of visible hippocampal neuropathology in our sample (e.g., large hippocampal infarcts, significant atrophy, dilation of perivascular channels), which could lead to automatic segmentation bias. Manual segmentation of the hippocampus was performed on 20 participants selected from our sample whose MRI's did not have obvious imaging artifact to create a set of custom templates. Images were registered to the templates using the SyN method (Avants, Epstein, Grossman, & Gee, 2008), followed by joint label fusion and corrective learning using the PICSL Multi-atlas segmentation tool from the Advanced Normalization Tools (ANTs) program (available for download at http://stnava.github.io/ANTs/).

3.3. Statistical Analysis

3.3.1. Cluster Analysis

All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) 22.0. First, a k-means cluster analysis was employed to cluster the original 249 participants with the additional community court participants, following procedures outlined in our earlier study of a subset of these participants (Gicas et al., 2014). Participants with invalid and/or missing data on two or more neurocognitive measures were excluded from the cluster analysis. Due to significant positive skew, the IDED adjusted error score was log transformed and subsequently multiplied by -1 so lower scores reflected poorer performance in accordance with the other measures. Age and education were regressed on HVLT, Stroop, RVIP, IDED, and IGT scores to control for variance associated with these demographic factors (see Manly et al., 2011). Standardized residuals generated from this procedure were used in the cluster analysis (N = 299). A kappa coefficient was used to determine whether participants from the original clusters were consistently re-assigned to the same clusters in the current analysis.

3.3.2. Multinomial Logistic Regression Analysis

A series of sequential multinomial logistic regression analyses were conducted to examine the associations between each brain region of interest (ROI) and the three neurocognitive clusters. The assumption of linearity in the logit was evaluated using the Box-Tidwell approach (Hosmer & Lemeshow, 2000) and models were inspected for multivariate outliers. One case was deemed a multivariate outlier and excluded from subsequent analyses, as it exceeded acceptable thresholds for influence and fit statistics according to standard cut-offs outlined in Cohen et al. (2003, p. 410). The results were unchanged with this case excluded from the models.

Independent variables of interest for the regression analyses included regional gyrification indices and cortical thicknesses (lOFC, mOFC, ERC, ACC), the corresponding ROI CT X age interaction terms, and hippocampal volume. Gender, age,

total years of education, total brain volume[1], and PANSS negative symptoms were included as covariates in each model. These covariates were selected on the basis of their known associations with brain structure and/or neurocognitive functioning. All continuous variables were converted to standard z-score units to ease interpretation. The neurocognitive clusters served as the dependent variable. A Bonferroni correction was applied to the four cortical ROI analyses to control for error inflation (p = .0125). The critical alpha value was set to p = .05 for all other independent variables.

A multinomial logistic regression model was run with only covariates included. Next, five separate full models were tested (one per ROI), each including the covariates plus the gyrification index, thickness, and the corresponding interaction term. The differences between the covariate-only model and the full models were calculated to determine whether the brain measures were significantly associated with the clusters after controlling for demographic factors and negative symptoms. Model differences were calculated using the following equation with 6 degrees of freedom: χ^2 = 2[LL(full model) – LL(covariate only model)] as recommended by Tabachnik and Fidell (2013). Pairwise comparisons were examined for all brain measures that were significant in the omnibus models (log-likelihood ratio tests).

3.3.3. Analysis of Proxy Variables

To evaluate cluster differences on proxy variables, ANOVAs and chi-square tests were conducted. Clusters were compared on proxy measures of possible developmental difficulties, which included a diagnosis of schizophrenia and a history of ever having received special education. Additionally, total NSS were used to represent subtle non-localizable motor and sensory abnormalities with putative neurodevelopmental origins. Total EPS were used as a measure to rule out the

[1] Although total brain volume is influenced by aging and pathological processes, we opted to include this measure rather than intracranial volume given that it is more proximal to neurocognition, which is our primary outcome measure. Total brain and intracranial volumes are highly correlated in this sample (r = .987), suggesting they capture the same underlying brain dimension.

possibility that observed motor and sensory abnormalities (NSS) could be attributed to neuroleptic side effects rather than microstructural brain integrity.

To index acquired brain insult, clusters were compared on the presence of any diagnosed MRI pathology and TBI. Proxies of risk exposure included substance dependence diagnosis, history of childhood physical and/or sexual abuse, and total virus exposure.

Chapter 4. Results

4.1. Cluster Analysis

The profiles of the original clusters in Gicas et al. (2014) were re-generated with a larger sample (N = 299) in the current analysis. Agreement between the original clusters and the current clusters was found to be excellent (kappa = .84). The three-cluster solution is depicted in Figure 4.1. A visual comparison with the original clusters depicted in Figure 2.1 also suggests high agreement. Briefly, Cluster 1 (n = 87; 29.1%) was characterized by the highest neurocognitive functioning across all domains. In contrast, Cluster 2 (n = 109; 36.5%) demonstrated abilities that generally fall intermediate to Clusters 1 and 3, but with pronounced weakness in decision-making. Finally, Cluster 3 (n = 103; 34.4%) was characterized by the overall lowest functioning, with the exception of relative strength in decision-making. The overall cluster patterns in the current sample were the same as previously reported (Gicas et al., 2014). For descriptive purposes, cluster profiles were constructed with demographically corrected T-scores (age and/or education) using the normative databases of the respective tests (see Figure 4.2).

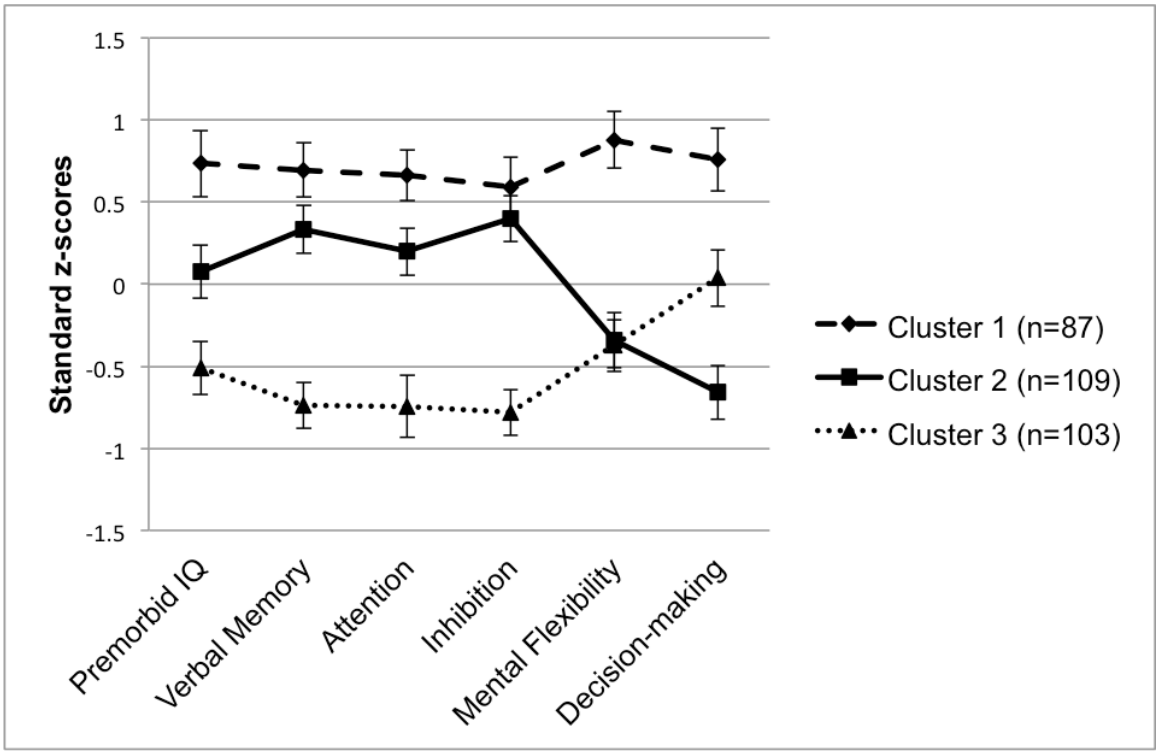

Figure 4.1 **Profiles of mean neurocognitive scores by cluster membership. Error bars represent 95% confidence intervals.**

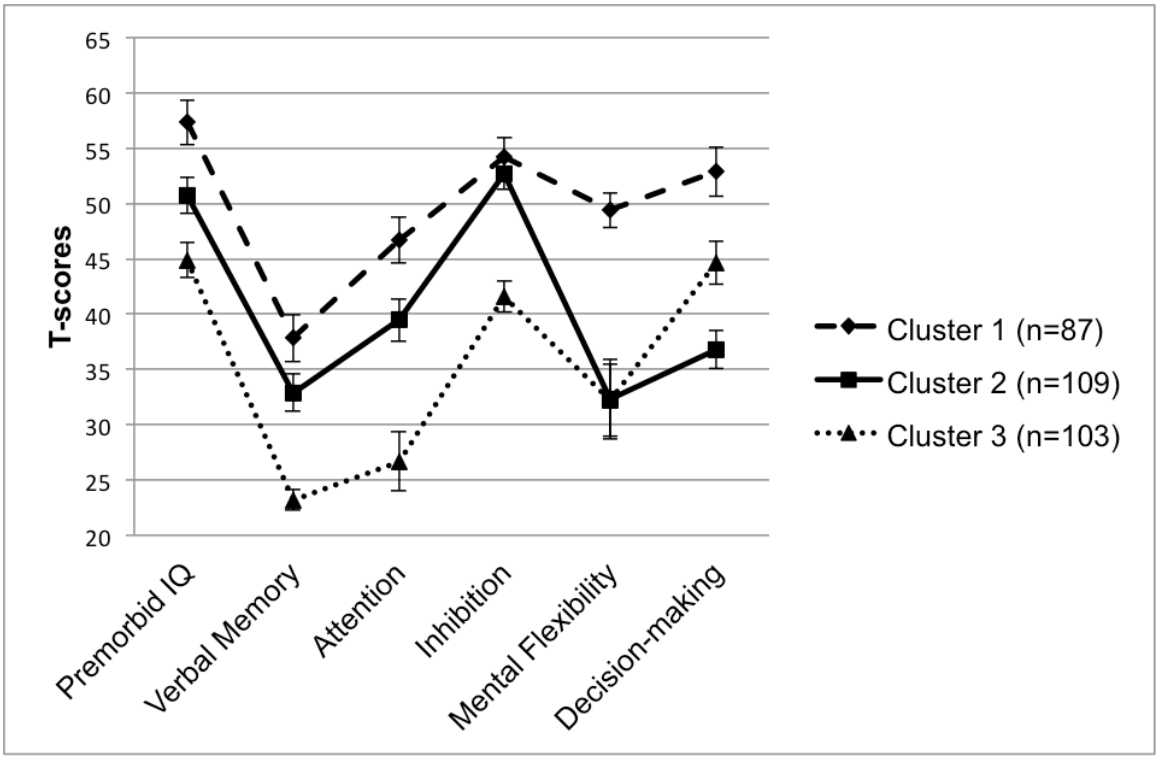

Figure 4.2 **Profiles of demographically corrected mean neurocognitive scores by cluster membership. Error bars represent 95% confidence intervals.**

4.2. Multinomial Logistic Regression Analysis

Based on the sample of individuals retained for cluster analysis (N = 299), no demographic differences (age, education, gender) were observed between individuals included (n = 211) versus excluded (n = 88) from regression analyses due to missing or invalid data ($p > .05$)[2]. Further, excluded cases showed a relatively even distribution across the three clusters.

In line with our hypotheses, omnibus testing revealed that ERC IGI ($\chi^2 = 13.60$, $p = .001$), mOFC IGI ($\chi^2 = 11.19$, $p = .004$), and lOFC IGI ($\chi^2 = 9.54$, $p = .008$) were

[2] The cluster profiles were reconstructed in the reduced sample (N = 211) and correlated with the profiles of the full sample (N = 299). Corresponding profiles correlated well with each other, demonstrating good internal validity. Visual inspection of the graphs revealed no differences in magnitude or shape between the full and reduced sample profiles.

differentially associated with the clusters. Further as predicted, we found that age was a significant moderator of brain-cluster associations. Specifically, the mOFC thickness X age interaction term was significant (χ^2 = 13.63, p = .001). The difference between the log-likelihood ratios for the covariate-only model and the full models revealed that brain measures were significantly associated with clusters above and beyond the effects of gender, age, total brain volume, education, and negative symptoms (ERC: χ^2 = 15.77, p < .025; lOFC: χ^2 = 13.67, p < .05; mOFC: χ^2 = 23.12, p < .001). No associations were found between the clusters and ACC gyrification or thickness, hippocampal volume, whole brain gyrification, or whole brain thickness (p > .05).

Parameter estimates were examined to determine which of the three clusters the brain measures differentiated. Table 4.1 lists the regression coefficients of significant pairwise comparisons, while Table D1 provides descriptive statistics (raw data), organized by cluster membership, for all independent variables included in the models. Briefly, for every SD unit increase in gyrification of the lOFC, mOFC, and ERC regions, there was a *decreased* likelihood of being in Cluster 1 (highest neurocognitive functioning), compared to Cluster 3 (lowest neurocognitive functioning, decision-making strength), by 51%, 53%, and 54% respectively. Likewise, with each SD unit increase in ERC and mOFC gyrification, there was a 34% and 39% *decreased* likelihood of being in Cluster 2 (intermediate functioning, decision-making weakness) compared to Cluster 3. In other words, greater gyrification in frontal and temporal regions was associated with a greater likelihood of being in Cluster 3.

To better understand the CT X age interactions, a median split was performed on age, and the associations between mOFC thickness and cluster membership by age group were visualized in Figures 4.3 and 4.4. As illustrated, in younger individuals, for every SD unit increase in mOFC thickness, there is a *decreased* likelihood of being Cluster 1 versus Clusters 2 or 3. Conversely, in older individuals, for every SD unit increase in mOFC thickness, there is an *increased* likelihood of being in Cluster 1 versus Clusters 2 or 3. Further post-hoc probing of the interaction was conducted using the "pick-a-point" approach described by Hayes and Matthes (2009) and formulas provided by Cohen et al. (2003). This entails picking a value within the range of the moderator variable (age in this case) and testing the simple slope using a t-test and confidence

intervals to determine if the effect of a specific value of the moderator (age) on the focal variable (mOFC thickness) is significantly different from zero. We chose a wide range of values from the 5th to the 95th percentiles to more fully capture the nature of the interactive effect across the age spectrum in this study. These results are provided for descriptive purposes in Table E1.

Table 4.1 Significant Associations Between Cortical Brain Measures and Neurocognitive Clusters

Group Comparison	Region of Interest	*B* (SE)	Wald χ^2 test (*p*-value)	Odds Ratio (95% CI)	Odds[a] of being in comparison cluster
C1 vs. C3	lOFC lGI	-0.72 (.24)	8.79 (.003)	0.49 (0.30 - 0.78)	51% ↓
	mOFC lGI	-0.76 (.25)	9.16 (.002)	0.47 (0.29 - 0.77)	53% ↓
	ERC lGI	-0.78 (.23)	12.06 (.001)	0.46 (0.29 - 0.71)	54% ↓
	mOFC CT X Age	0.72 (.22)	10.67 (.001)	2.05 (1.33 - 3.15)	na
C2 vs. C3	mOFC lGI	-0.49 (.20)	5.88 (.015)	0.61 (0.41 - 0.91)	39% ↓
	ERC lGI	-0.42 (.19)	4.91 (.027)	0.66 (0.45 - 0.95)	34% ↓
C1 vs. C2	mOFC CT X Age	0.58 (.21)	7.36 (.007)	1.79 (1.17 - 2.72)	na

Note. Underline indicates reference group and non-underline indicates target comparison group. SE = Standard error; CI = Confidence interval; C1 = Cluster 1; C2 = Cluster 2; C3 = Cluster 3. lOFC = lateral orbitofrontal cortex; mOFC = medial orbitofrontal cortex; ERC = entorhinal cortex; lGI = local gyrification index; CT = cortical thickness; na = not applicable.

[a]Percent change in odds ratio = |(1 – OR)| X 100.

Regression analyses were repeated excluding those with a diagnosis of schizophrenia or schizoaffective disorder (n = 33) to rule out the possibility that these are solely explanatory of the structural brain differences observed between clusters. The findings were unchanged. Likewise, when left and right hemispheres were analyzed separately in the regression models, the pattern of findings remained the same. We also repeated regression analyses excluding two older participants that appeared to have outlying mOFC thickness points (z-scores less than -3) evident in Figures 4.3 and 4.4.

Our results were similar, thus we opted to retain the cases given that they did not emerge as influential points in our check for multivariate outliers.

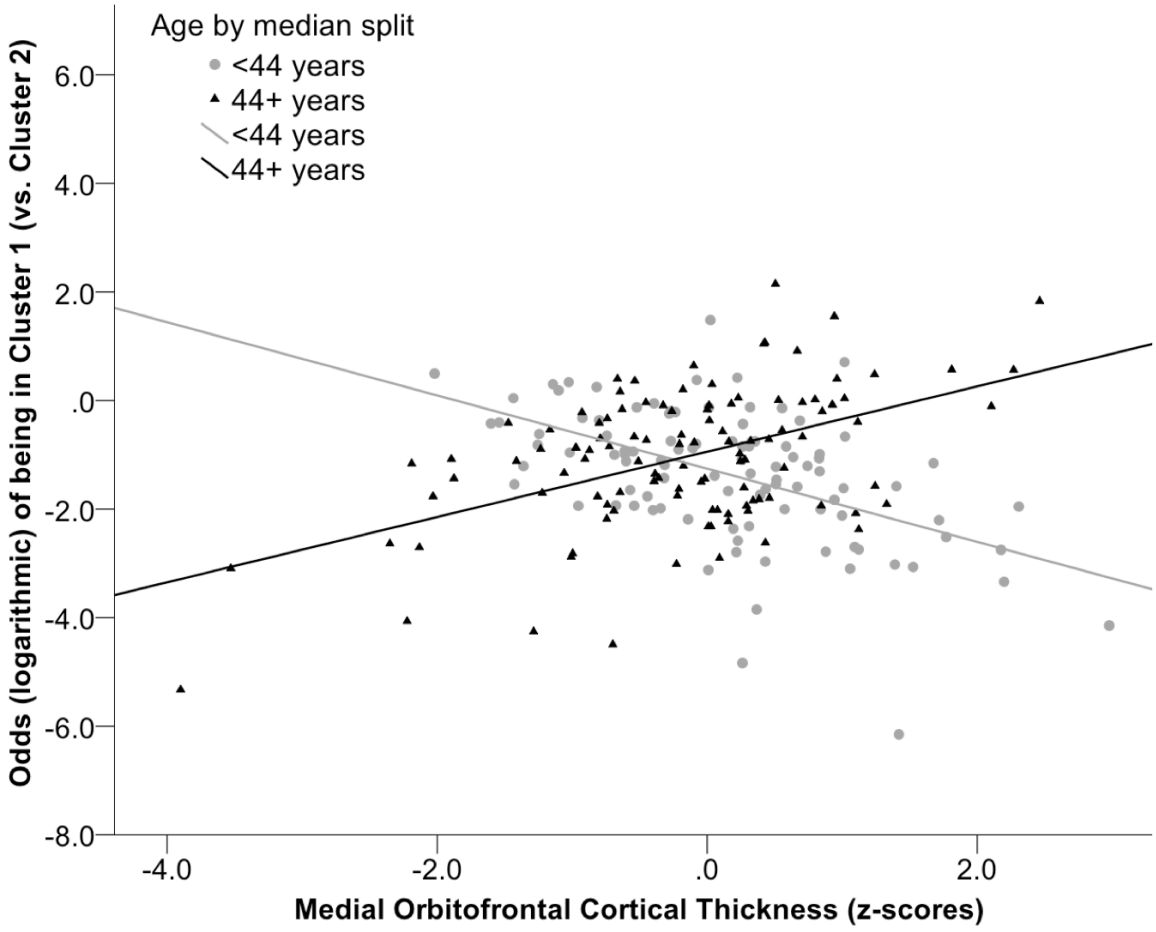

Figure 4.3 Odds (in logarithmic units) of being in Cluster 1 (versus Cluster 2) as a function of medial orbitofrontal cortical thickness and age.

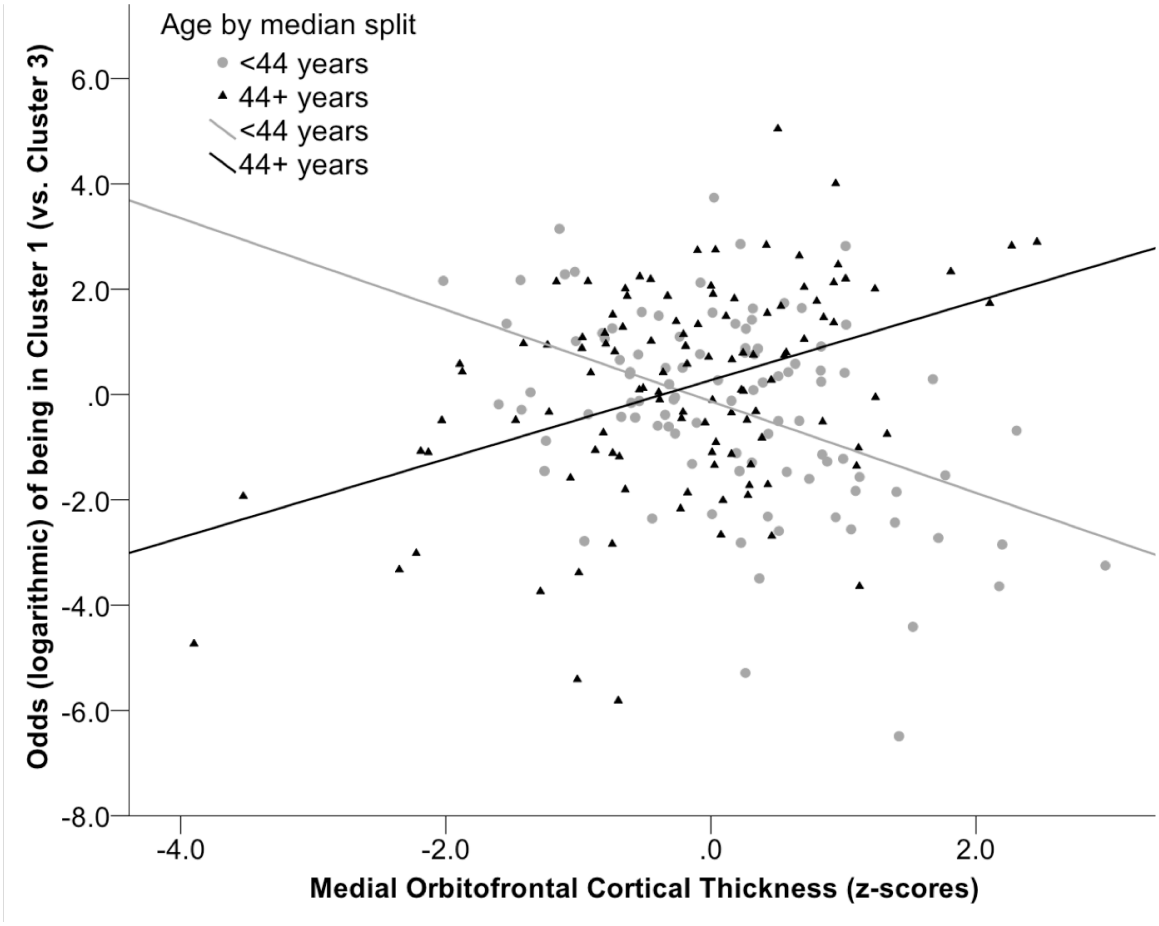

Figure 4.4 Odds (in logarithmic units) of being in Cluster 1 (versus Cluster 3) as a function of medial orbitofrontal cortical thickness and age.

4.3. Analysis of Proxy Variables

On developmental proxy variables, Cluster 3 was characterized by a higher rate of schizophrenia (χ^2 = 6.91, p = .009), and a higher incidence of ever having received special education (χ^2 = 4.10, p = .043), compared to Cluster 1. Further, higher mean total NSS (F = 12.96, p < .001) were observed in Cluster 3 compared to Clusters 1 (t = 4.77, p < .001) and 2 (t = 4.19, p < .001), in alignment with our previous findings (Gicas et al., 2014). No differences were observed for total EPS (p > .05).

Regarding acquired brain insult/risk exposure proxies, higher rates of any MRI pathology were observed in Cluster 2 (χ^2 = 7.84, p = .005) and Cluster 3 (χ^2 =5.46, p = .019) relative to Cluster 1. When further inspected, the rates of stroke and aneurysm appeared to drive the group differences on MRI pathology. A higher prevalence of stroke was observed in Cluster 2 (χ^2 = 9.95, p = .002), and Cluster 3 (χ^2 = 7.33, p = .007) compared to Cluster 1, with the same pattern of higher aneurysm prevalence in Cluster 2 (χ^2 = 4.14 p = .042) and Cluster 3 (χ^2 = 4.81, p = .028) compared to Cluster 1. Additionally, Cluster 2 exhibited significantly higher rates of opioid dependence (χ^2 = 4.74, p = .029) and stimulant dependence (χ^2 = 5.12, p = .024) relative to Cluster 3. Likewise, the rate of opioid dependence was significantly higher in Cluster 1 compared to Cluster 3 (χ^2 = 6.01, p = .014). Cluster differences on substance dependence are consistent with our previous report (Gicas et al., 2014). The rate of reported childhood abuse was significantly higher in Cluster 1 (χ^2 = 5.90, p =.015), and marginally higher in Cluster 2 (χ^2 = 3.53, p = .060) compared to Cluster 3. No cluster differences were found for total virus exposure (F = 2.10, p = .124).

When the clusters were compared on basic sociodemographics, the findings were consistent with our previous report with more years of education (F = 4.06, p = .018) in Cluster 1 compared to Cluster 2 (t = 2.50, p = .013) and Cluster 3 (t = 2.50, p = .013). Likewise, there were a greater proportion of females in Cluster 2 compared to Cluster 1 (χ^2 = 10.48, p = .001) and Cluster 3 (χ^2 = 10.75, p = .001). No age differences were observed (p > .05). A summary of these results is provided in Table 4.2.

4.4. Secondary Analyses

To further understand the nature of the cortical thickness X age interaction, we conducted a median split on age (median = 44) to examine differences between younger individuals (n = 100) and older individuals (n = 111) on key proxy measures described above. Independent samples t-tests and chi-square tests were used for continuous and categorical variables respectively. Given the exploratory nature of these analyses, we did not apply a Bonferroni correction. To summarize, older participants demonstrated a significantly higher rate of MRI pathology (χ^2 = 9.77, p = .002) and total virus exposure (t = -3.60, p < .001) compared to younger participants. Conversely, in younger

participants, there was a higher instance of a history of special education (χ^2 = 13.76, p < .001), a higher proportion of individuals with a schizophrenia diagnosis (χ^2 = 4.53, p = .033), and a higher rate of cannabis dependence (χ^2 = 13.90, p < .001). Results are further reported in Table 4.3. Importantly, the interaction term remains significant when we exclude select subsets of participants with any MRI pathology, schizophrenia diagnosis, history of special education, and cannabis dependence. This demonstrates the robustness of the effect and that confounds of the age groups are not the primary drivers of the interactive effect.

Table 4.2 Descriptive Statistics of Proxy Measures by Cluster Membership

Proxy Measure	Cluster 1	Cluster 2	Cluster 3	Comparisons
Developmental				
Schizophrenia diagnosis[a], n (%)	2 (2.3)	9 (8.3)	13 (12.6)	C3 > C1**
Special education[b], n (%)	19 (22.4)	30 (27.5)	37 (35.9)	C3 > C1*
Total NSS[c], *M* (SD)	10.1 (7.5)	11.1 (7.4)	15.7 (6.6)	C3 > C1****, C3 > C2****
Total EPS[d], *M* (SD)	9.6 (8.3)	12.1 (11.4)	11.8 (10.2)	ns
Acquired Brain Insult and Risk Exposure				
MRI pathology[e], n (%)				
Any pathology	9 (12.2)	29 (30.2)	23 (27.1)	C2 > C1**, C3 > C1*
Stroke	0 (0.0)	12 (12.5)	8 (9.4)	C2 > C1***, C3 > C1**
Hemorrhage	1 (1.4)	1 (1.0)	0 (0.0)	ns
Aneurysm[f]	1 (1.4)	8 (8.4)	8 (9.4)	C2 > C1*, C3 > C1*
TBI[a], n (%)				
Possible	38 (43.7)	37 (33.9)	42 (40.8)	ns
Probable	16 (18.4)	17 (15.6)	11 (10.7)	ns
Definite	6 (6.9)	12 (11.0)	11 (10.7)	ns
Drug dependence[a], n (%)				
Stimulant	72 (82.8)	98 (89.9)	81 (78.6)	C2 > C3*
Opioid	44 (50.6)	52 (47.7)	34 (33.0)	C1 > C3*, C2 > C3*
Alcohol	14 (16.1)	17 (15.6)	16 (15.5)	ns
Cannabis	30 (35.4)	39 (35.8)	33 (32.0)	ns
Childhood abuse[g], n (%)	14 (20.3)	13 (16.5)	6 (7.1)	C1 > C3*, C2 > C3†
Total virus exposure[h], *M* (SD)	2.6 (1.1)	2.8 (1.2)	3.0 (1.3)	ns
Sociodemographics				
Age (years), *M* (SD)	43.2 (9.1)	43.3 (9.7)	43.4 (9.8)	ns
Education (years), *M* (SD)	10.9 (2.2)	10.1 (2.5)	10.2 (2.0)	C1 > C2*, C1 > C3*
Gender, n (% female)	12 (13.8)	37 (33.9)	15 (14.6)	C2 > C1***, C2 > C3***

Note. NSS = neurological soft signs; EPS = extrapyramidal symptoms; TBI = traumatic brain injury.
[a]*N* = 299; [b]*N* = 297; [c]*N* = 229; [d]*N* = 271; [e]*N* = 255; [f]*N* = 254; [g]*N* = 233; [h]*N* = 290
†*p* = .06. **p* < .05. ** *p* < .01. *** *p* < .005. **** *p* < .001

Table 4.3 Proxy Measure Differences by Age Group

Proxy Measure	Younger (<44 years) n = 100	Older (44+ years) n = 111	Test statistic (*p*-value)
Developmental			
Schizophrenia diagnosis, n (%)	14 (14.0)	6 (5.4)	χ^2 = 4.529 (**.033**)
Special education[a], n (%)	40 (40.4)	19 (17.3)	χ^2 = 13.760 (**<.001**)
Total NSS, *M* (SD)	11.41 (7.5)	12.30 (7.2)	*t* = -0.816 (.415)
Total EPS, *M* (SD)	11.63 (10.8)	9.86 (7.7)	*t* = 1.368 (.173)
Acquired Brain Insult and Risk Exposure			
Any MRI pathology[b], n (%)	15 (15.0)	37 (33.6)	χ^2 = 9.765 (**.002**)
Definite TBI, n (%)	7 (7.0)	16 (14.4)	χ^2 = 2.978 (.084)
Stimulant Dependence, n (%)	81 (81.0)	99 (89.2)	χ^2 = 2.815 (.093)
Opioid Dependence, n (%)	43 (43.0)	45 (40.5)	χ^2 = 0.131 (.718)
Alcohol Dependence, n (%)	16 (16.0)	18 (16.2)	χ^2 = 0.002 (.966)
Cannabis Dependence, n (%)	49 (49.0)	27 (24.3)	χ^2 = 13.899 (**<.001**)
Childhood Abuse[c], n (%)	12 (16.2)	8 (8.5)	χ^2 = 2.344 (.126)
Total Virus Exposure[a], *M* (SD)	2.52 (1.2)	3.12 (1.2)	*t* = -3.604 (**<.001**)
Demographics			
Education, *M* (SD)	10.16 (1.9)	10.46 (2.7)	*t* = -0.958 (.339)
Gender, n (% female)	18 (18.0)	22 (19.8)	χ^2 = 0.113 (.736)

Note. Reflects data for participants used in logistic regression analyses (*N* = 211). Bold text denotes statistical significance at p < .05.
[a]*N* = 209. [b]*N* = 210. [c]*N* = 168.

Chapter 5. Discussion

We established that structural brain measures are differentially associated with distinct neurocognitive profiles in a multimorbid marginalized sample. Greater gyrification in frontal and temporal regions was associated with Cluster 3 (overall lowest neurocognitive functioning, relative decision-making strength) compared to the other clusters. Further, regional frontal cortical thicknesses differentiated clusters, but this effect was moderated by age. Specifically, for older persons, greater mOFC thickness was associated with an increased likelihood of being in Cluster 1 (overall highest neurocognitive functioning) compared to Cluster 2 (intermediate neurocognitive capacities, prominent decision-making weakness) and Cluster 3. The reverse pattern was observed for younger individuals in that greater mOFC thickness predicted membership in Cluster 3 versus Cluster 1. With respect to developmental proxy measures, Cluster 3 exhibited the highest rates of schizophrenia, a history of having received special education, and greater NSS. With respect to proxy measures of acquired brain insult, Cluster 2 exhibited the highest rate of MRI pathology. For indices of risk exposure, Cluster 1 and Cluster 2 demonstrated higher rates of substance dependence and childhood abuse, relative to Cluster 3.

Our findings support the contention that broad-level etiologies of neurocognitive impairments are relatively different between groups. Specifically, the pattern of greater frontal and medial temporal gyrification being associated with Cluster 3 may be reflective of early neurodevelopmental aberrations. Indeed, a number of schizophrenia studies have reported increased gyrification in select regions of the frontal (Falkai et al., 2007; Palaniyappan et al., 2011; Vogeley et al., 2000) and temporal cortices (Harris et al., 2004; Schultz et al., 2010) in patients, in individuals at-risk for schizophrenia (Harris et al., 2007; Stanfield et al., 2008), and in unaffected first-degree relatives (Falkai et al., 2007). Regional increases in gyrification have also been observed in autism spectrum disorders (Libero, DeRamus, Deshpande, & Kana, 2014; Wallace et al., 2013) and

Williams syndrome (Fahim et al., 2012). However, a number of these studies have also reported regional decreases in gyrification relative to healthy comparisons. Such findings simultaneously highlight the heterogeneity of cortical alterations that can result from early deviations in neurodevelopment and the need for further studies on gyrification abnormalities in clinical populations. Although we ruled out the possibility of global group differences in gyrification, we selectively focused on key fronto-temporal regions. Therefore, we may not have captured the full spectrum of gyrification differences that exists across groups, which could have also included regions of decreased gyrification in Cluster 3 relative to the others. Our interpretations should be further tempered by the fact that we do not have a healthy comparison group to determine the actual direction and extent of gyrification differences.

While we observed that Cluster 3 was associated with greater regional gyrification, it was also differentiated from Cluster 1 by frontal cortical thickness. More specifically, and what emerged as most interesting, is that our hypothesized pattern of "bigger is better" only held true for older individuals. Follow-up analyses revealed that there are higher rates of MRI pathology and total virus exposure in older individuals compared to their younger counterparts. We conjecture that, as these older individuals face diminishing brain reserve as a result of biological and/or environmental insults, there is a greater reliance on remaining brain structure to maintain adequate neurocognitive functioning (Burzynska et al., 2012). On the other hand, in younger individuals, the reverse was true whereby *greater* mOFC thickness was associated with a *poorer* profile of neurocognitive functioning (Cluster 3). While this latter finding was unexpected, it remains consistent with typical lifespan developmental patterns in which thinner cortices are associated with better intellectual functioning up until early adulthood, but the association reverses in middle-age such that there is a positive association between regional thicknesses and function (Schnack et al., 2015).

In young clinical samples, thicker cortices may reflect aberrant neurodevelopmental pruning processes (Jacobus, Squeglia, Sorg, Nguyen-Louie, & Tapert, 2014; Lacerda et al., 2007). Such an interpretation is consistent with our finding that there is a higher rate of schizophrenia diagnoses in younger individuals within this sample, as well as a higher proportion of individuals with a history of special education.

While this latter finding may be reduced to cohort effects, it is also plausible that it may signal the greater degree of neurodevelopmental difficulties in this age group, consistent with the higher rates of schizophrenia. Similarly, we observed a higher rate of cannabis dependence in younger individuals, which is not surprising given that marijuana is a commonly used illicit substance in adolescence. Recent research has demonstrated that heavy marijuana use in adolescence is later associated with thicker cortex in multiple brain regions, and this may be a consequence of altered neurodevelopmental trajectories during the highly dynamic yet vulnerable period of adolescent brain maturation (Filbey, McQueeny, DeWitt, & Mishra, 2015; Jacobus et al., 2015). It is important to note that, while any of the aforementioned factors could independently contribute to cortical alterations, it is more likely that a confluence of endogenous (e.g., genetic liability for psychopathology) and exogenous factors (e.g. substance use) explains the dynamic structure-function associations observed here, especially because our results held even when specific subsets of participants were excluded.

Although our neurodevelopmental hypothesis of Cluster 3 is limited by the parameters of our study design, our interpretation is bolstered by the fact that Cluster 3 exhibited higher rates of schizophrenia and special education, in addition to greater negative symptoms and NSS (also see Gicas et al., 2014). Both negative symptoms and NSS are considered to be relatively stable, trait markers of schizophrenia (Ventura et al., 2015; Chan & Gottesman, 2008), but have also been observed in other psychiatric populations (Foussias, Agid, Fervaha, & Remington, 2014; Kaiser, Heekeren, & Simon, 2011; Chen et al., 1995) and in clinical at-risk samples (Lyne et al., 2014; Piskulic et al., 2012). These markers may be considered as reflective of diffuse cerebral dysfunction related to aberrant development of neurocognitive systems.

The neuroanatomic and proxy variable differences between Cluster 3 and the other clusters persisted despite exclusion of participants with a schizophrenia or schizoaffective diagnosis. This suggests that the findings of elevated psychiatric and neurological symptoms, along with greater gyrification, in Cluster 3 might ultimately reflect a continuum of putative neurodevelopmental psychopathology, rather than markers of a categorical disease entity. This lends further support to the hypothesis that the observed neurocognitive deficits of Cluster 3 are apt to have been longstanding, and

may serve as a vulnerability marker for further brain and neurocognitive degradation with a lifetime of accumulating risk exposures.

In contrast to Cluster 3, the neurocognitive deficits associated with Cluster 2 are more circumscribed and thus may be more aptly characterized as acquired impairment as a function of exposure to various environmental insults. Cluster 2 exhibited the most pronounced impairment in, and poorest overall, decision-making ability. Affective decision-making processes are thought to be subserved by the ventromedial prefrontal cortex (Bechara, 2003; Stuss & Levine, 2002), which supports our finding that cortical thinning in the mOFC was associated with a greater likelihood of being in Cluster 2, compared to Cluster 1, albeit only for older individuals. Cortical thinning in this subgroup may be extensively related to environmental risk exposures. Indeed, Cluster 2 had elevated rates of MRI pathology, substance dependence, and childhood abuse (compared to Cluster 3), all of which are likely to make a unique contribution to brain integrity in this group. For example, frontal thinning has been observed in polysubstance users (Lawyer et al., 2010; Momenam et al., 2012) and in those exposed to early life adversities, such as childhood abuse (Kelly et al., 2013) and low socioeconomic status (Noble et al., 2015). Cortical thinning may also be exacerbated with aging under certain conditions, such as HIV infection (Holt et al., 2012; Pfefferbaum et al., 2014) and history of concussion (Goswami et al., 2015; Tremblay et al., 2013). Although cortical thickness is much more vulnerable to degradation over the lifespan than gyrification, it is important to note that there is some evidence suggesting reductions in gyrification with early life risk exposures, including childhood abuse (Kelly et al., 2013) and cannabis use (Shollenbarger, Price, Wieser, & Lisdahl, 2015). Maturation of tertiary aspects of cortical folding continues through adolescence (White et al., 2010), and environmental insults during this highly dynamic period could plausibly result in focal gyrification abnormalities in persons with otherwise normal neurodevelopmental trajectories. The interaction between early risk exposures and brain maturation, as well as the degree to which multiple co-occurring conditions exert a cumulative or synergistic impact on cortical brain integrity are matters ripe for future investigation.

Our findings that regional frontal thicknesses, but not medial temporal thickness or hippocampal volume, differentiated the clusters may ultimately reflect the vulnerability

of the prefrontal structures and fronto-striatal neural circuitry that subserves decision-making and inhibitory control processes in a substance dependent population. Structural (Ersche et al., 2011; Ersche et al., 2012) and functional (Ersche et al., 2005; Hester & Garavan, 2004; Luo et al., 2013) abnormalities in the OFC and ACC have been consistently reported in persons with substance dependence disorders compared to healthy controls. These regions both receive primary inputs from the ventral portion of the striatum (O'Callaghan, Bertoux, & Hornberger, 2014), and dysfunction in this network has been strongly implicated in the development and maintenance of drug addiction (Everitt & Robbins, 2013), and to a lesser extent in other psychiatric illnesses (Pujara & Koenigs, 2014). For instance, poorer white matter tract integrity in the fronto-subcortical circuitry has been linked with longer durations of stimulant use (Ersche et al., 2012) and opioid use (Upadhyay et al., 2010). Frontal structures are also exceptionally vulnerable to normal aging processes. A clear anterior-posterior gradient of cortical degradation exists in which the prefrontal cortex is affected earliest, followed by relatively milder effects in temporal regions, consistent with the "last in, first out" hypothesis (Fjell et al., 2009; Raz & Rodrigue, 2006; Thambisetty et al., 2010). Moreover, these effects are already observed by middle age (McGinnis et al., 2011). Together, this may indicate heightened risk for premature or accelerated aging in a middle-aged, multimorbid population.

Relatedly, the degradation of frontal structures may also help to explain the lack of association between hippocampal volume and neurocognitive clusters despite substantial memory impairment across all three groups (see Figure 3). Indeed, successful verbal recall is dependent on one's ability to initially attend to and process relevant stimuli, which is regulated by dorsolateral prefrontal structures (Stuss and Levine, 2002). Thus, in our sample, memory performance may be more reflective of a generalized impairment in lower level attentional and processing speed abilities and associated neural circuitry, rather than true memory impairment.

The current findings should be interpreted in light of certain limitations. First, the cross-sectional nature of this study limits our understanding of the extent to which the cluster differences are truly representative of neurodevelopmental and/or aging processes. When directly compared to a longitudinal approach, a cross-sectional design

has demonstrated to underestimate age-related changes in cortical thickness (Fjell et al., 2014). Second, we focused exclusively on cortical brain structure, but there are likely to be important differences between the clusters on other brain measures. For example, the ventromedial prefrontal cortex and ventral striatum must work in concert to mediate complex decision-making and inhibitory control processes, and it is likely that degradation in key cortical regions is also associated with decreased subcortical volumes and/or decreased white matter tract integrity in the relevant circuitry. Explorations of these brain structures in future studies will help to further elucidate the drivers of neurocognitive impairment.

Additionally, we attempted to corroborate self-report data whenever possible (verifying self-report of TBI against imaging data), but some measures relied solely on self-report (childhood trauma, history of special education, years of education) and this data may be less reliable as a function of memory impairment and/or selective reporting. Lastly, research suggests that lower socioeconomic status (SES) in childhood (Noble et al., 2015) and stressful childhood events (Kelly et al., 2013; Luby et al., 2013) can have a negative downstream impact on numerous cortical and subcortical brain structures. These "hidden" factors limit our interpretation in the current study as we are not able to directly observe the effects of childhood events on this adult sample. Despite these limitations, we offer the first study that directly examines the link between cortical brain structure and neurocognition in a socially marginalized sample, thus laying the necessary foundation for future explorations of brain-behaviour associations in an emerging literature.

Chapter 6. Study 2: Introduction

We conducted a complementary follow-up investigation to expand on the findings from Study 1, which focused exclusively on cortical structure and its association with neurocognition. In Study 2, we adopted a similar approach to examine the association between white matter integrity and neurocognition, thereby providing a more comprehensive understanding of structure-function relationships in a socially marginalized sample. Examining both gray and white matter structural properties of the brain is important considering that these have demonstrated independent contributions to neurocognitive dysfunction (Stricker et al., 2013).

Diffusion tensor imaging (DTI) can serve as a powerful tool to investigate brain structure by capitalizing on the relative differences in diffusion of water molecules between grey and white matter tissue, thus providing an indirect yet sensitive measure of white matter microstructural integrity (Alexander, Lee, Lazar, & Field, 2007; Assaf & Pasternak, 2008). Fractional anisotropy (FA) is the most commonly used DTI metric, which reflects diffusion of water molecules restricted to one direction by the presence of axonal membranes and myelin sheaths (Assaf & Pasternak, 2008). Degradation of these neural tissues leads to a decrease in FA values as water molecules are less constrained and more readily able to diffuse in multiple directions. Although FA is a non-specific index of white matter integrity, complementary information can be provided by examination of the constituent components of the diffusion tensors. As demonstrated in animal models, decreased diffusion of water molecules parallel to the axon (axial diffusivity) and increased diffusion perpendicular to the axon (radial diffusivity) are associated with degraded axonal and myelin integrity, respectively (Song et al., 2003; Song et al., 2005).

White matter is an important target for examining overall brain integrity given its extensive implication in physical and psychiatric conditions that are endemic in socially

marginalized populations. Specifically, dysfunction of the fronto-subcortical circuitry, namely connectivity of prefrontal cortex and ventral striatum, has been consistently linked with the development and maintenance of addiction (Everitt & Robbins, 2013; Koob & Volkow, 2010). Indeed, significant reductions in white matter integrity of major frontal and interhemispheric tracts are reliably observed in stimulant users (London, Kohno, Morales, & Ballard, 2015; Romero, Asensio, Palau, Sanchez, & Romero, 2010), opioid users (Wollman et al., 2015), alcohol users (Fortier et al., 2014), and polysubstance users (Unterrainer et al., 2015) compared to healthy controls. Moreover, longer duration of substance use is correlated with poorer white matter integrity (Ersche et al., 2012; Fortier et al., 2014; Wollman et al., 2015). Fronto-subcortical circuitry has also been implicated in a range of major psychiatric conditions such as schizophrenia and depression (Pujara & Koenigs, 2014), and white matter deficits are found to correlate with illness severity (Lagopoulos et al., 2013). Similar white matter alterations have also been documented in HIV infection (Holt, Kraft-Terry, & Chang, 2012; Leite et al., 2013).

While white matter integrity has been studied fairly extensively in the context of discrete mental and physical disorders, a paucity of literature exists on this subject in the context of multimorbidity, which is arguably a more accurate reflection of real world settings, especially as it relates to socially marginalized populations. Even fewer studies have examined the relationship between white matter integrity and neurocognition in multimorbid samples. One of the most relevant studies to date comes from Tang and colleagues (2015) who reported that psychostimulant users with comorbid HIV infection demonstrated significantly lower FA and higher diffusivity in select frontal and interhemispheric tracts, and poorer neurocognitive functioning compared to healthy controls. Further, decreased tract-specific white matter integrity differentially correlated with poorer performance on tasks of motor speed, sustained attention, verbal learning and memory, and executive functioning (Tang et al., 2015). Similarly, in alcohol users with comorbid HIV infection, lower FA and higher diffusivity in the corpus callosum was found to correlate with slowed motor speed (Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007). Further investigation of these associations is highly important given the mediating role of white matter in cognitive aging (Bennett & Madden, 2014).

Degradation of white matter in a middle-aged multimorbid population may have serious implications for long-term cognitive trajectories and functional outcomes.

6.1. Objectives and Hypotheses

Our aim for the current study was to investigate whether differences in white matter integrity underlie the distinct neurocognitive profiles defined and outlined in Study 1 (see results section 4.1, page 20). We selected several major white matter tracts that have projections to frontal and temporal regions including the corpus callosum, cingulum, superior longitudinal fasciculus, and anterior corona radiata. These tracts are commonly examined within the DTI literature and consistently implicated in various clinical conditions such as schizophrenia (Samartzis, Dima, Fusar-Poli, & Kyriakopoulos, 2014), HIV (Leite et al., 2013), and polysubstance abuse (Unterrainer et al., 2015; Willi et al., 2016). Our *a priori* ROI approach was followed by a whole-brain approach using Tract-Based Spatial Statistics (TBSS; Smith et al., 2006) to provide a complementary and more comprehensive understanding of white matter integrity in this sample.

We hypothesized that lower FA, with corresponding decreased AD and increased RD, in the aforementioned tracts would be associated with the neurocognitive subgroup that exhibits the lowest functioning and greatest burden of physical and psychiatric illness (Cluster 3). Given that the tracts we examined have diffuse projections to multiple frontal and temporal sub-regions, we did not put forth additional hypotheses regarding further differentiation of the neurocognitive subgroups on the basis of white matter integrity.

Chapter 7. Method

7.1. Participants

The same participants used in Study 1 were included in Study 2 and full details are provided in the method section of Study 1 (see page 10). Of the 299 participants that were included in the cluster analysis, a total of 202 individuals had valid DTI data and were retained for inclusion in the current analyses. Ethics approvals for this work were obtained from the Clinical Research Ethics Board of the University of British Columbia and the Simon Fraser University Office of Research Ethics.

7.2. Materials and Procedures

7.2.1. Neuroimaging Acquisition and Processing

Two DTI sequences per subject were acquired on a Philips Achieva 3.0T scanner with an eight-channel SENSE-Head coil. The DTI scanning parameters were as follows: 32 gradient directions, acquisition matrix = 100 x 100 (reconstruction matrix = 112 x 112), field of view = 224 x 224 mm^3, reconstructed voxel size = 2.0 x 2.0 X 2.20 mm, 70 slices with slice thickness = 2.2 mm (no gaps), TR/TE = 6452/60 ms, flip angle = 90°, b factor = 700 s/mm^2, total acquisition time = 3:45.8 minutes.

All scans were visually inspected by trained raters. Participants with DTI sequences containing greater than four slices with artifacts, with moderate to severe motion artifacts, or scans not completed proximal to neurocognitive testing were excluded from analyses (n = 47). Images were not acquired for 50 participants, yielding a total sample of 202 with valid scans for analysis. The DTI sequences were averaged after eddy current correction using the FMRIB's Diffusion Toolkit (FDT) part of FMRIB's Software Library (FSL; Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). DTI

fitting was run using a nonlinear least squares approach with shifted negative eigenvalues. Finally, a non-linear registration method was used to co-register DTI data with the John Hopkins University International Consortium Brain Mapping (JHU) ICBM-DTI-81 atlas (Mori et al., 2008). Left and right hemisphere measurements for the cingulum, superior longitudinal fasciculus, and anterior corona radiata were extracted and combined to create bilateral indices. Correlations between left and right hemisphere FA, AD, and RD values were strong, $.51 < rs < .94$, suggesting they can be reasonably combined. The genu and body of the corpus callosum were summed for each DTI parameter to create an overall measure.

7.3. Statistical Analysis

7.3.1. Multinomial Logistic Regression Analysis – ROI Approach

A series of multinomial logistic regression analyses were performed to examine the associations between tract-specific white matter integrity and the neurocognitive clusters using SPSS 22.0. Independent variables were examined for univariate outliers and three cases were identified on the DTI variables and adjusted by setting their values to be .25 SDs above or below the next highest or lowest values, respectively (see Tabachnik & Fidell, 2013). Data was inspected for the presence of multivariate outliers according to criteria outlined in Cohen et al. (2003), and all cases were deemed appropriate for retention in the models. The Box-Tidwell approach was used to test the assumption of linearity in the logit (Hosmer & Lemeshow, 2000), with no evidence of violation.

Separate regression models were conducted using FA values for each of the ROIs (cingulum, corpus callosum, superior longitudinal fasciculus, anterior corona radiata). Additionally, total brain FA was examined to distinguish between global versus tract-specific effects. For ROIs that were significant in the omnibus model (log-likelihood ratio test), parameter estimates were examined to determine which clusters were differentiated by the DTI variables, and follow-up regressions were conducted to examine cluster differences on AD and RD values. Independent models for each of the DTI parameters were necessary to avoid multicollinearity. The DTI measures were

entered as the independent variables along with age and gender as covariates. The three neurocognitive clusters served as the dependent variable. Given that this is a novel exploration of white matter integrity in a marginalized sample, we did not want to be overly conservative by applying a Bonferroni correction, thus we maintained the conventional critical alpha value of $p = .05$. However, error inflation was controlled to the extent that only DTI variables that emerged as significant in the log likelihood test were further explored for between group differences. A summary of DTI descriptive statistics is organized by cluster in Table F1.

7.3.2. Tract-Based Spatial Statistics – Whole Brain Approach

Tract-Based Spatial Statistics (Smith et al., 2006) from FSL and the randomise algorithm (Winkler et al., 2014) were used for comparisons of the DTI metrics FA, AD, and RD between the three clusters, with age and gender entered as covariates into a single design matrix. TBSS first non-linearly registers each FA image onto the JHU-ICBM FA 1x1x1mm standard space. The average of all the FA images was then created and skeletonised to form the mean FA skeleton, thresholded at a standard FA value of 0.25. Individual FA values were projected to this mean FA skeleton, along with AD and RD values using the same FA skeleton projection. Voxelwise statistics were then performed using the randomise command with the Threshold-free Cluster Enhancement (TFCE) option applied. TBSS results were visualized using FSLview thresholded at $p < 0.05$, and overlaid with the JHU-ICBM-DTI-81 white-matter atlas to identify the neuroanatomical areas that significantly differed between groups.

Chapter 8. Results

8.1. Multinomial Logistic Regression Analysis – ROI Approach

White matter tract FA values that significantly differentiated neurocognitive clusters in the omnibus tests included the cingulum (χ^2 = 8.07, p = .018), corpus callosum (χ^2 = 6.86, p = .032), superior longitudinal fasciculus (χ^2 = 7.15, p = .028), and anterior corona radiata (χ^2 = 6.72, p = .035). Total brain FA trended towards significance (χ^2 = 5.88, p = .053). Examination of the parameter estimates revealed that lower FA was consistently associated with Cluster 3 compared to Clusters 1 and 2 (which did not significantly differ from each other in any of the models). Regression coefficients for significant pairwise comparisons are outlined in Table 8.1.

Follow-up regression analyses revealed that AD values significantly differentiated neurocognitive clusters only in the anterior corona radiata (χ^2 = 8.02, p = .018). In contrast, RD values significantly differentiated clusters in all ROIs: cingulum (χ^2 = 7.76, p = .021), superior longitudinal fasciculus (χ^2 = 7.53, p = .023), anterior corona radiata (χ^2 = 11.50, p = .003), and corpus callosum (χ^2 = 7.54, p = .023). For all the above noted significant ROIs, pairwise comparisons were investigated and significant associations are outlined in Table 8.1

Table 8.1 Significant Associations Between DTI Measures and Neurocognitive Clusters

Group Comparison	Region of Interest	*B* (SE)	Wald χ^2 test (*p*-value)	Odds Ratio (95% CI)	Odds[a] of being in comparison cluster
C1 vs C3	Cingulum				
	FA	.58 (.24)	5.89 (.015)	1.78 (1.12 – 2.84)	78% ↑
	RD	-.61 (.27)	5.18 (.023)	0.55 (0.32 – 0.92)	45% ↓
	Anterior Corona Radiata	.			
	FA	64 (.26)	6.06 (.014)	1.89 (1.14 – 3.14)	89% ↑
	RD	-.73 (.30)	6.05 (.014)	0.48 (0.27 – 0.86)	52% ↓
	Superior Longitudinal Fasciculus				
	FA	.57 (.26)	4.84 (.028)	1.77 (1.06 – 2.95)	77% ↑
	RD	-.62 (.31)	4.06 (.044)	0.54 (0.29 – 0.98)	46% ↓
C2 vs C3	Cingulum				
	FA	.51 (.22)	5.37 (.021)	1.67 (1.08 – 2.58)	67% ↑
	RD	-.58 (.25)	5.44 (.020)	0.56 (0.35 – 0.91)	44% ↓
	Anterior Corona Radiata				
	FA	.42 (.24)	3.14 (.076)	1.52 (0.96 – 2.43)	52% ↑
	AD	-.64 (.24)	7.12 (.008)	0.53 (0.33 – 0.84)	47% ↓
	RD	-.78 (.29)	7.40 (.007)	0.46 (0.26 – 0.80)	54% ↓
	Superior Longitudinal Fasciculus				
	FA	.56 (.25)	5.18 (.023)	1.75 (1.08 – 2.85)	75% ↑
	RD	-.73 (.30)	5.81 (.016)	0.48 (0.27 – 0.87)	52%↓
	Corpus Callosum				
	FA	.61 (.24)	6.39 (.011)	1.84 (1.15 – 2.96)	84% ↑
	RD	-.67 (.27)	6.22 (.013)	0.51 (0.30 – 0.87)	49% ↓

Note. Underline indicates reference group and non-underline indicates target comparison group. Results depict comparisons of independent variables that were significant at $p < .05$ in the omnibus models. SE = Standard error; CI = Confidence interval; C1 = Cluster 1; C2 = Cluster 2; C3 = Cluster 3. FA = fractional anisotropy; AD = axial diffusivity; RD = radial diffusivity.
[a]Percent change in odds ratio = |(1 – OR)| X 100.

8.2. Tract-Based Spatial Statistics – Whole Brain Approach

Widespread and predominantly bilateral reductions in FA, with corresponding increases in AD and RD, were observed in Cluster 3 compared to Clusters 1 and 2 ($p < .05$, corrected for multiple comparisons). Nearly all major projection, association, and commissural fibre tracts exhibited some degree of difference between Cluster 3 and the other clusters, whereas no tracts in the brainstem emerged as significant. When Clusters 1 and 3 were compared on FA values, widespread bilateral differences were observed, although visual inspection suggested more extensive reductions in FA were evident in the left hemisphere for Cluster 3. The differences between Clusters 2 and 3 were also widespread, however Cluster 3 demonstrated relatively greater reductions in the frontal and interhemispheric tracts. These results are depicted in Figures 8.1 and 8.2. When comparing clusters on diffusivity metrics, tract differences were more extensive for RD, as oppose to AD.

While it is convention to summarize TBSS results by describing patterns of group differences visualized with significance maps that are projected onto the mean skeleton (as seen in Figures 8.1 and 8.2), we opted to supplement this with a more objective approach that aims to quantify the *relative* degree of group differences. In Table G1, we listed all left and right hemisphere tracts that significantly differed on FA. The same information is provided for AD and RD differences in Tables G2 and G3. Additionally, for each tract listed, we noted the percentage of the total tract volume that significantly differed between clusters and the corresponding average *p*-value. This enables identification of tracts that exhibited more extensive between-group differences (i.e., greater number of significant voxels) versus tracts with only a small number of significant voxels.

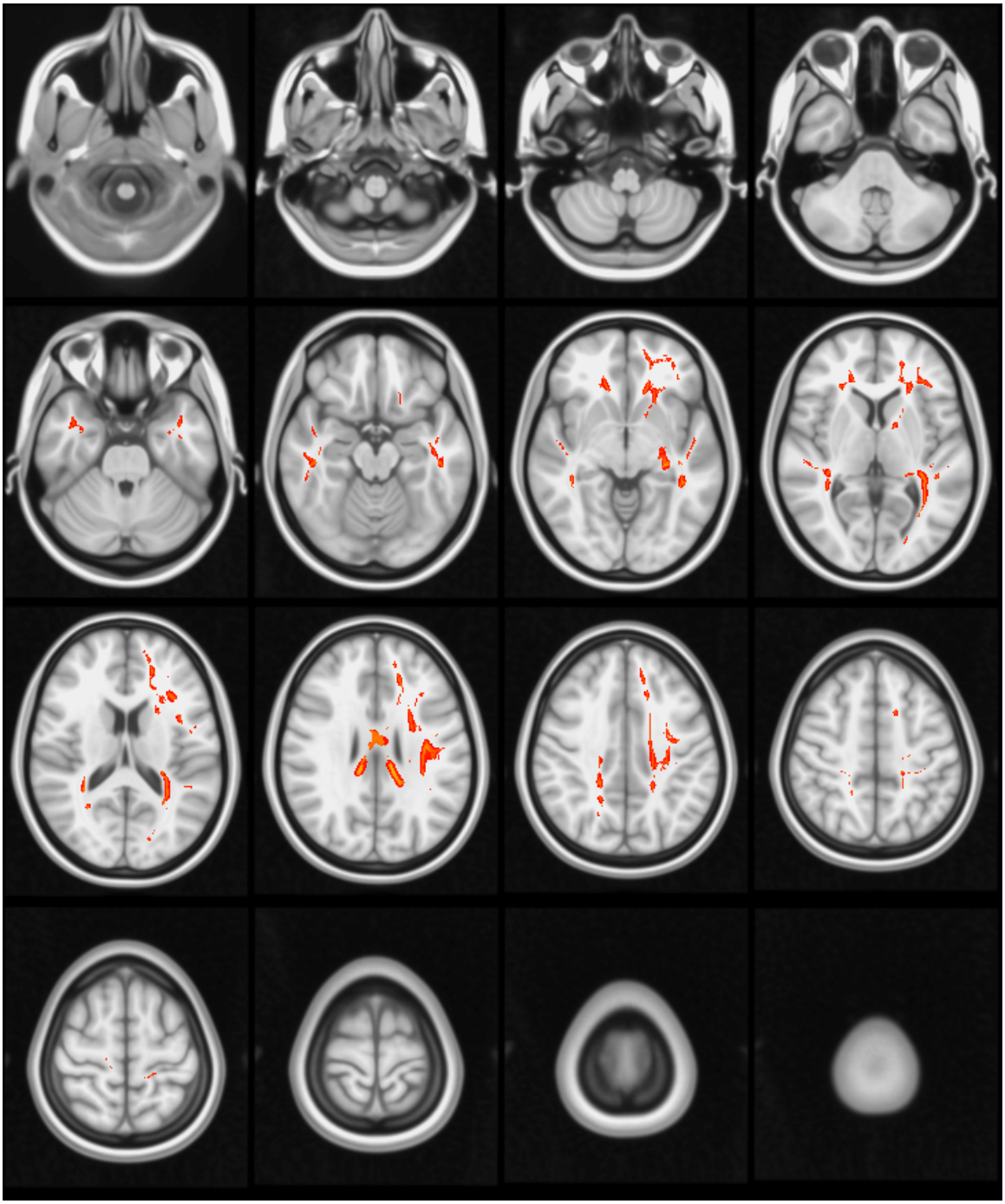

Figure 8.1 TBSS FA Differences Between Cluster 1 and Cluster 3.
Note. Regions of red/yellow signify decreased FA in Cluster 3, relative to Cluster 1, at $p < .05$ (corrected for multiple comparisons).

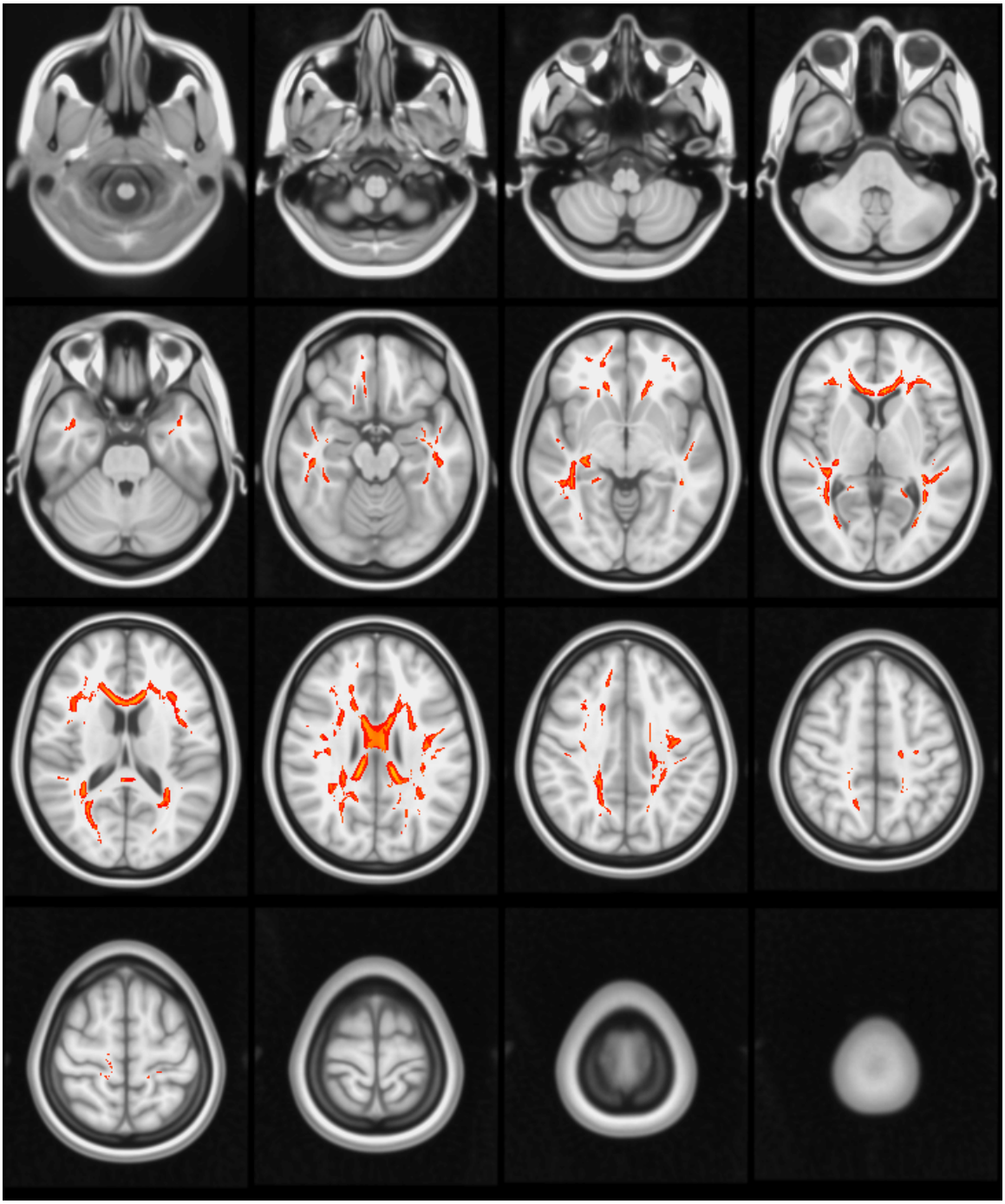

Figure 8.2 TBSS FA Differences Between Cluster 2 and Cluster 3.
Note. Regions of red/yellow signify decreased FA in Cluster 3, relative to Cluster 2 at $p < .05$ (corrected for multiple comparisons).

Chapter 9. Discussion

Using two complementary approaches to the investigation of brain integrity, we have demonstrated white matter microstructural differences within a large marginally-housed sample of persons with physical and psychiatric multimorbidity. Specifically, we compared white matter integrity between three subgroups each characterized by unique profiles of neurocognitive functioning and relatively different rates of substance use, viral infection, and psychiatric illness (see Study 1). As hypothesized, poorer white matter integrity was associated with individuals who have lower neurocognitive functioning and a higher rate of multimorbidity (Cluster 3). The ROI approach and a whole brain voxel-wise analysis (TBSS) yielded comparable findings that indicated widespread, bilateral reductions in FA, with corresponding increases in AD and RD. This pattern is consistent with generalized, as oppose to focal, white matter degradation in Cluster 3. However, in the context of pervasive white matter differences, tract degradation appeared to be proportionally greater in frontal and interhemispheric regions of Cluster 3 when compared to Cluster 2, and more extensive for the left hemisphere of Cluster 3 compared to Cluster 1. Additionally, the relatively greater number of regions showing increased RD compared to AD suggests that the generalized reduction in white matter integrity may be predominately driven by erosion of myelin rather than axonal injury (Song et al., 2003; Song et al., 2005).

We found associations between poorer white matter integrity and poorer neurocognitive functioning, and this is in line with findings from clinical and healthy samples. For example, in schizophrenia patients, FA correlates with measures of verbal memory, attention, and executive functions in tracts specifically known to mediate these respective functions (Lim et al., 2006). Likewise, lower FA and higher diffusivity in frontal and parietal tracts has been linked with poorer performance on an affective decision-making task in cocaine-dependent (Lane et al., 2010) and heroin-dependent subjects (Qiu et al., 2013). On the other hand, when age and motor function were controlled for in cognitively normal adults, associations were identified between

executive functioning, memory, and information processing, and white matter tract integrity in the corresponding functional regions (Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2012). There is further evidence from healthy adults to suggest that variability in neurocognitive performance may also be attributed to global reductions in white matter degradation with coinciding tract-specific reductions (Bennett & Madden, 2014). Thus, our findings of more extensive white matter degradation in the frontal and interhemispheric tracts of Cluster 3 in the context of generalized white matter differences is consistent with the larger DTI literature.

At a broader level, the frontal pattern of results is consistent with typical lifespan trajectories (Burzynska et al., 2010). During development, myelination for higher-order cortical brain regions, specifically the prefrontal cortex, is the last to take place (Toga, Thompson, & Sowell, 2006), and these same regions are the first to degrade in the context of normal aging, following an anterior-posterior gradient (Bennett & Madden, 2014). Admittedly, these typical trajectories may not generalize to a highly multimorbid population. However, emerging evidence suggests that cognitive aging may actually be pre-mature and/or accelerated in substance users (Cheng et al., 2013) and persons with HIV infection (Pfefferbaum et al., 2014), thus it may be realistic to expect early signs of biological and/or cognitive aging in our multimorbid middle-aged population. These effects may be further compounded by the selective impairment of fronto-subcortical circuitry and associated structures involved in addiction and psychiatric illness (Ersche, Williams, Robbins, & Bullmore, 2013; Koob & Volkow, 2010; Pujara & Koenig, 2014).

The pattern of more widespread increases in RD compared to AD suggests that the poorer white matter integrity of Cluster 3 is primarily reflective of demyelination rather than axonal injury (Song et al., 2003; Song et al., 2005). The finding of increased AD was somewhat surprising, and in contrast to our initial expectation, given that *decreased* AD is thought to be reflective of axonal injury (Song et al., 2003). However, the current findings mirror what has been observed in normal aging; specifically consistent increases in RD with less prominent, but more variable, changes in AD involving both region-specific increases and decreases (Burzynska et al., 2010; Madden, Bennett, & Song, 2009). Thus, demyelination appears to play a significant role in degradation of white matter microstructure with age, but other factors are also likely to be contributory

and could account for the varying changes in AD, including decrease in axonal membrane density or reduction in number of axons and/or axonal spacing (Sen & Basser, 2005). In animal models of ischemia, Song and others (2003) observed an initial decrease in AD followed by a trend towards increasing values with concurrent normalization of mean diffusivity, and this was interpreted to be a function of tissue loss. The dynamic nature of these DTI parameters suggests that longitudinal DTI studies are needed to better understand the relationship between these measures and underlying tissue architecture. Nevertheless, it is noteworthy that the pattern of differential diffusivities (more prominent increases in RD) has been frequently observed in clinical samples including substance use (Qiu et al., 2013; Willi et al., 2016), HIV infection (Leite et al., 2013), and related comorbid conditions (Tang et al., 2015). Collectively, this pattern is thought to be characteristic of chronic white matter degeneration (Burzynska et al., 2010).

We also observed a pattern of relatively greater white matter differences in the left hemisphere of Cluster 3 when compared to Cluster 1. Left lateralization of white matter abnormalities is common in the schizophrenia literature (Ellison-Wright & Bullmore, 2009), though a complementary number of studies also report bilateral differences (Kubicki et al., 2007). Recently, Asami and others (2014) demonstrated strong correlations between left hemisphere FA and negative symptoms of chronic schizophrenia patients within the frontal lobe, internal capsule, superior fronto-occipital fasciculus, and the anterior portion of the corpus callosum. It is possible that this could, in part, account for our left hemisphere findings given that Cluster 3 was previously associated with significantly more severe negative symptoms than Cluster 1 (Gicas et al., 2014) and a greater proportion of persons with a schizophrenia diagnosis (see Study 1). There is also some evidence of a predominant left hemisphere effect in heroin users (Wollman et al., 2015) and in persons with cocaine-induced psychosis (Willi et al., 2016), though these findings still exist within the context of global differences.

Along the same lines, the coinciding global and tract-specific white matter degradation observed in Cluster 3, the poorest neurocognitive subgroup, may be largely driven by the differential burden of multimorbid illness across the clusters. This conjecture is supported by our previous work (Gicas et al., 2014) in which Cluster 3 was

characterized as having greater neurological soft signs and more severe negative symptoms. Additionally, in Study 1, we observed relatively higher incidences of schizophrenia spectrum disorders in this subgroup, leading us to characterize the impairments observed in Cluster 3 as having a neurodevelopmental etiology (Marenco & Weinberger, 2000). White matter abnormalities are consistently identified early in the course of psychotic illness in key frontal and temporal tracts, including the superior longitudinal fasciculus, cingulum, uncinate fasciculus, and corpus callosum (see for review Samartzis et al., 2014). More recent evidence has suggested that abnormal neurodevelopment of cerebellar-thalamic circuitry in the prodrome is associated with neurological soft signs and negative symptoms (Mittal et al., 2014). Moreover, white matter integrity in the anterior corona radiata has been shown to worsen as psychiatric disorders progress from the subsyndromal stage to illness onset, and later more chronic stages (Lagopoulos et al., 2013).

It is plausible that the inherently poorer white matter integrity associated with major psychopathology may confer an increased risk for further microstructural degradation with added environmental risk exposure. This notion is highlighted by our recent work with a subset of subjects from the Hotel Study in which poorer FA was observed in frontal and interhemispheric tracts of subjects with cocaine-dependence and substance-induced psychosis, compared to those with cocaine-dependence alone (Willi et al., 2016). In this case, pre-existing aberrant neural circuitry may predispose individuals to psychosis following prolonged or heavy cocaine use – an illicit substance with well known adverse effects on frontal-subcortical white matter integrity (Lane et al., 2010; Romero et al., 2010). At the same time, persons may also be vulnerable to brain degradation as a result of white matter abnormalities that predate development of addiction, which is supported by findings from biological siblings of stimulant dependent persons (Ersche et al., 2012).

Relatedly, Pfefferbaum and colleagues (2007) offer compelling evidence for cumulative white matter damage from other risk exposures. They reported that those with comorbid alcoholism and HIV had lower FA and high mean diffusivity in the corpus callosum compared to those with either condition alone and controls. Further, they reported a large effect for exacerbation of HIV illness by alcohol, whereby those with

AIDS and alcoholism exhibited white matter deficits approximately 2 SDs below expectation. The functional significance of these findings is highlighted by moderately large correlations between various dimensions of motor performance and FA in subsections of the corpus callosum (.34 < r*s* < .48; Pfefferbaum et al., 2007). It is conceivable that any other combination of risk exposures not measured here (e.g., trauma, brain injury, vascular illness) is likely to exert a cumulative impact on white matter integrity and its neurocognitive correlates, yet there remains a clear lack of empirical data that specifically quantify these interactions. The large scope of existing morbidities in this sample and the ways in which these interact are certain to be revealing, making this a prime target for future research with marginalized populations.

Novel findings are presented here but the inherent limitations of the technological tools used to ascertain and analyze white matter integrity warrant acknowledgement. One of the main drawbacks with DTI is the partial voluming effect, which occurs when anisotropy is artificially lowered due to fibres crossing or when tissues are mixed at the white matter/gray matter boundary (Assaf & Pasternak, 2008). Because of this, it is difficult to ascertain reliable white matter data from deep subcortical white matter tracts and smaller, thinner tracts. Attempts to mitigate this problem include thresholding the FA between 0.2 and 0.3 (0.25 in the current study) and using TBSS to create a mean skeleton that generates FA values from tract centers, thus avoiding standard smoothing and alignment procedures that increase partial voluming (Smith et al., 2006). The other main drawback of DTI is the assumption that diffusion of water molecules in white matter follows a Gaussian distribution, which is apt to be violated under conditions of abnormal white matter (Assaf & Pasternak, 2008). Again, TBSS is able to address this issue by demonstrating that Gaussianity is greatly improved when FA values are taken from tract centers, and this was shown to be true in both schizophrenia and healthy control samples (Smith et al., 2006). Lastly, interpretations regarding the underlying tissue microstructure associated with radial and axial diffusivity should be taken with caution. It has been demonstrated that the three principal eigenvalues of the diffusion tensor (in other words “axial” and “radial” diffusivities) can be influenced by eigenvector rotation, which varies across conditions, such as in regions of partial voluming for example (Wheeler-Kingshot & Cercignani, 2009).

Despite technological limitations, DTI measures have demonstrated to be highly robust in identifying white matter abnormalities that are associated with significant neurocognitive consequences (Marquez de la Plata et al., 2011). Moreover, our multi-method approach yielded converging results, which increased our confidence that our pattern of findings reflected meaningful differences across the neurocognitive clusters. To the best of our knowledge, this is the first study to examine the association between white matter integrity and neurocognition in a large socially marginalized sample, making an important contribution to our understanding of the neurobiological vulnerabilities this population faces.

Chapter 10. General Discussion

In two independent and complementary studies, we demonstrated that gray and white matter structural brain markers are differentially associated with unique profiles of neurocognitive functioning in a multimorbid, socially marginalized sample. In Study 1, we re-generated previously derived neurocognitive subgroups described as higher functioning (Cluster 1), lower functioning with a relative decision-making strength (Cluster 3), and intermediate functioning with a relative decision-making weakness (Cluster 2). We linked these clusters with cortical brain measures, and found that greater fronto-temporal gyrification was associated with Cluster 3, compared to the other clusters. Further, we found that age moderated the association between medial orbitofrontal cortical thickness and clusters, whereby greater thickness was associated with Cluster 1 in older individuals, but thinner cortex was associated with Cluster 1 in younger individuals. Lastly, we found a higher number of developmental proxy variables associated with Cluster 3, and a higher number of acquired brain insult/risk exposure variables associated with Clusters 1 and 2. In Study 2, we found widespread and bilateral decreases in white matter integrity in Cluster 3 compared to the others.

Taken altogether, these studies are the first to examine structural brain integrity and neurocognition in a socially marginalized sample. We presented comprehensive data from a large sample, with minimal exclusion criteria, thereby providing a rich representation of the inherent complexity that exists in this population. The significance of our findings can be highlighted in three broad messages: 1) The three neurocognitive clusters represent meaningful and robust subgroups within a heterogeneous population; 2) Gray and white matter structural brain indices are related to neurocognitive subgroups in unique ways – cortical gray matter differences appear to be localized, while white matter differences are more diffuse; 3) Individuals with the poorest neurocognitive functioning are more likely to have experienced longstanding difficulties stemming from early alterations in neurodevelopment, whereas others with selective neurocognitive

impairments are more likely to have experienced acute losses due to environmental insults. Just as there are multiple pathways to becoming homeless or marginally housed, there are also multiple pathways to neurocognitive impairment. Collectively, our findings stand as a significant contribution to our understanding of these dynamic processes in marginalized persons.

10.1. Implications

Our novel findings have important real-world implications. First of all, the characterization of meaningful subgroups is of great utility to the optimization of health service delivery. Centering efforts on identifying the specific factors that result in acute neurocognitive losses for select subgroups with high rates of risk exposures could inform early interventions that help to mitigate future impairments. This is especially critical for younger cohorts who are likely to have had less lifetime risk exposure. Poor outcomes resulting from preventable illnesses, such as viral infection and psychosis (Jones et al., 2015) and geriatric syndromes (Brown, Kiely, Bharel, & Mitchell, 2007) suggest that early and targeted interventions, with prevention in mind, are necessary.

In contrast, those who appear to have a longstanding history of lower neurocognitive functioning with putative neurodevelopmental origins, and who may have an increased risk for further structural and neurocognitive losses in older age, represent a particularly vulnerable subgroup. Such individuals may require more intensive supports at all stages during their lifetime to maintain optimum neurocognitive functioning. This knowledge is particularly relevant for determining which housing interventions (Intensive Case Management versus Aggressive Community Treatment) are most appropriate given differential levels of physical and mental health care needs (Stergiopoulos et al., 2015). Relatedly, those with substantial impairments in executive functioning and memory would benefit most from a supportive group home environment as oppose to living alone (Schutt et al., 2007). A practical recommendation moving forward would be to screen for cognitive impairment given the central role of neurocognition in performing complex everyday activities (Gorman et al., 2009; Morgan & Heaton, 2009). Moreover, screening should be considered especially important in

older adults, around 45 years and over, given neurocognition is more strongly tied to brain integrity in later life (Burzynska et al., 2012).

Additionally, the differential patterns of gray versus white matter across the neurocognitive clusters could offer a unique angle to address the multiple challenges associated with delivering successful interventions. For example, better white matter integrity at the start of treatment for cocaine dependence (Xu et al., 2010) and alcohol dependence (Sorg et al., 2012) has been linked with better treatment outcomes. Moreover, evidence suggests that indices of gray and white matter integrity independently contribute to the differentiation of normal versus pathological neurocognitive aging (Stricker et al., 2013; Wang et al., 2012). Such findings highlight structural brain indices as viable biomarkers that could be used to inform the degree and type of intervention required to maximize treatment gains and outcomes. This also highlights the importance of preserving brain integrity as individuals transition to older adulthood, and relates back to the need for early preventative approaches to health care.

With rising rates of homelessness in high-income countries, recommendations have been put forth that call for integrated and specialized health care teams that are equipped to deal with the multimorbid nature of this population (Fazel et al., 2014). In the face of ineffective health care delivery, we are implored to shift our thinking to embrace a model that enables us to meet individuals at their level. Our findings suggest that, in order to do this we must consider many factors, including the dynamic relationships between brain and behaviour and how these interface with multimorbidity.

10.2. Limitations and Future Directions

We have already noted limitations specific to each of the two studies, however some more general caveats should be considered. First, we do not have a healthy comparison group to determine the extent to which gyrification, cortical thickness, and white matter integrity within clusters is truly abnormal. Unfortunately, recruiting a reasonably matched healthy control group of middle-aged persons with low socioeconomic status and limited years of formal education is challenging. Further, well-

developed normative databases for imaging data do not exist, due in part to the fact that imaging protocols vary widely across studies and thus cannot be directly compared. Nonetheless, our within sample comparisons are still highly informative to our understanding of the unique vulnerabilities confronted by different subgroups.

Secondly, it is possible that there may be a latent fourth cluster that we did not capture, which may represent a particularly low functioning subgroup that were not able to engage with the study. This potentially invisible sub-population may be difficult to make contact with or may be unable to consent to participation in the study. Despite this, all persons who were dwelling in our four target SRO hotels or who had contact with the community court during our target recruitment period were approached for enrolment in the study.

Thirdly, the clusters represent profiles of relative strengths and weaknesses across several core neurocognitive domains, but the associations between structural brain measures and individual neurocognitive measures may reveal a unique and complementary pattern of structure-function associations, which should be addressed in follow-up investigations. Additionally, it would be interesting to directly examine associations between various risk factors and structural measures to better clarify the drivers of brain integrity.

Finally, we studied an inherently heterogeneous population and the drivers of degradation in brain structure and neurocognitive functioning is apt to be multifactorial. It is likely that there are both independent and cumulative impacts as a consequence of neurodevelopmental disorders and environmental risk exposures, including childhood trauma, substance use, viral infection, psychiatric illness, traumatic brain injury, and neurodegenerative diseases associated with aging. Quantifying the cumulative impact of mental and physical illnesses on brain and neurocognition will be an especially important next step, as existing evidence suggests the presence of synergistic effects (Carey et al., 2006; Chang, Ernst, Speck, & Grob, 2005; Pfefferbaum et al., 2007).

The current cross-sectional design and available data preclude our ability to make any definitive conclusions about causal associations. Future longitudinal research investigating the extent to which risk exposures are differentially associated with

changes in brain and neurocognition over time will help contribute to our understanding. Ideally, our current work will enable subsequent investigations to adopt more sophisticated modelling techniques with the overarching aim of conducting a more comprehensive, theoretically-driven analysis of the complex associations between risk factors, brain integrity, and neurocognition.

10.3. Conclusion

We presented novel findings that link gray and white matter structural brain markers to distinct profiles of neurocognitive functioning. This work paves the way for future explorations of brain-behaviour relationships in socially marginalized populations with important implications for health service planning and delivery. There remains much work to be done to understand the risks and challenges marginalized individuals face, especially as these individuals transition to older adulthood. Ultimately, timely development of specialized, integrated, and accessible services is contingent upon further empirical research that aims to elucidate the nature of this heterogeneous and multimorbid population.

References

Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics, 4*(3), 316-329. doi: 10.1016/j.nurt.2007.05.011

Allen, D. N., & Goldstein, G. (Eds.). (2013). *Cluster Analysis in Neuropsychological Research.* New York: Springer.

American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text revision). Washington, DC: Author.

Armstrong, E., Schleicher, A., Omran, H., Curtis, M., & Zilles, K. (1995). The ontogeny of human gyrification. *Cerebral Cortex, 5*(1), 56-63.

Argintaru, N., Chambers, C., Gogosis, E., Farrell, S., Palepu, A., Klodawsky, F., & Hwang, S. (2013). A cross-sectional observational study of unmet health needs among homeless and vulnerably housed adults in three Canadian cities. *BMC Public Health, 13*(577). doi: 10.1186/1471-2458-13-577

Asami, T., Lee, S. H., Bouix, S., Rathi, Y., Whitford, T. J., Niznikiewicz, M.,…Kubicki, M. (2014). Cerebral white matter abnormalities and their associations with negative but not positive symptoms of schizophrenia. *Psychiatry Research: Neuroimaging, 222,* 52-59. doi: 10.1016/j.pscychresns.2014.02.007

Assaf, Y. & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. *Journal of Molecular Neuroscience, 34,* 51-61. doi: 10.1007/s12031-007-0029-0

Assunção Leme, I. B. A., Gadelha, A., Sato, J. R., Ota, V. K., de Jesus Mari, J., Melaragno, M. I.,…Jackowski, A. P. (2013). Is there an association between cortical thickness, age of onset, and duration of illness in schizophrenia? *CNS Spectrums, 18*(6), 315-321. doi:10.1017/S1092852913000333

Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis, 12,* 26-41. doi:10.1016/j.media.2007.06.004

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. *Cognition, 50,* 7-15.

Bechara, A. (2003). Risky business: Emotion, decision-making, and addiction, *Journal of Gambling Studies, 19*(1), 23-51.

Bennett, I. J. & Madden, D. J. (2014). Disconnected aging: Cerebral white matter integrity and age-related differences in cognition. *Neuroscience, 276,* 187-205. Doi: 10.1016/j.neuroscience.2013.11.026

Brandt, J., & Benedict, R. H. B. (2001). *Hopkins verbal learning test-revised: Professional manual.* Lutz, FL: Psychological Assessment Resources Inc.

Brown, R. T., Kiely, D., Bharel, M., & Mitchell, S. L. (2012). Geriatric syndromes in older homeless adults. *Journal of General Internal Medicine, 27*(1), 16-22. doi: 10.1007/s11606-011-1848-9

Buelow, M. T., & Suhr, J. A. (2009). Construct validity of the iowa gambling task. *Neuropsychology Review*, *19*, 102-114. doi:10.1007/s11065-009-9083-4

Burra, T. A., Stergiopoulos, V., & Rourke, S. B. (2009). A systematic review of cognitive deficits in homeless adults: Implications for service delivery. *Canadian Journal of Psychiatry, 54*(2), 123-133.

Burzynska, A. Z., Nagel, I. E., Preuschhof, C., Gluth, S., Bäckman, L., Li, S-C.,…Heekeren, H. R. (2012). Cortical Thickness is linked to executive functioning in adulthood and aging. *Human Brain Mapping, 33,* 1607-1620. doi: 10.1002/hbm.21311

Burzynska, A. Z., Preuschhof, C., Bäckman, L., Nyberg, L., Li, S-C., Lindenberger, U., & Heekeren, H. R. (2010). Age-related differences in white matter microstructure: Region-specific patterns of diffusivity. *NeuroImage, 49,* 2104-2112. doi: 10.1016/j.neuroimage.2009.09.041

Carey, C. L., Woods, S. P., Rippeth, J. D., Gonzalez, R., Heaton, R. K., Grant, I., & the HNRC Group. (2006). Additive deleterious effects of methamphetamine dependence and immunosuppression on neuropsychological functioning in HIV infection. *AIDS and Behavior*, *10*(2), 185-190. doi:10.1007/s10461-005-9056-4

Chan, R. C. K., & Gottesman, I. I. (2008). Neurological soft signs as candidate endophenotypes for schizophrenia: A shooting star or a northern star? *Neuroscience of Biobehavioral Reviews, 32,* 957-971.

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

Chen, E. Y. H., Shapleske, J., Luque, R., McKenna, P. J., Hodges, J. R., Calloway, S. P.,…Berrios, G. E. (1995). The Cambridge Neurological Inventory: A clinical instrument for assessment of soft neurological signs in psychiatric patients. *Psychiatry Research, 56,* 183-204.

Cheng, G. L. F., Zeng, H., Leung, M-K., Zhang, H-J., Lau, B. W. M., Liu, Y-P.,…Lee, T. M. C. (2013). Heroin abuse accelerates biological aging: a novel insight from telomerase and brain imaging interaction. *Translational Psychiatry, 3,* e260. Doi: 10.1038/tp.2013.36

Chouinard, G., & Margolese, H. C. (2005). Manual for the extrapyramidal symptom rating scale (ESRS). *Schizophrenia Research, 76,* 247-265. doi:10.1016/j.schres.2005.02.013

Cohen, J., Cohen, P., West, S. G., & Aiken, L. S. (2003). *Applied multiple regression/correlation analysis for the behavioral sciences* (3rd ed.). Mahwah, NJ: Erlbaum.

Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D.,…Killiany, R. J. (2006). An automatic labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage, 31,* 968-980. doi:10.1016/j.neuroimage.2006.01.021

Ellison-Wright, I. & Bullmore, E. (2009). Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research, 108,* 3-10. doi: 10.1016/j.schres.2008.11.021

Endicott, J. (1988). *Best estimate clinical evaluation and diagnosis form (BECED)*. Department of Research Assessment and Training, New York State Psychiatric Institute, New York, NY.

Ersche, K. D., Fletcher, P. C., Lewis, S. J. G., Clark, L., Stocks-Gee, G., London, M.,…Sahakian, B. J. (2005). Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. *Psychopharmacology*, *180*(4), 612-23. doi:10.1007/s00213-005-2205-7

Ersche, K. D., Barnes, A., Jones, P. S., Morein-Zamir, S., Robbins, T. W., & Bullmore, T. E. (2011). Abnormal structure of frontostriatal brain systems is associated with aspects of impulsivity and compulsivity in cocaine dependence. *Brain, 134,* 2013-2024. doi: 10.1093/brain/awr138

Ersche, K. D., Jones, P. S., Williams, G. B., Turton, A. J., Robbins, T. W., & Bullmore, E. T. (2012). Abnormal brain structure implicated in stimulant drug addiction. *Science, 335*, 601-604. doi: 10.1126/science.1214463

Ersche, K. D., Williams, G. B., Robbins, T. W., & Bullmore, E. T. (2013). Meta-analysis of structural brain abnormalities associated with stimulant drug dependence and neuroimaging of addiction vulnerability and resilience. *Current Opinions in Neurobiology, 25,* 615-624. Doi: 10.1016/j.conb.2013.02.017

Everitt, B. J., & Robbins, T. W. (2013). From the ventral to the dorsal striatum: Devolving views of their roles in drug addiction. *Neuroscience and Biobehavioral Reviews, 37,* 1946-1954. doi: 10.1016/j.neubiorev.2013.02.010

Fahim, C., Yoon, U., Nashaat, N. H., Khalil, A. K., El-Belbesy, M., Mancini-Marie, A.,…Meguid, N. (2012). Williams syndrome: A relationship between genetics, brain morphology and behaviour. *Journal of Intellectual Disability Research, 56*(9), 879-894. doi: 10.1111/j.1365-2788.2011.01490.x

Falkai, P., Honer, W. G., Kamer, T., Dustert, S., Vogeley, K., Schneider-Axmann, T.,…Tepest, R. (2007). Disturbed frontal gyrification within families affected with schizophrenia. *Journal of Psychiatric Research, 41,* 805-813. doi:10.1016/j.jpsychires.2006.07.018

Fazel, S., Geddes, J. R., & Kushel, M. (2014). The health of homeless people in high-income countries: descriptive epidemiology, health consequences, and clinical and policy recommendations, *Lancet, 384,* 1529-1540. doi: 10.1016/S0140-6736(14)61132-6

Fazel, S., Khosla, V., Doll, H., & Geddes, J. (2008). The prevalence of mental disorders among the homeless in western countries: Systematic review and meta-regression analysis. *PLoS Medicine*, *5*(12), 1670-1681. doi:10.1371/journal.pmed.0050225

Fett, A. J., Viechtbauer, W., Dominguez, M., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 35*, 573-588. doi: 10.1016/j.neubiorev.2010.07.001

Filbey, F. M., McQueeny, T., DeWitt, S. J., & Mishra, V. (2015). Preliminary findings demonstrating latent effects of early adolescent marijuana use onset on cortical architecture. *Developmental Cognitive Neuroscience, 16,* 16-22. doi: 10.1016/j.dcn.2015.10.001

Fischl, B. & Dale, A. M. (2000). Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proceedings of the National Academy of Sciences, 97*(20), 11050-11055. doi: 10.1073/pnas.200033797

Fischl, B., van der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H.,…Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex, 14,* 11-22. doi:10.1093/cercor/bhg087

Fjell, A. M., Westlye, L. T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N.,…Walhovd, K. B. (2009). High consistency of regional cortical thinning in aging across multiple samples. *Cerebral Cortex, 19,* 2001-2012. doi:10.1093/cercor/bhn232

Fjell, A. M., Westlye, L. T., Grydeland, H., Amlien, I., Espeseth, T., Reinvang, I.,…the Alzheimer Disease Neuroimaging Initiative. (2014). Accelerating cortical thinning: Unique to dementia or universal in aging? *Cerebral Cortex, 24,* 919-934. doi:10.1093/cercor/bhs379

Fortier, C. B., Leritz, E. C., Salat, D. H., Lindemer, E., Maksimovskiy, A. L., Shepel, J.,…McGlinchey, R. E. (2014). Widespread effects of alcohol on white matter microstructure. *Alcoholism: Clinical and Experimental Research, 38*(12), 2925-2933. Doi: 10.1111/acer.12568

Foussias, G., Agid, O., Fervaha, G., & Remington, G. (2014). Negative symptoms of schizophrenia: Clinical features, relevance to real world functioning and specificity versus other CNS disorders. *European Neuropsychopharmacology, 24,* 693-709. doi: 10.1016/j.euroneuro.2013.10.017

Fray, P.J., Robbins, T.W., & Sahakian, B.J. (1996). Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychiatry, 11*, 329-336.

Gawron, N., Lojek, E., Kijanowska-Haladyna, B., Nestorowicz, J., Harasim, A., Pluta, A., & Sobanska, M. (2014). Cognitive patterns of normal elderly subjects are consistent with frontal cortico-subcortical and frontal-parietal neuropsychological models of brain aging. *Applied Neuropsychology: Adult, 21,* 195-209. doi: 10.1080/09084282.2013.789965

Gicas, K., Vila-Rodriguez, F., Paquet, K., Barr, A. M., Procyshyn, R. M., Lang, D. J.,…Thornton, A. E. (2014). Neurocognitive profiles of marginally housed persons with comorbid substance dependence, viral Infection, and psychiatric illness. *Journal of Clinical and Experimental Neuropsychology, 36*(10), 1009-1022. doi: 10.1080/13803395.2014.963519

Gilbert, E., Merette, C., Jomphe, V., Emond, C., Rouleau, N., Bouchard, R-H.,…Maziade, M. (2014). Cluster analysis of cognitive deficits may mark heterogeneity in schizophrenia in terms of outcome and response to treatment. *European Archives in Psychiatry and Clinical Neuroscience, 264,* 333-343. doi: 10.1007/s00406-013-0463-7

Goldman, A. L., Pezawas, L., Mattay, V. S., Fischl, B., Verchinski, B. A., Chen, Q.,…Meyer-Lindenberg, A. (2009). Widespread reductions of cortical thickness in schizophrenia and spectrum disorders and evidence of heritability. *Archives of General Psychiatry, 66*(5), 467-477. doi:10.1001/archgenpsychiatry.2009.24

Gorman, A. A., Foley, J. M., Ettenhofer, M. L., Hinkin, C. H., & van Gorp, W. G. (2009). Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychological Review, 19,* 186-203.

Goswami, R., Dufort, P., Tartaglia, M. C., Green, R. E., Crawley, A., Tator, C. H.,…Davis, K. D. (2015). Frontotemporal correlates of impulsivity and machine learning in retired professional athletes with a history of multiple concussions. *Brain Structure and Function.* Advance online publication. doi: 10.1007/s00429-015-1012-0

Harris, J. M., Yates, S., Miller, P., Best, J. J. K., Johnstone, E. C., & Lawrie, S. M. (2004). Gyrification in first-episode schizophrenia: A morphometric study. *Biological Psychiatry, 55,* 141-147. doi: 10.1016/S0006-3223(03)00789-3

Harris, J. M., Moorhead, T. W. J., Miller, P., McIntosh, A. M., Bonnici, H. M., Owens, D. G. C.,…Lawrie, S. M. (2007). Increased prefrontal gyrification in a large high-risk cohort characterizes those who develop schizophrenia and reflects abnormal prefrontal development. *Biological Psychiatry, 62,* 722-729. doi:10.1016/j.biopsych.2006.11.027

Hayes, A. F., & Matthes, J. (2009). Computational procedures for probing interactions in OLS and logistic regression: SPSS and SAS implementations. Behavior Research Methods, 41(3), 924-936. doi: 10.3758/BRM.41.3.924

Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2004). *Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults*. Lutz, FL: Psychological Assessment Resources.

He, J., Wong, V. S. S., Fletcher, E., Maillard, P., Lee, D. Y., Iosif, A-M.,…DeCarli, C. (2012). The contributions of MRI based measures of gray matter, white matter hyperintensity, and white matter integrity to late life cognition. *American Journal of Neuroradiology, 33,* 1797-1803. doi:10.3174/ajnr.A3048

Hester, R. & Garavan, H. (2004). Executive dysfunction in cocaine addiction: Evidence for discordant frontal, cingulate, and cerebellar activity. *The Journal of Neuroscience, 24*(49), 11017-11022. doi: 10.1523/JNEUROSCI.3321-04.2004

Hogstrom, L. J., Westlye, L. T., Walhovd, K. B., & Fjell, A. M. (2013). The structure of the cerebral cortex across adult life: Age-related patterns of surface area, thickness, and gyrification. *Cerebral Cortex, 23,* 2521-2530. doi: 10.1093/cercor/bhs231

Holt, J. L., Kraft-Terry, S. D., & Chang, L. (2012). Neuroimaging studies of the aging HIV-1-infected brain. *Journal of Neurovirology, 18,* 291-302. doi: 10.1007/s13365-012-0114-1

Honer, W. G., Cervantes-Larios, A., Vila-Rodriguez, F., Montaner, J. S., Tran, H., Panenka, W. J.,…Schultz, K. (2016). *The Hotel Study – Adapting Global Health for a Global City.* Manuscript submitted for publication.

Hooper, L. M., Stockton, P., Krupnick, J. L., & Green, B. L. (2011). Development, use, and psychometric properties of the trauma history questionnaire. *Journal of Loss and Trauma, 16*(3), 258-283. doi: 10.1080/15325024.2011.572035

Hosmer, D. W., & Lemeshow, S. (2000). *Applied Logistic Regression.* New York: Wiley.

Hwang, S. W., Aubry, T., Palepu, A., Farrell, S., Nisenbaum, R., Hubley, A. M.,…Chambers, C. (2011). The health and housing transition study: a longitudinal study of the health of homeless and vulnerably housed adults in three canadian cities. *International Journal of Public Health, 56,* 609-623. doi: 10.1007/s00038-011-0283-3

Hwang, S. W., Chambers, C., Chiu, S., Katic, M., Kiss, A., Redelmeier, D. A., & Levinson, W. (2013). A comprehensive assessment of health care utilization among homeless adults under a system of universal heath insurance. *American Journal of Public Health, 103*(52), s294-s301. doi: 10.2105/AJPH.2013.301369

Hwang, S. W., Weaver, J., Aubry, T., & Hoch, J. S. (2011). Hospital costs and length of stay among homeless patients admitted to medical, surgical, and psychiatric services. *Medical Care, 49*(4), 350-354. doi: 10.1097/MLR.0b013e318206c50d

Hwang, S. W., Wilkins, R., Tjepkema, M., O'Campo, P. J., & Dunn, J. R. (2009). Mortality among residents of shelters, rooming houses, and hotels in Canada: 11 year follow-up study. *British Medical Journal*, *339*, b4036. doi:10.1136/bmj.b4036

Infante, M. A., Moore, E. M., Bischoff-Grethe, A., Migliorini, R., Mattson, S. N., & Riley, E. P. (2015). Atypical cortical gyrification in adolescents with histories of heavy prenatal alcohol exposure. *Brain Research, 1624,* 446-454. doi: 10.1016/j.brainres.2015.08.002

Jacobson, M. W., McEvoy, L. K., Dale, A., & Fennema-Notestine, C. (2009). Cognitive phenotypes, brain morphometry and the detection of cognitive decline in preclinical AD. *Behavioral Neurology, 21*(1), 29-37. doi:10.3233/BEN-2009-0229

Jacobus, J., Squeglia, L. M., Sorg, S. F., Nguyen-Louie, T. T., & Tapert, S. F. (2014). Cortical thickness and neurocognition in adolescent marijuana and alcohol users following 28 days of monitored abstinence. *Journal of Studies on Alcohol and Drugs, 75,* 729-743.

Jacobus, J., Squeglia, L. M., Meruelo, A. D., Castro, N., Brumback, T., Giedd, J. N., & Tapert, S. F. (2015). Cortical thickness in adolescent marijuana and alcohol users: A three-year prospective study from adolescence to young adulthood. *Developmental Cognitive Neuroscience, 16,* 101-109. doi: 10.1016/j.dcn.2015.04.006

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage, 62,* 782-790. Doi: 10.1016/j.neuroimage.2011.09.015

Jones, A. A., Vila-Rodriguez, F., Leonova, O., Langheimer, V., Lang, D. J., Barr, A. M.,…Honer, W. G. (2015). Mortality from treatable illnesses in marginally housed adults: A prospective cohort study. *BMJ Open,* 5, e008876. doi: 10.1136/bmjopen-2015-008876

Kaiser, S., Heekeren, K., & Simon, J. J. (2010). The negative symptoms of schizophrenia: Category or continuum? *Psychopathology, 44,* 345-353. doi: 10.1159/000325912

Kay, S.R., Fiszbein, A., & Opler, L.A. (1987). The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*, 261-276.

Kelly, P. A., Viding, E., Wallace, G. L., Schaer, M., De Brito, S. A., Robustelli, B., & McCrory, E. J. (2013). Cortical thickness, surface area, and gyrification abnormalities in children exposed to maltreatment: Neural markers of vulnerability? *Biological Psychiatry, 74,* 845-852. doi:10.1016/j.biopsych.2013.06.020

Koob, G. F., & Volkow, N. D. (2010). Neurocircuitry of addiction. *Neuropsychopharmacology, 35,* 217-238. doi: 10.1038/npp.2009.110

Krausz, R. M., Clarkson, A. F., Strehlau, V., Torchalla, I., Li, K., & Scheutz, C. (2013). Mental disorder, service use, and barriers to care among 500 homeless people in 3 different urban settings. *Social Psychiatry and Psychiatric Epidemiology, 48,* 1235-1243. doi: 10.1007/s00127-012-0649-8

Kubicki, M., McCarley, R., Westin, C-F., Park, H-J., Maier, S., Kikinis, R.,…Shenton, M. E. (2007). A review of diffusion tensor imaging studies in schizophrenia. *Journal of Psychiatric Research, 41,* 15-30. doi:10.1016/j.jpsychires.2005.05.005

Lacerda, A. L. T., Hardan, A. Y., Yorbik, O., Vemulapalli, M., Prasad, K. M., & Keshavan, M. S. (2007). Morphology of the orbitofrontal cortex in first-episode schizophrenia: Relationship with negative symptomatology. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 31*(510-516). doi: 10.1016/j.pnpbp.2006.11.022

Lagopoulos, J., Hermens, D. F., Hatton, S. N., Battisti, R. A., Tobias-Webb, J., White, D.,…Hickie, I. B. (2013). Microstructural white matter changes are correlated with the stage of psychiatric illness. *Translational Psychiatry, 3*, e248. Doi: 10.1038/tp.2013.25

Lane, S. D., Steinberg, J. L., Ma, L., Hasan, K. M., Kramer, L. A., Zuniga, E. A.,…Moeller, F. G. (2010). Diffusion tensor imaging and decision making in cocaine dependence. *PLoS One, 5*(7), e11591. doi: 10.1371/journal.pone.0011591

Lawyer, G., Bjerkan, P. S., Hammarberg, A., Jayaram-Lindström, N., Franck, J., & Agartz, I. (2010). Amphetamine dependence and co-morbid alcohol abuse: Associations to brain cortical thickness. BMC Pharmacology, 10(5), 1-10. doi: 10.1186/1471-2210-10-5

Leite, S. C. B., Correa, D. G., Doring, T. M., Kubo, T. T. A., Netto, T. M., Ferracini, R.,…Gasparetto, E. L. (2013). Diffusion tensor MRI evaluation of the corona radiata, cingulate gyri, and corpus callosum in HIV patients. *Journal of Magnetic Resonance Imaging, 38,* 1488-1493. doi: 10.1002/jmri.24129

Lemaitre, H., Golman, A. L., Sambataro, F., Verchinski, B. A., Meyer-Lindenberg, A., Weinberger, D. R., & Mattay, V. S. (2012). Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area, and gray matter volume? *Neurobiology of Aging, 32,* 617.e1-617.e9. doi:10.1016/j.neurobiolaging.2010.07.013

Lim, K. O., Ardekani, B. A., Nierenberg, J., Butler, P. D., Javitt, D. C., & Hoptman, M. J. (2006). Voxelwise correlational analyses of white matter integrity in multiple cognitive domains in schizophrenia. *American Journal of Psychiatry, 163,* 2008-2010.

London, E. D., Kohno, M., Morales, A. M., & and Ballard, M. E. (2015). Chronic methamphetamine abuse and corticostriatal deficits revealed by neuroimaging. *Brain Research, 1628*(Pt A), 174-185. doi: 10.1016/j.brainres.2014.10.044

Lowe, C., & Rabbitt, P. (1998). Test\re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. *Neuropsychologia*, *36*(9), 915-923. doi:10.1016/S0028-3932(98)00036-0

Luo, X., Zhang, S., Hu, S., Bednarski, S. R., Erdman, E., Farr, O. M.,…Li, C-S. (2013). Error processing and gender-shared and –specific neural predictors of relapse in cocaine dependence. *Brain, 136,* 1231-1244. doi: 10.1093/brain/awt040

Lyne, J., Renwick, L., Madigan, K., O'Donoghue, B., Bonar, M., Grant, T.,…Clarke, M. (2014). Do psychosis prodrome onset negative symptoms predict first presentation negative symptoms? *European Psychiatry, 29,* 153-159. doi: 10.1016/j.eurpsy.2013.02.003

Madden, D. J., Bennett, I. J., & Song, A. W. (2009). Cerebral white matter integrity and cognitive aging: Contributions from diffusion tensor imaging. *Neuropsychological Review, 19,* 415-435. doi: 10.1007/s11065-009-9113-2

Manly, J. J., Smith, C., Crystal, H. A., Richardson, J., Golub, E. T., Greenblatt, R.,…Young, M. (2011). Relationship of ethnicity, age, education, and reading level to speed and executive function among HIV+ and HIV- women: The woman's interagency HIV study (WIHS) neurocognitive substudy. *Journal of Clinical and Experimental Neuropsychology*, *33*(8), 853-863. doi: 10.1080/13803395.2010.547662

Marenco, S. & Weinberger, D. R. (2000). The neurodevelopmental hypothesis of schizophrenia: Following a trail of evidence from cradle to grave. *Development and Psychopathology, 12,* 501-527.

Marquez de la Plata, C. D., Yang, F. G., Wang, J. Y., Krishnan, K., Bakhadirov, K., Paliotta, C.,…Diaz-Arrastia, R. (2011). Diffusion tensor imaging biomarkers for traumatic axonal injury: Analysis of three analytic methods. *Journal of the International Neuropsychological Society, 17,* 24-35. doi: 10.1017/S1355617710001189

McGinnis, S. M., Brickhouse, M., Pascual, B., & Dickerson, B. D. (2011). Age-related changes in the thickness of cortical zones in humans. *Brain Topography, 24,* 279-291. doi:10.1007/s10548-011-0198-6

Miller, E. K., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience, 24,* 167-202.

Mittal, V. A., Dean, D. J., Bernard, J. A., Orr, J. M., Pelletier-Baldelli, A., Carol, E. E.,…Millman, Z. B. (2014). Neurological soft signs predict abnormal cerebellar-thalamic tract development and negative symptoms in adolescents at high risk for psychosis: A longitudinal perspective. *Schizophrenia Bulletin, 40*(6), 1204-1215. doi: 10.1093/schbul/sbt199

Momenam, R., Steckler, L. E., Saad, Z. S., van Rafelghem, S., Kerich, M. J., & Hommer, D. W. (2012). Effects of alcohol dependence on cortical thickness as determined by magnetic resonance imaging. *Psychiatry Research: Neuroimaging, 204,* 101-111. doi: 10.1016/j.pscychresns.2012.05.003

Morgan, E. E., & Heaton, R. K. (2009). Neuropsychology in relation to everyday functioning. In I. Grant & K. M. Adams (Eds.), *Neuropsychological Assessment of Neuropsychiatric and Neuromedical Disorders* (3rd ed., pp. 632-651). New York, New York: Oxford University Press.

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K.,…Mazziota, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage, 40,* 570-582. doi: 10.1016/j.neuroimage.2007.12.035

Mueser, K. T., Salyers, M. P., Rosenberg, S. D., Ford, J. D., Fox, L., & Carty, P. (2001). Psychometric evaluation of trauma and posttraumatic stress disorder assessments in persons with severe mental illness. *Psychological Assessment, 13*(1), 110-117. Doi:10.1037//1040-3590.13.1.110

O'Callaghan, C., Bertoux, M., & Hornberger, M. (2014). Beyond and below the cortex: The contribution of striatal dysfunction to cognition and behaviour in neurodegeneration. *Journal of Neurology, Neurosurgery, and Psychiatry, 86*(7), 371-378. doi: 10.1136/jnnp-2012-304558

Palaniyappan, L., Mallikarjun, P., Joseph, V., White, T. P., & Liddle, P. F. (2011). Folding of the prefrontal cortex in schizophrenia: Regional differences in gyrification. *Biological Psychiatry, 69,* 974-979. doi:10.1016/j.biopsych.2010.12.012

Pfefferbaum, A., Rogosa, D. A., Rosenbloom, M. J., Chu, W., Sassoon, S. A., Kemper, C.A.,…Sullivan, E. V. (2014). Accelerated aging of selective brain structures in human immunodeficiency virus infection: A controlled, longitudinal magnetic resonance imaging study. *Neurobiology of Aging, 35,* 1755-1768. doi: 10.1016/j.neurobiolaging.2014.01.008

Pfefferbaum, A., Rosenbloom, M. J., Adalsteinsson, E., & Sullivan, E. V. (2007). Diffusion tensor imaging with quantitative fibre tracking in HIV infection and alcoholism comorbidity: synergistic white matter damage. *Brain, 130,* 48-64. doi: 10.1093/brain/awl242

Piskulic, D., Addington, J., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., Heinssen, R.,…McGlashan, T. H. (2012). Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Research, 196,* 220-224. doi: 10.1016/j.psychres.2012.02.018

Pluck, G., Lee, K-H., David, R., Spence, S. A., & Parks, R. W. (2012). Neuropsychological and cognitive performance of homeless adults. *Canadian Journal of Behavioural Science*, *44*(1), 9-15. doi: 10.1037/a0025382

Premkumar, P., Kumari, V., Corr, P. J. J., Fannon, D., & Sharma, T. (2008). Neuropsychological function-brain structure relationships and stage of illness: An investigation into chronic and first episode schizophrenia. *Psychiatry Research: Neuroimaging, 162,* 195-204. doi:10.1016/j.pscychresns.2007.08.005

Pujara, M., & Koenigs, M. (2014). Mechanisms of reward circuit dysfunction in psychiatric illness: Prefrontal-striatal interactions. *The Neuroscientist, 20*(1), 82-95. Doi: 10.1177/1073858413499407

Qiu, Y., Jiang, G., Su, H., Lv, X., Zhang, X., Tian, J., & Zhuo, F. (2013). Progressive white matter microstructure damage in male chronic heroin dependent individuals: A DTI and TBSS study. *PLoS One, 8*(5), e63212. Doi: 10.1371/journal.pone.0063212

Raz, N., & Rodrigue, K. M. (2006). Differential aging of the brain: Patterns, cognitive correlates and modifiers. *Neuroscience and Biobehavioral Reviews, 30,* 730-748. doi:10.1016/j.neubiorev.2006.07.001

Robertson, M. J., Clark, R. A., Charlebois, E. D., Tulsky, J., Long, H. L., Bangsberg, D. R., & Moss, A. R. (2004). HIV seroprevalence among homeless and marginally housed adults in San Francisco. *American Journal of Public Health*, *94*(7), 1207-1217.

Romero, M. J., Asensio, S., Palau, C., Sanchez, A., & Romero, F. J. (2010). Cocaine addiction: Diffusion tensor imaging study of the inferior frontal and anterior cingulate white matter. *Psychiatry Research: Neuroimaging, 181,* 57-63. doi: 10.1016/j.pscychresns.2009.07.004

Samartzis, L., Dima, D., Fusar-Poli, P., & Kyriakopoulos, M. (2014). White matter alterations in early stages of schizophrenia: A systematic review of diffusion tensor imaging studies. *Journal of Neuroimaging, 24,* 101-110. doi: 10.1111/j.1552-6569.2012.00779.x

Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2012). Structural correlates of cognitive domains in normal aging with diffusion tensor imaging. *Brain Structure and Function, 217,* 503-515. doi: 10.1007/s00429-011-0344-7

Schaer, M., Cuadra, M. B., Tamarit, L., Lazeyras, F., Eliez, S., & Thiran, J-P. (2008). A surface-based approach to quantify local cortical gyrification. *IEEE Transactions on Medical Imaging, 27*(2), 161-170. doi: 10.1109/TMI.2007.903576

Schnack, H. G., van Haren, N. E. M., Brouwer, R. M., Evans, A., Durston, S., Boomsma, D. I.,…Hulshoff Pol, H. E. (2015). Changes in thickness and surface area of the human cortex and their relationship with intelligence. *Cerebral Cortex, 25,* 1608-1617. doi: 10.1093/cercor/bht357

Schultz, C. C., Koch, K., Wagner, G., Roebel, M., Nenadic, I., Gaser, C.,…Schlösser, R. G. M. (2010). Increased parahippocampal and lingual gyrification in first-episode schizophrenia. *Schizophrenia Research, 123,* 137-144. doi: 10.1016/j.schres.2010.08.033

Schutt, R. K., Seidman, L. J., Caplan, B., Martsinkiv, A., & Goldfinger, S. M. (2007). The role of neurocognition and social context in predicting community functioning among formerly homeless seriously mentally ill persons. *Schizophrenia Bulletin, 33*(6), 1388-1396. doi: 10.1093/schbul/sbm037

Sen, P. N. & Basser, P. J. (2005). A model for diffusion in white matter in the brain. *Biophysical Journal, 69,* 2927-2938. doi: 10.1529/biophysj.105.063016

Shannon, K., Ishida, T., Lai, C., & Tyndall, M. W. (2006). The impact of unregulated single room occupancy hotels on the health status of illicit drug users in Vancouver. *International Journal of Drug Policy*, *17*(2), 107-114. doi:10.1016/j.drugpo.2005.09.002

Sheehan, D. V., Lecrubier, Y., Sheehan, K. H., Amorim, P., Janavs, J., Weiller, E.,…Dunbar, G. C. (1998). The Mini-international neuropsychiatric interview (M.I.N.I): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry, 59*(s20), 22-33.

Shollenbarger, S. G., Price, J., Wieser, J., & Lisdahl, K. (2015). Impact of cannabis use on prefrontal and parietal cortex gyrification and surface area in adolescents and emerging adults. *Developmental Cognitive Neuroscience.* Advance online publication. doi: 10.1016/j.dcn.2015.07.004

Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E.,…Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *NeuroImage, 31,* 1487-1505. Doi: 10.1016/j.neuroimage.2006.02.024

Song, S-K., Sun, S-W., Ju, W-K., Lin, S-J., Cross, A. H., & Neufeld, A. H. (2003). Diffusion tensor imaging detects and differentiates axon and myelin degeneration in mouse optic nerve after retinal ischemia. *NeuroImage, 20,* 1714-1722. Doi: 10.1016/j.neuroimage.2003.07.005

Song, S-K., Yoshino, J., Le, T. Q., Lin, S-J., Sun, S-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage, 26,* 132-140. Doi: 10.1016/j.neuroimage.2005.01.028

Sorg, S. F., Taylor, M. J., Alhassoon, O. M., Gongvatana, A., Theilmann, R. J., Frank, L. R., & Grant, I. (2012). Frontal white matter integrity predictors of adult alcohol treatment outcome. *Biological Psychiatry, 71,* 262-268. doi: 10.1016/j.biopsych.2011.09.022

Stanfield, A. C., Moorhead, T. W. J., Harris, J. M., Owens, D. G. C., Lawrie, S. M., & Johnstone, E. C. (2008). Increased right prefrontal cortical folding in adolescents at risk of schizophrenia for cognitive reasons. *Biological Psychiatry, 63,* 80-85. doi: 10.1016/j.biopsych.2007.04.012

Stergiopoulos, V., Burra, T., Rourke, S., & Hwang, S. (2011). Housing status as an independent predictor of functional capacity in patients with schizophrenia. *The Journal of Nervous and Mental Disease, 199*(11), 854-860. doi: 10.1097/NMD.0b013e3182349cfc

Stergiopoulos, V., Cusi, A., Bekele, T., Skosireva, A., Latimer, E., Schütz, C.,…Rourke, S. B. (2015). Neurocognitive impairment in a large sample of homeless adults with mental illness. *Acta Psychiatrica Scandinavica, 131*(4), 256-268. doi: 10.1111/acps.12391

Stergiopoulos, V., Hwang, S. W., Gozdzik, A., Nisenbaum, R., Latimer, E., Rabouin, D.,...Goering, P. N. (2015). Effect of scattered-site housing using rent supplements and intensive case management on housing stability among homeless adults with mental illness: A randomized trial. *JAMA, 313*(9), 905-915. doi: 10.1001/jama.2015.1163

Storsve, A. B., Fjell, A. M., Tamnes, C. K., Westlye, L. T., Overbye, K., Aasland, H. W., & Walhovd, K. B. (2014). Differential longitudinal changes in cortical thickness, surface area, and volume across the adult lifespan: Regions of accelerating and decelerating change. *The Journal of Neuroscience, 34*(25), 8488-8498. doi:10.1523/JNEUROSCI.0391-14.2014

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms, and commentary* (3rd ed.). New York: Oxford University Press.

Stricker, N. H., Salat, D. H., Foley, J. M., Zink, T. A., Kellison, I. L., McFarland, C. P.,…Leritz, E. C. (2013). Decreased white matter integrity in neuropsychologically define mild cognitive impairment is independent of cortical thinning. *Journal of the International Neuropsychological Society, 19,* 925-937. doi: 10.1017/S1355617713000660

Stuss, D. T., & Levine, B. (2002). Adult clinical neuropsychology: Lessons from studies of the frontal lobes. *Annual Review of Psychology, 53,* 401-433.

Tabachnik, B. G., & Fidell, L. S. (2013). *Using Multivariate Statistics* (6th ed.). Boston, MA: Pearson.

Tang, V. M., Lang, D. J., Giesbrecht, C. J., Panenka, W. J., Willi, T., Procyshyn, R. M.,…Barr, A. M. (2015). White matter deficits assessed by diffusion tensor imaging and cognitive dysfunction in psychostimulant users with comorbid human immunodeficiency virus infection. *BMC Research Notes, 8*, 515. doi: 10.1186/s13104-015-1501-5

Thambisetty, M., Wan, J., Carass, A., An, Y., Prince, J. L., & Resnick, S. M. (2010). Longitudinal changes in cortical thickness associated with normal aging. *NeuroImage, 52,* 1215-1223. doi:10.1016/j.neuroimage.2010.04.258

Toga, A. W., Thompson, P. M., & Sowell, E. R. (2006). Mapping brain maturation. *TRENDS in Neurosciences, 29*(3), 148-159. Doi: 10.1016/j.tins.2006.01.007

Tremblay, S., De Beaumont, L., Henry, L. C., Boulanger, Y., Evans, A. C., Bourgouin, P.,…Lassonde, M. (2013). Sports concussions and aging: A neuroimaging investigation. *Cerebral Cortex, 23,* 1159-1166. doi:10.1093/cercor/bhs102

Unterrainer, H. F., Hiebler, M., Ragger, K., Froehlich, L., Koschutnig, K., Schoeggl, H.,…Fink, A. (2015). White matter integrity in polydrug users in relation to attachment and personality: A controlled diffusion tensor imaging study. *Brain Imaging and Behavior.* Advance online publication. doi: 10.1007/s11682-015-9475-4

Upadhyay, J., Maleki, N., Potter, J., Elman, I., Rudrauf, D., Knudsen, J.,…Borsook, D. (2010). Alterations in brain structure and functional connectivity in prescription opioid-dependent patients. *Brain, 133,* 2098-2114. doi: 10.1093/brain/awq/138

Van Haren, N. E. M., Schnack, H. G., Cahn, W., van den Heuvel, M. P., Lepage, C., Collins, L.,…Kahn, R. S. (2011). Changes in cortical thickness during the course of illness in schizophrenia. *Archives of General Psychiatry, 68*(9), 871-880. doi: 10.1001/archgenpsychiatry.2011.88.

Van Petten, C. (2004). Relationship between hippocampal volume and memory ability in healthy individuals across the lifespan: review and meta-analysis. *Neuropsychologia, 42*, 1394-1413. doi: 10.1016/j.neuropsychologia.2004.04.006

Ventura, J., Subotnik, K. L., Gitlin, M. J., Gretchen-Doorly, D., Ered, A., Villa, K. F.,…Nuechterlein, K. H. (2015). Negative symptoms and functioning during the first year after a recent onset of schizophrenia and 8 years later. *Schizophrenia Research, 161,* 407-413. doi: 10.1016/j.schres.2014.10.043

Vernooij, M. W., Ikram, M. A., Tanghe, H. L., Vincent, A. J. P. E., Hofman, A., Krestin, G. P.,…van der Lugt. (2007). Incidental findings on brain MRI in the general population. *New England Journal of Medicine, 357,* 1821-1828. doi: 10.1056/NEJMoa070972

Vila-Rodriguez, F., Panenka, W. J., Lang, D. J., Thornton, A. E., Vertinsky, T., Wong, H.,…Honer, W. G. (2013). The Hotel Study: Multimorbidity in a community sample living in marginal housing. *American Journal of Psychiatry, 170*(12), 1413-1422. doi: 10.1176/appi.ajp.2013.12111439

Vogeley, K., Schneider-Axmann, T., Pfeiffer, U., Tepest, R., Bayer, T. A., Bogerts, B.,…Falkai, P. (2000). Disturbed gyrification of the prefrontal region in male schizophrenic patients: A morphometric postmortem study. *American Journal of Psychiatry, 157*(1), 34-39.

Wallace, G. L., Robustelli, B., Dankner, N., Kenworthy, L., Giedd, J. N., & Martin, A. (2013). Increased gyrification, but comparable surface area in adolescents with autism spectrum disorders. *Brain, 136,* 1956-1967. doi: 10.1093/brain/awt106

Wang, L., Goldstein, F. C., Veledar, E., Levey, A. I., Lah, J. J., Meltzer, C. C., Holder, C. A., & Mao, H. (2012). Alterations in cortical thickness and white matter integrity in mild cognitive impairment measured by whole-brain cortical thickness mapping and diffusion tensor imaging. *American Journal of Neuroradiology, 30*, 893-899. doi: 10.3174/ajnr.A1484

Wechsler, D. (2001). *Wechsler test of adult reading (WTAR).* San Antonio, TX: The Psychological Corporation.

Wheeler-Kingshott, C. A. M. & Cercignani, M. (2009). About "axial" and "radial" diffusivities. *Magnetic Resonance in Medicine, 61,* 1255-1260. doi: 10.1002/mrm.21965

White, T., Su, S., Schmidt, M., Kao, C-Y., & Sapiro, G. (2010). The development of gyrification in childhood and adolescence. *Brain and Cognition, 72,* 36-45. doi: 10.1016/j.bandc.2009.10.009

Willi, T. S., Barr, A. M., Gicas, K., Lang, D. J., Vila-Rodriguez, F., Su, W.,…Panenka, W. J. (2015). Characterization of white matter integrity deficits in cocaine-dependent individuals with substance-induced psychosis compared with non-psychotic cocaine users. *Addiction Biology.* Advance online publication. doi: 10.1111/adb.12363

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. M. (2014). Permutation inference for the general linear model. *NeuroImage, 92,* 381-397. doi: 10.1016/j.neuroimage.2014.01.060

Wollman, S. C., Alhassoon, O. M., Stern, M. J., Hall, M. G., Rompogren, J., Kimmel, C. L., & Perez-Figueroa, A. M. (2015). White matter abnormalities in long-term heroin users: a preliminary neuroimaging meta-analysis. *The American Journal of Drug and Alcohol Abuse, 4*(12), 133-138. Doi: 10.3109/00952990.2014.985829

Xu, J., DeVito, E. E., Worhunsky, P. D., Carroll, K. M., Rounsaville, B. J., & Potenza, M. N. (2010). White matter integrity is associated with treatment outcome measures in cocaine dependence. *Neuropsychopharmacology, 35,* 1541-1549. doi: 10.1038/npp.2010.25

Appendix A.

SRO and Community Court Sample Comparisons

Table A1. Comparison of SRO and Community Court Sample Characteristics

Variable	Participants		Test statistic (p-value)
	SRO (n = 251)	CC (n = 48)	
Age, M (SD)	43.53 (9.36)	42.17 (10.41)	*t* = 0.91 (.362)
Education, M (SD)	10.35 (2.27)	10.33 (2.12)	*t* = 0.06 (.952)
Gender (M:F)	195:56	40:8	χ^2 = .05 (.382)
WTAR FSIQ, M (SD)	97.43 (8.70)	97.90 (9.15)	*t* = -0.34 (.734)
HVLT Immediate Recall, M (SD)	19.10 (5.26)	20.46 (5.87)	*t* = -1.60 (.110)
Stroop Color-Word Trial, M (SD)	35.71 (10.13)	36.34 (9.91)	*t* = -0.39 (.694)
RVIP A', M (SD)	0.86 (0.07)	0.87 (0.05)	*t* = -0.70 (.485)
IDED Total Adjusted Errors, M (SD)	56.72 (45.75)	56.98 (47.93)	*t* = -0.04 (.972)
IGT Net Score, M (SD)	-5.95 (32.48)	-0.65 (32.35)	*t* = -0.89 (.373)
Total PANSS, M (SD)	66.69 (17.10)	72.00 (12.15)	*t* = -2.44 **(.017)**
Positive subscale	15.22 (5.61)	16.05 (5.54)	*t* = -0.89 (.376)
Negative subscale	16.12 (6.09)	16.55 (3.59)	*t* = -0.63 (.531)
General subscale	35.35 (8.19)	39.40 (7.45)	*t* = -2.99 **(.003)**
Total NSS, M (SD)	12.53 (7.67)	10.79 (6.66)	*t* = 1.20 (.232)
Total EPS, M (SD)	10.80 (10.45)	13.92 (8.11)	*t* = -1.82 (.070)
Total Viral Exposure, M (SD)	2.89 (1.19)	2.52 (1.42)	*t* = 1.81 (.071)

Note. Bold text represents statistical significance at p < .05. SRO = Single room occupancy; CC = Community court; WTAR = Wechsler Test of Adult Reading; HVLT = Hopkins Verbal Learning Test; RVIP = Rapid Visual Information Processing; IDED = Intra Dimensional Extra Dimensional; IGT = Iowa Gambling Task; PANSS = Positive and Negative Syndrome Scale; NSS = Neurological soft signs; EPS = Extrapyramidal symptoms.

Appendix B.

Neurocognitive Measures

Premorbid IQ

The Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) was used to estimate premorbid intellectual functioning. Participants were provided with a page printed with 50 irregularly spelled English words and were instructed to read the words aloud in a continuous manner. The total score (number of words read correctly) was used, in conjunction with age, gender, ethnicity[3], and years of education, to derive an estimate of full scale IQ using the WTAR normative database. For participants with missing or invalid WTAR data, estimated premorbid IQ was obtained using the WTAR normative database that derives a predicted score on the basis of demographic data only (age, gender, ethnicity, years of education). The WTAR demonstrates strong psychometric properties. Test-retest reliability values are excellent (>.90; Wechsler, 2001) and construct validity is demonstrated by strong correlations between the WTAR and verbal and full scale IQ scores on the Wechsler Adult Intelligence Scale 3rd edition (r = .75 and r = .73 respectively).

Verbal Memory

The Hopkins Verbal Learning Test-Revised (HVLT-R; Brandt & Benedict, 2001) was used to index verbal learning and memory. Parallel forms (Versions 1 and 2) were administered to participants in counterbalanced fashion. Participants were read aloud a list of 12 words from three semantic categories and asked to recall as many words as possible immediately following the end of the list. This was repeated for 3 consecutive trials. The total number of words recalled across the three trials was summed to create an index of immediate verbal memory. Although other sub-measures can be obtained from the HVLT-R, including scores for delayed and recognition memory, the immediate verbal memory score represents the most stable and reliable sub-measure. Test-retest for the immediate recall score has been deemed good (r = .74; Brandt & Benedict, 2001). Additionally, the HVLT-R demonstrates acceptable construct validity as it correlates with similar standardized tests including the California Verbal Learning Test (r = .36) and the Logical Memory subtest from the Wechsler Memory Scale (r = .65-.77).

Attention

Sustained attention (or vigilance) was measured with the Rapid Visual Information Processing (RVIP) subtest from the Cambridge Neuropsychological Test Automated Battery (Fray, Robbins, & Sahakian, 1996). Participants were seated in front of a laptop computer and viewed a series of digits appearing one at a time in a pseudo-random

[3] The WTAR provides separate normative databases for Caucasians and African Americans. Given the ethnic diversity in this sample and the lack of appropriate norms for other ethnicities, I opted to use the Caucasian norms for all participants.

fashion at a fixed location in the centre of the screen. Participants were instructed to identify a series of target digit sequences (e.g. 3-5-7, 2-4-6, 4-6-8) and respond using a press pad as quickly as possible following target detection. This task proceeded for approximately seven minutes. The CANTAB generates a number of sub-scores, including a coefficient of signal detection (A prime), which was used for the current study. The CANTAB demonstrates good test-retest reliability (*r* = .76 - .80; Fray, Robbins, & Sahakian, 1996; Lowe & Rabbit, 1998).

Inhibition

The Stroop Color-Word subtest of the Stroop Color-Word Test was used to measure response inhibition – a component of executive functioning. Participants were first presented with a page printed with a series of coloured XXXX's in different coloured inks (e.g. blue, red, green) and asked to name the colours aloud as quickly as possible within a 45 second period. Next, participants were shown a page printed with words denoting the same colours (but appearing in black ink) and asked to read the words aloud as quickly as possible for 45 seconds. On the third and final trial, participants were shown a page printed with words denoting colours that were printed in alternate colours of ink. They were instructed to verbalize the colour of ink while ignoring the word as quickly as possible for 45 seconds. The total number of correct responses on the third trial was used for this study. The Stroop Color-Word Test demonstrates acceptable psychometric properties. Test-retest reliability is good (*r* = .75) and construct validity has been demonstrated through modest correlations with other measures of inhibition (Strauss, Sherman, & Spreen, 2006).

Mental Flexibility

The Intra-Dimensional Extra-Dimensional (IDED) subtest from the CANTAB was used to measure mental flexibility (or attention set-shifting). On the same laptop used previously for the RVIP task, participants viewed two simple shapes and were instructed to determine the correct response (rule) by touching a shape on the screen. Participants were then provided with feedback about their response (correct or incorrect) to learn the correct rule. Following six consecutive correct responses, the rule was switched without participant awareness, and they were required to learn the new rule using the feedback as a guide. During the eighth stage, an extra dimension was added to the shapes (lines) and the rule shifted between these two dimensions. Stages could only be completed following six consecutive correct responses within 50 trials, with nine stages in total. The task ended following completion of all nine stages or completion of 50 trials within a stage without meeting the six-correct criterion. The IDED yields a number of different sub-measures, but the total errors score (adjusted for trials completed) represents the best overall index of mental flexibility and thus was used for the current study. The IDED demonstrates good test-retest reliability (*r* = .70; Lowe & Rabbitt, 1998).

Decision-making

The Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) was used as a measure of decision-making and response to reward. Participants were seated in front of a laptop computer and were presented with four decks of cards (labelled A, B, C, D) on the screen. They were instructed to make a card selection from

one of the four decks (total of 100 selections) and were immediately provided with on-screen feedback regarding how much money they won AND lost as a result of their selection. Green and red bars were displayed at the top of the screen representing the cumulative total of gains and losses, with the difference between the bars representing net earnings. Two of the decks (A and B) were associated with large monetary gain (reward) and large, but less frequent, monetary loss (punishment), amounting to an overall net loss. Conversely, decks C and D were associated with less monetary gain and loss, but punishment was more frequent resulting in an overall net gain. Given the net gain in the latter two decks, these choices were considered to be more advantageous. A net score was computed using the total number of selections from each card deck with the following formula: (C + D) – (A + B). The construct validity of the IGT has been established primarily through lesion and imaging studies where damage to areas known to mediate decision-making behaviour (ventral medial and orbitofrontal regions) has demonstrated selective impact on IGT performance (Buelow & Suhr, 2009).

Appendix C.

Clinical Measures

Neurological Soft Signs

Neurological soft signs (NSS) consist of motor or sensory abnormalities that are a result of diffuse or non-localizable central nervous system dysfunction. The Cambridge Neurological Inventory (CNI) is a standardized clinical measure originally developed for use with a psychiatric population and is designed to assess a range of neurological markers (Chen et al., 1995). In the current study, a subset of items from this inventory were chosen to specifically measure NSS along the dimensions of motor coordination, sensory integration, complex sequencing, and disinhibition. An experienced neurologist administered the CNI and each item was rated on a scale that generally ranged from 0 to 2. A full description of the inventory and definition of scoring criteria for individual items are reported by Chen et al. (1995). The subset of items selected for use in this study is outlined in Table C1. The scores on each item were summed and a total NSS score was used for analyses. The CNI has demonstrated acceptable interrater reliability when raters are trained in the standardized administration of this measure (Chen et al., 1995).

Extrapyramidal Symptoms

Extrapyramidal symptoms (EPS) consist of motor abnormalities that result in movement disorders as a consequence of taking neuroleptic drugs, specifically antipsychotic medication. The Extrapyramidal Symptom Rating Scale (ESRS; Chouinard & Margolese, 2005) is a standardized clinical measure developed to assess drug-induced movement disorders in schizophrenia. In the current study, EPS were measured along three subscales: parkinsonism, dystonia, and dyskinetic movements. Subscale scores were summed to yield a total EPS score. This measure was used to rule out the possibility that any differences on NSS could be attributed to medication effects.

Trauma History Questionnaire

The Trauma History Questionnaire (THQ) is a self-report measure designed for use with a wide range of different populations (community, clinical) with the aim of capturing lifetime exposure to a broad array of traumatic events (Hooper et al., 2011). There are 24-items yes/no items that capture trauma experiences that fall into three broad categories: crime-related events, general disaster and trauma, unwanted physical and sexual experiences. If an individual endorsed any of the six items physical and sexual trauma questions, they were asked if the experience was repeated, how often, and at what age(s) it occurred. For the current study, a dichotomous variable was used to indicate whether or not an individual endorsed physical and/or sexual trauma up to age 12. The THQ has demonstrated moderate to high test-retest reliability for persons with severe mental illness (kappas = .37 - .89; Mueser et al., 2001).

Positive and Negative Syndrome Scale

The Positive and Negative Syndrome Scale (PANSS) is a 30-item questionnaire used routinely with psychotic populations to measure psychiatric symptoms using a rating scale from 1 (absent) to 7 (extreme; Kay, Fiszbein, & Opler, 1987). Subscales scores can be generated for positive (7 items), negative (7 items), and general (16 items) symptoms, as well as a total score with higher scores reflecting more severe psychiatric symptoms. The PANSS demonstrates acceptable test-retest reliability (r = .68 - .80), and correlates well with other measures of clinical symptoms and with changes in symptoms observed as a function of pharmacological interventions.

Table C 1. Items Administered from the Cambridge Neurological Inventory

Item	Scoring Criteria
Snout reflex	0, 0.5, 1, 9
Grasp reflex	0, 0.5, 1, 2, 3, 9
Palmomental reflex	0, 0.5, 1, 9
Finger-nose test (left/right)	0, 0.5, 1, 2, 3, 9
Finger-thumb tapping (left/right)	0, 0.5, 1, 2, 3, 9
Finger-thumb opposition (left/right)	0, 0.5, 1, 2, 3, 9
Mirror movements 1 (left/right)	0, 0.5, 1, 2, 3, 9
Diadochokinesia (left/right)	0, 0.5, 1, 2, 3, 9
Mirror movements 2 (left/right)	0, 0.5, 1, 2, 3, 9
Fist-edge-palm test (left/right)	0, 0.5, 1, 2, 3, 9
Oseretsky (left/right)	0, 0.5, 1, 2, 3, 9
Rhythm tapping test	0, 0.5, 1, 2, 3, 9
Go/no-go test	0, 0.5, 1, 2, 3, 9
Extinction	0, 0.5, 1, 2, 3, 9
Finger agnosia (left/right)	0, 0.5, 1, 2, 3, 9
Stereognosia (left/right)	0, 0.5, 1, 2, 3, 9
Graphesthesia (left/right)	0, 0.5, 1, 2, 3, 9
Left-right orientation	0, 0.5, 1, 2, 3, 9

Appendix D.

Descriptive Statistics for Independent Variables in Cortical Regression Analyses

Table D 1. Descriptive Statistics for Independent Variables by Cluster Membership

Independent Variable	Cluster 1, *n* = 59 *M* (SD)	Cluster 2, *n* = 82 *M* (SD)	Cluster 3, *n* = 70 *M* (SD)
Medial orbitofrontal CT (mm)	4.64 (0.25)	4.61 (0.26)	4.63 (0.29)
Lateral orbitofrontal CT (mm)	5.04 (0.31)	5.02 (0.29)	4.99 (0.32)
Anterior cingulate CT (mm)	5.43 (0.27)	5.36 (0.31)	5.39 (0.40)
Entorhinal CT (mm)	6.75 (0.50)	6.81 (0.59)	6.70 (0.72)
Average whole brain CT (mm)	2.40 (0.11)	2.40 (0.11)	2.38 (0.13)
Medial orbitofrontal lGI	4.08 (0.14)	4.07 (0.14)	4.11 (0.20)
Lateral orbitofrontal lGI	4.93 (0.20)	4.97 (0.22)	5.02 (0.28)
Anterior cingulate lGI	3.92 (0.16)	3.90 (0.18)	3.93 (0.22)
Entorhinal lGI	4.89 (0.18)	4.91 (0.19)	4.98 (0.27)
Average whole brain lGI	2.94 (0.10)	2.93 (0.11)	2.95 (0.13)
Hippocampal Volume (mm^3)	7406.86 (891.58)	7129.34 (746.37)	7028.53 (773.87)
Total Brain Volume (mm^3)	1501009.71 (120980.79)	1429579.44 (106811.72)	1435146.06 (111064.03)
Negative PANSS	13.58 (3.65)	16.24 (6.26)	17.51 (5.77)
Age (years)[a]	44.10 (9.03)	43.07 (9.39)	42.94 (9.80)
Education (years)	11.00 (2.41)	10.13 (2.47)	9.96 (1.90)

Note. Brain measures were available for 211 participants. This data has not been corrected for covariates. CT = Cortical thickness; lGI = Local gyrification index; PANSS = Positive and Negative Syndrome Scale.
[a]Age was included as a dichotomous variable in the regression analysis, but reported in this table as a continuous variable for descriptive purposes.

Appendix E.

Post-Hoc Probe of Interaction

Table E 1. Tests of Significance of Simple Slopes as a Function of Age

Cluster 1 versus Cluster 2			
Age percentile (age in years)	Simple slope (SE)	*t*-statistic	95% CI
5th (28)	-0.9507 (.4358)	-2.1815*	[-1.8092, -0.0922]
10th (29)	-0.8912 (.4174)	-2.1351*	[-1.7135, -0.0689]
25th (36)	-0.4748 (.3020)	-1.5722	[-1.0697, 0.1201]
50th (44)	0.0011 (.2337)	0.0049	[-0.4593, 0.4615]
75th (55)	0.3581 (.2600)	1.3772	[-0.1541, 0.8703]
90th (56)	0.7150 (.3399)	2.1036*	[0.0454, 1.3846]
95th (59)	0.8935 (.3906)	2.2874*	[0.1240, 1.6630]
Cluster 1 versus Cluster 3			
Age percentile (age in years)	Simple slope (SE)	*t*-statistic	95% CI
5th (28)	-1.3717 (.4512)	-3.0401***	[-2.2606, -0.4828]
10th (29)	-1.2982 (.4326)	-3.0010***	[-2.1504, -0.4460]
25th (36)	-0.7842 (.3156)	-2.4848**	[-1.4059, -0.1625]
50th (44)	-0.1967 (.2581)	-0.7619	[-0.7052, 0.3118]
75th (55)	0.2440 (.2706)	0.9016	[-0.2891, 0.7771]
90th (56)	0.6846 (.3496)	1.9582	[-0.0041, 1.3733]
95th (59)	0.9049 (.4009)	2.2572*	[0.1152, 1.6946]

Note. df = 202. Critical t-value = 1.97 (p = .05). Standardized age values (z-scores) were used in the equations to compute t-tests and standard errors, but unstandardized age values are depicted here for descriptive purposes.
*p < .05. **p < .02. *** p < .005.

Appendix F.

Descriptive Statistics for Independent Variables in DTI Regression Analyses

Table F 1 Descriptive Statistics of White Matter Variables by Cluster

Independent Variable	Cluster 1 (n = 58)	Cluster 2 (n = 78)	Cluster 3 (n = 66)
Cingulum (*M*, SD)			
FA	.760 (.080)	.765 (.057)	.737 (.094)
AD	.023 (.001)	.023 (.001)	.022 (.001)
RD	.013 (.001)	.012 (.001)	.013 (.002)
Superior Longitudinal Fasciculus (*M*, SD)			
FA	.796 (.048)	.799 (.054)	.777 (.082)
AD	.022 (.001)	.022 (.001)	.023 (.001)
RD	.012 (.001)	.012 (.001)	.013 (.002)
Anterior Corona Radiata (*M*, SD)			
FA	.749 (.064)	.748 (.071)	.728 (.089)
AD	.024 (.001)	.024 (.001)	.024 (.002)
RD	.013 (.001)	.013 (.001)	.014 (.002)
Corpus Callosum[a] (*M*, SD)			
FA	1.015 (.075)	1.039 (.074)	1.005 (.113)
AD	.003 (.001)	.003 (.001)	.003 (.002)
RD	.013 (.002)	.013 (.001)	.014 (.003)
Whole brain (*M*, SD)			
FA	.215 (.015)	.218 (.015)	.212 (.017)
AD	.014 (.001)	.014 (.003)	.017 (.020)
RD	.011 (.001)	.011 (.002)	.012 (.007)

Note. N = 202. This table reflects data that is not corrected for age or education. DTI data represents bilateral tract values. AD and RD values have been multiplied by 10.
[a]Sum of genu and body of corpus callosum.

Appendix G.

TBSS Results for Fractional Anisotropy and Diffusivities

Table G 1 White Matter Tracts and Corresponding Percent of Tract Volume that Significantly Differs on Fractional Anisotropy Between Clusters

FA: Cluster 1 > Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Anterior	15.24 (.031)	6.48 (.040)
Superior	7.69 (.031)	0.51 (.036)
Posterior	5.49 (.037)	3.89 (.038)
Anterior limb of internal capsule	9.11 (.042)	--
Retrolenticular part of internal capsule	12.39 (.035)	5.21 (.048)
Posterior thalamic radiation	12.44 (.035)	8.61 (.047)
Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	13.48 (.033)	--
Superior fronto-occipital fasciculus	0.99 (.042)	--
Uncinate fasciculus	0.53 (.044)	--
Sagittal stratum	11.61 (.036)	5.34 (.047)
Cingulum		
Cingulate gyral region	--	0.34 (.040)
External Capsule	0.57 (.033)	--
Fornix (cres)/Stria terminalis	20.44 (.045)	--
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Genu	1.48 (.034)	
Body	5.92 (.038)	
Splenium	3.55 (.035)	
Tapetum	3.00 (.037)	1.85 (.046)

FA: Cluster 2 > Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Anterior	12.83 (.012)	10.75 (.025)
Superior	7.03 (.015)	5.00 (.031)
Posterior	8.35 (.016)	14.78 (.009)
Anterior limb of internal capsule	--	0.06 (.042)
Posterior limb of internal capsule	--	0.05 (.030)
Retrolenticular part of internal capsule	3.65 (.020)	11.73 (.017)
Posterior thalamic radiation	10.03 (.022)	14.20 (.015)
Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	10.40 (.016)	11.03 (.031)
Uncinate fasciculus	5.05 (.043)	--
Sagittal stratum	7.84 (.042)	9.61 (.016)
Cingulum		
Hippocampal region	0.26 (.028)	10.44 (.014)
Cingulate gyral region	0.58 (.007)	--
External capsule	--	1.32 (.025)
Fornix (cres)/Stria terminalis	0.80 (.043)	11.39 (.015)
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Genu	18.02 (.007)	
Body	17.66 (.011)	
Splenium	9.88 (.013)	
Tapetum	7.50 (.016)	8.73 (.010)

Note. N = 202. *P*-values represent average values. FA = fractional anisotropy; LH = left hemisphere; RH = right hemisphere.

Table G 2 White Matter Tracts and Corresponding Percent of Tract Volume that Significantly Differs on Axial Diffusivity Between Clusters

AD: Cluster 1 < Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Superior	2.69 (.038)	--
Posterior	7.35 (.031)	--
Anterior limb of internal capsule	0.86 (.042)	--
Posterior limb of internal capsule	6.45 (.037)	--
Retrolenticular part of internal capsule	7.57 (.034)	--
Posterior thalamic radiation	8.20 (.033)	--
Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	1.60 (.048)	--
Superior fronto-occipital fasciculus	3.55 (.042)	--
Sagittal stratum	9.86 (.034)	--
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Splenium	3.50 (.034)	
Tapetum	10.00 (.025)	--
AD: Cluster 2 < Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Anterior	8.96 (.038)	12.57 (.037)
Superior	9.18 (.036)	1.29 (.038)
Posterior	4.15 (.041)	--
Anterior limb of internal capsule	5.30 (.035)	2.17 (.034)
Posterior limb of internal capsule	6.66 (.039)	--
Retrolenticular part of internal capsule	12.56 (.043)	--
Posterior thalamic radiation	2.54 (.043)	--

Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	6.75 (.040)	0.44 (.038)
Uncinate fasciculus	1.06 (.043)	--
Superior fronto-occipital fasciculus	13.02 (.033)	2.56 (.041)
Sagittal stratum	9.10 (.042)	--
External capsule	4.65 (.037)	2.25 (.035)
Fornix (cres)/Stria terminalis	1.07 (.042)	--
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Genu		3.21 (.041)
Body		0.43 (.043)
Splenium		4.23 (.042)
Tapetum	5.50 (.042)	--

Note. N = 202. *P*-values represent averages across all significant voxels within a given tract. AD = axial diffusivity; LH = left hemisphere; RH = right hemisphere.

Table G 3 White Matter Tracts and Corresponding Percent of Tract Volume that Significantly Differs on Radial Diffusivity Between Clusters

RD: Cluster 1 < Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Anterior	17.44 (.021)	19.39 (.029)
Superior	11.72 (.016)	6.68 (.027)
Posterior	12.52 (.015)	9.09 (.018)
Anterior limb of internal capsule	1.49 (.029)	1.08 (.036)
Retrolenticular part of internal capsule	15.92 (.012)	7.28 (.026)
Posterior thalamic radiation	15.66 (.013)	16.29 (.019)
Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	16.34 (.015)	6.81 (.031)

Superior fronto-occipital fasciculus	9.86 (.037)	1.38 (.036)
Uncinate fasciculus	1.06 (.029)	1.84 (.032)
Sagittal stratum	23.94 (.014)	15.62 (.030)
Cingulum		
Hippocampal region	--	2.99 (.043)
Cingulate gyral region	2.69 (.037)	1.67 (.030)
External capsule	0.48 (.029)	0.25 (.036)
Fornix (cres)/stria terminalis	20.62 (.028)	0.98 (.035)
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Genu	6.70 (.030)	
Body	10.12 (.020)	
Splenium	5.95 (.018)	
Tapetum	9.17 (.011)	10.91 (.016)
RD: Cluster 2 < Cluster 3		
Projection Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corona Radiata		
Anterior	18.89 (.009)	22.34 (.007)
Superior	10.74 (.010)	7.53 (.011)
Posterior	11.98 (.014)	15.16 (.010)
Anterior limb of internal capsule	5.57 (.026)	6.02 (.013)
Retrolenticular part of internal capsule	7.61 (.039)	9.70 (.017)
Posterior thalamic radiation	10.58 (.018)	14.55 (.016)
Association Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Superior longitudinal fasciculus	15.93 (.014)	15.32 (.014)
Superior fronto-occipital fasciculus	12.62 (.023)	7.69 (.009)
Uncinate fasciculus	6.65 (.039)	--
Sagittal stratum	15.51 (.038)	10.01 (.014)
Cingulum		
Hippocampal region	--	7.12 (.023)
Cingulate gyral region	1.02 (.017)	--

External capsule	1.27 (.025)	5.10 (.021)
Fornix (Cres)/stria terminalis	1.51 (.036)	8.36 (.021)
Commissural Fibers	LH % vol sig (*p*-value)	RH % vol sig (*p*-value)
Corpus Callosum		
Genu	18.53 (.008)	
Body	17.17 (.011)	
Splenium	11.29 (.012)	
Tapetum	10.17 (.010)	10.57 (.009)

Note. N = 202. *P*-values represent averages across all significant voxels within a given tract. RD = radial diffusivity; LH = left hemisphere; RH = right hemisphere.