EXERCISE, SYMPTOM SEVERITY, AND NEUROPLASTICITY IN SCHIZOPHRENIA

by

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Abstract

Schizophrenia is a debilitating disorder marked by psychosis and deficits in cognition and social functioning. It is further characterized by metabolic, neurovascular and cardiovascular deficits that interact with, or compound adverse medication-linked cardiovascular effects. Neuroanatomic deficits are seen even at early stages of illness. Reductions in frontal and temporal lobe grey matter, particularly the hippocampus, are among the most consistent findings. Prefrontal-limbic network deficits are associated with more severe positive symptoms and more cognitive impairments in psychosis patients. Additionally, reduced cardiorespiratory fitness has been linked to decreased hippocampal volume and cortical thickness. Exercise interventions are known to mitigate the negative antipsychotic-associated cardiometabolic side effects and promote hippocampal growth and cortical expansion. Yet, the efficacy of exercise as a non-pharmacological intervention to address anatomic and clinical deficits in psychosis patients is unclear. This study examines the effect of exercise on hippocampal and neocortical plasticity, and clinical outcomes in chronic schizophrenia, early psychosis and in an animal model as proof of principle. First, hippocampal volume increase and symptom severity decrease in chronically treated schizophrenia patients were observed. Compared to healthy volunteers, chronically treated patients had decreased fusiform cortical thickness. Patients who participated in the aerobic intervention had a greater increase in orbitofrontal cortical thickness compared to patients in the resistance training group. Second, early psychosis patients who completed the aerobic intervention had increased thickness in the entorhinal and fusiform cortices. For the aerobic group only, increases in the entorhinal and fusiform temporal gyri were associated with decreasing psychosis symptom severity, particularly for general psychopathology. Last,
exercising rats had greater layer II entorhinal cortical thickness compared to sedentary rats, but there was no effect of exercise observed for rats treated with olanzapine. Greater entorhinal cortical thickness was associated with increased activity and improved fasting glucose and fasting insulin levels in rats. The cardiovascular burden in schizophrenia, and antipsychotic treatment has a strong negative impact on patient outcomes. Clinically appropriate exercise represents a non-pharmacologic, safe approach to reduce psychotic symptoms, and remediate neuroanatomic deficits while improving cardiovascular health, counteracting the adverse effects of antipsychotic medication.
Lay Summary

Schizophrenia is a severe mental health disorder with concomitant cardiovascular problems and structural abnormalities of key brain hubs associated with memory and learning. Exercise is expected to improve cardiovascular health, reduce severity of mental dysfunction, and promote regional brain growth in schizophrenia patients, but study results have been inconsistent. It is unclear what exercise program will be most helpful to schizophrenia patients, how the beneficial effects of exercise will be reflected in brain changes, and how commonly prescribed medical treatments contribute to abnormalities in brain. Significant structural brain changes and reductions in symptom severity were observed in both chronic and newly diagnosed patients following a 12-week aerobic exercise intervention. In rats administered schizophrenia medication, a greater exercise volume was associated with greater regional brain increases and improved metabolic health. Exercise may counteract negative cardiovascular effects of medications, improve brain deficits, and improve symptoms in both early and chronic schizophrenia.
Preface

The work for Chapter 2 was conducted as part of the Brain Health and Exercise in Schizophrenia (PEHP) Study, a longitudinal investigation of the effects of exercise in chronic schizophrenia patients at the BC Psychosis Program at UBC Hospital in Vancouver, BC. This study was approved by the Clinical Research Ethics Board of the University of British Columbia (certificate number H10-02919) and was registered as a Clinical Trial (NCT01392885).

A portion of Chapter 2 has been published [Woodward ML, Gicas KM, Warburton DE, White RF, Rauscher A, Leonova O, Su W, Smith GN, Thornton AE, Vertinsky AT, Phillips AA, Goghari VM, Honer WG, Lang DJ. (2018). Hippocampal volume and vasculature before and after exercise in treatment-resistance schizophrenia. Schizophrenia Research, 202, 158-165. doi.org/10.1016/j.schres.2018.06.054]. As lead author, I was responsible for data collection/analysis, including research interviews and clinical chart reviews, and made major contributions to the writing of the manuscript. I also conducted all hippocampal manual segmentation. Lang DJ was responsible for the management and oversight of the study, analytical oversight for this study and was a key contributing author of the manuscript. Gicas KM conducted the neuropsychometric assessments associated with this study, provided guidance on design of primary analyses, and assisted with data collection, analysis, and writing of the manuscript. Goghari VM assisted with the evaluation of the post-processed imaging files and the exploratory analysis. Leonova O conducted the assessments of extrapyramidal symptoms and contributed to the authorship of the paper. Smith GN conducted evaluations of patient histories and duration of illness for this paper. Su W developed the volumetric segmentation pipeline for this study. Phillips AA conducted cardiovascular fitness assessments for this study. Rauscher A
developed a novel susceptibility weighted imaging paradigm for this study. Thornton AE created the neuropsychological battery for this study and oversaw final analyses of these data. Vertinsky AT conducted all clinical evaluations of structural imaging for this study. Warburton DE developed the individualized exercise prescriptions for all participants in this study. White RF assisted with patient recruitment and conducted all clinical evaluations of symptom severity for this study. Honer WG was responsible for leading all consensus diagnostic evaluations for patients involved in this study. All authors contributed to and approved of the final manuscript.

The work for Chapter 3 was conducted as part of the Yoga and Aerobic Exercise in Psychosis (YEP) Study, a longitudinal study to evaluate the impact of aerobic exercise and yoga in early psychosis patients in Hong Kong, China. This study was registered as a Clinical Trial (NCT01207219). The protocol was approved by the Institutional Review Board of the University of Hong Kong.

A version of Chapter 3 has been prepared as a manuscript and submitted for peer-review [Woodward ML, Lin J, Gicas KM, Su W, Hui CLM, Honer WG, Chen EYH, Lang DJ. Medial temporal lobe cortical changes in response to exercise interventions in early psychosis patients: A randomized controlled trial]. I developed research questions from existing data, conducted all data analysis and drafted the manuscript and figures. Lin J was responsible for patient recruitment and data collection. Gicas KM provided critical guidance on the data analysis and contributed to the manuscript. Su W developed the volumetric segmentation pipeline for this study. Hui CLM assisted with patient recruitment and data collection. Honer WG contributed to study design. Chen EYC was responsible for management and oversight of the study. Lang DJ was responsible for overseeing data analysis and manuscript preparation. All authors contributed to and approved of the final manuscript.
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# Table of Contents

Abstract........................................................................................................... iii

Lay Summary....................................................................................................... v

Preface................................................................................................................ vi

Table of Contents ............................................................................................... ix

List of Tables ...................................................................................................... xiv

List of Figures .................................................................................................... xv

List of Abbreviations ......................................................................................... xvii

Acknowledgements ............................................................................................ xxi

Dedication ........................................................................................................... xxiii

## Chapter 1: Introduction ................................................................................. 1

1.1 Schizophrenia.............................................................................................. 1

1.1.1 Historical Perspective ........................................................................... 1

1.1.2 Diagnostic Criteria .............................................................................. 2

1.1.3 Etiology of Schizophrenia....................................................................... 4

1.1.4 Prodromal Schizophrenia ..................................................................... 7

1.1.5 Cognitive Impairment ........................................................................... 7

1.2 Neuroanatomy........................................................................................... 8

1.2.1 Overview of Magnetic Resonance Imaging ......................................... 8

1.2.2 Historical Perspective of Imaging in Schizophrenia ............................... 9

1.2.3 Neuroanatomic Characteristics of Schizophrenia ................................ 10

1.2.4 Risk Factors for Cortical Deficits ......................................................... 13
1.3 Current Treatment Paradigms ................................................................. 14
1.4 Cardiovascular Characteristics of Schizophrenia ....................................... 17
  1.4.1 Cardiovascular Risk and Antipsychotics ............................................. 17
  1.4.2 Cardiovascular Risk and Genetics ..................................................... 18
  1.4.3 Cardiovascular Risk and Lifestyle Factors ....................................... 19
1.5 Exercise as a Non-Pharmacological Intervention ..................................... 20
  1.5.1 Cognitive Effects ............................................................................ 20
  1.5.2 Clinical Effects ............................................................................... 21
  1.5.3 Neuroanatomic Effects .................................................................... 22
  1.5.4 Cerebrovascular and Cardiovascular Effects ..................................... 23
  1.5.5 Cellular Mechanisms for Exercise-Mediated Neuroanatomical Changes ... 24
  1.5.6 Exercise Type ................................................................................ 25
1.6 Assessment Measures .............................................................................. 26
  1.6.1 Clinical Symptom Assessment Measures ......................................... 26
  1.6.2 Neurocognition Assessment Measures ............................................ 28
1.7 Treatment-Resistant Schizophrenia .......................................................... 29
1.8 Sex Differences ..................................................................................... 31
  1.8.1 Clinical Differences ........................................................................ 31
  1.8.2 Sex Differences and Exercise Interventions ..................................... 32
1.9 Overview and Research Goals .................................................................. 32
  1.9.1 Specific Aims and Hypotheses ....................................................... 34

Chapter 2: Structural neuroimaging before and after exercise in treatment-resistant schizophrenia ................................................................. 36
Chapter 3: Medial temporal lobe cortical changes in response to exercise interventions in early psychosis patients
4.3.3 Mediation Analysis........................................................................................................... 90

4.4 Discussion.......................................................................................................................... 91
   4.4.1 Limitations ....................................................................................................................... 94
   4.4.2 Conclusion ....................................................................................................................... 95

Chapter 5: Discussion ..............................................................................................................96

5.1 Overview of Findings ........................................................................................................ 96
   5.1.1 Effects of Exercise in Treatment-Resistant Schizophrenia........................................... 96
   5.1.2 Effects of Exercise on Hippocampal Vascular Volume ............................................. 97
   5.1.3 Baseline Neocortical Deficits in Chronic Schizophrenia Patients ............................. 98
   5.1.4 Effect of Exercise on Neocortical Deficits in Psychosis Patients ............................... 99
   5.1.5 Effect of Exercise and Olanzapine on Entorhinal Cortical Thickness....................... 101

5.2 Strengths and Limitations ................................................................................................ 103

5.3 Clinical Implications ........................................................................................................ 105

5.4 Conclusion ........................................................................................................................ 107

Bibliography ..........................................................................................................................109
List of Tables

Table 2.1 Summary demographic and clinical measures.......................................................... 39
Table 2.2 Summary neurocognitive measures for schizophrenia patients.............................. 46
Table 2.3 Preliminary correlational assessments of potential confounding factors for schizophrenia patients (N = 17)............................................................................................................. 48
Table 2.4 Summary volumetric data (mm$^3$) for schizophrenia patients (N = 17)................ 52
Table 2.5 Baseline descriptive statistics ..................................................................................... 54
Table 2.6 Hippocampal volume (mm$^3$) at baseline and follow-up........................................ 55
Table 2.7 Neocortical brain volume (mm$^3$) and thickness (mm) measures at baseline and follow-up................................................................................................................................. 56
Table 3.1 Baseline descriptive statistics ..................................................................................... 70
Table 3.2 Group brain volume (mm$^3$) and thickness (mm) measures at baseline and follow-up. 71
Table 4.1 Entorhinal cortical thickness and subregions (µm) in rats across olanzapine and exercise subgroups ......................................................................................................................... 86
Table 4.2 Descriptive statistics for exercising rats (N = 36) ......................................................... 89
List of Figures

Figure 1.1 Cortical parcellation of neocortical regions of interest from the Desikan-Killiany atlas including entorhinal, fusiform, parahippocampal, and orbitofrontal cortices .................................... 12

Figure 2.1 Sample segmentation of whole and subfield hippocampal volume (A: Axial plane, B: Coronal plane, C: Subfield segmentation) ............................................................................................................. 42

Figure 2.2 Sample of hippocampal venule segmentation from SWI (A: Raw axial SWI image, B: Segmented axial SWI image) .......................................................................................................................... 44

Figure 2.3 Healthy volunteer (N = 9) and schizophrenia patient (N = 17) comparison of fusiform cortical thickness (mm) at baseline. * p < 0.05 ......................................................................................................................... 57

Figure 2.4 Change in orbitofrontal cortical thickness across groups. Percent change in orbitofrontal cortical thickness with aerobic patients (N = 9), resistance patients (N = 8), aerobic healthy volunteers (N = 3) and resistance training healthy volunteers (N = 6). Error bars represent +/- 1 SE. * p < 0.05 ......................................................................................................................... 59

Figure 2.5 Healthy volunteer (N = 9) and schizophrenia patient (N = 17) comparison of orbitofrontal cortical thickness at baseline. * p < 0.05 ......................................................................................................................... 57

Figure 3.1 Change in fusiform cortical thickness across groups. Mean percent change in fusiform cortical thickness across yoga (N = 21), aerobic exercise (N = 18), and waitlist groups (N = 12). Error bars represent +/- 1 SE. * p < 0.05 ......................................................................................................................... 73

Figure 4.1 Sample manual segmentation of Nissl histology stains of rat entorhinal cortex indicating subdivisions of lateral (LEC) and medial (MEC) entorhinal cortex and layer II (LII). Scale bar indicates 100 µm. ......................................................................................................................... 84

Figure 4.2 Layer II thickness (µm) across olanzapine and exercise groups. Error bars represent +/- 1 SE. * p < 0.05 ......................................................................................................................... 87
Figure 4.3 Mediation analysis. Standardized regression coefficients for the relationship between average activity and entorhinal cortical thickness as mediated by reduced fasting insulin. The standardized regression coefficient between average activity and entorhinal cortical thickness, controlling for fasting insulin, is in parentheses. * p < 0.05 .......................................................... 91
List of Abbreviations

5-HT$_{2A}$ Receptor: 5-Hydroxytryptamine 2A (Serotonin) Receptor
ANOVA: Analysis of Variance
ANCOVA: Analysis of Covariance
ANTS: Advanced Normalization Tools
ASL: Arterial Spin Labelling
AUC: Area Under the Curve
BC: British Columbia
BDNF: Brain-Derived Neurotrophic Factor
BET: Brain Extraction Tool
BMI: Body Mass Index
CBV: Cerebral Blood Volume
CDS: Calgary Depression Scale
CI: Confidence Interval
CPZ: Chlorpromazine
CPZE: Chlorpromazine Equivalents
D1 Receptor: Dopamine 1 Receptor
D2 Receptor: Dopamine 2 Receptor
DSM: Diagnostic and Statistical Manual of Mental Disorders
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders 4th Edition
EC: Entorhinal Cortex
ELISA: Enzyme-Linked ImmunoSorbent Assay
ESRS: Extrapyramidal Symptom Rating Scale
F: Female
FAST: FMRIB Automated Segmentation Tool
FLAIR: Fluid-Attenuated Inversion Recovery
FLIRT: FMRIB Linear Image Registration Tool
FMRIB: Oxford Centre for Functional Magnetic Resonance Imaging of the Brain
FOV: Field of View
FSL: FMRIB Software Library
GWAS: Genome-Wide Association Study
HAM-A: Hamilton Anxiety Rating Scale
HIIT: High-Intensity Interval Training
HSD: Honestly Significant Difference
IGF: Insulin-Like Growth Factor
IGTT: Intraperitoneal Glucose Tolerance Test
IP: Intraperitoneal
IQ: Intelligence Quotient
KBIT: Kaufman Brief Intelligence Test
L: Left-Handed
LCD: Liquid Crystal Display
LEC: Lateral Entorhinal Cortex
LII: Layer II
M: Male
MATLAB: Matrix Laboratory
MEC: Medial Entorhinal Cortex

MNI: Montreal Neurological Institute

MPRAGE: Magnetization-Prepared Rapid Acquisition with Gradient Echo

MRI: Magnetic Resonance Imaging

mTOR: Mechanistic Target of Rapamycin

NIH: National Institute of Health

NS: Not Significantly Different Between Groups

PANSS: Positive and Negative Syndrome Scale

PBS: Phosphate-Buffered Saline

PNOS: Psychosis Not Otherwise Specified

R: Right-Handed

RF: Radio Frequency

RHR: Resting Heart Rate

SA: Schizoaffective

SC: Subcutaneous

SD: Standard Deviations

SE: Standard Error

SENSE: Sensitivity Encoding

SNR: Signal-to-Noise Ratio

SOFAS: Social and Occupational Functioning Assessment Scale

SPSS: Statistical Package for the Social Sciences

SWI: Susceptibility Weighted Imaging

SZ: Schizophrenia
T: Tesla

T₁: Longitudinal Relaxation Time

T₂: Transverse Relaxation Time

TBS: Tris-Buffered Saline

TE: Echo Time

TR: Relaxation Time

TrkB: Tyrosine Receptor Kinase B

TRS: Treatment-Resistant Schizophrenia

UBC: University of British Columbia

VEGF: Vascular Endothelial Growth Factor

VO₂max: Maximal Oxygen Uptake

WTAR: Weschler Test of Adult Reading
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And when she stood, she stood tall. – The Lumineers

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Chapter 1: Introduction

1.1 Schizophrenia

Schizophrenia is a chronic psychiatric disorder that is among the top fifteen leading causes of disability worldwide despite a relatively low global lifetime prevalence of approximately 0.8% (Moreno-Küstner, Martin, & Pastor, 2018; Vos et al., 2017). Characterized by functional decline and psychotic symptoms, a diagnosis of schizophrenia requires the presence of these symptoms for a minimum of six months (American Psychiatric Association, 2013). Social, cognitive and occupational dysfunction are common and debilitating sequelae, and are less amenable to traditional pharmaceutical treatments than psychotic symptoms. Schizophrenia causes an immense burden on individuals, caregivers and society at large.

1.1.1 Historical Perspective

Emil Kraepelin, a German psychiatrist in the late 19\textsuperscript{th}/early 20\textsuperscript{th} century, was among the first to note the critical cognitive impairment associated with schizophrenia with his use of the term ‘dementia praecox’ meaning ‘premature dementia’ or ‘precocious madness’ (Falkai et al., 2015). He posited that biological differences in the central nervous system may be the cause of this deteriorating mental disorder with onset in late teens or early adulthood (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999). A Swiss psychiatrist, Eugene Bleuler, was the first to use the term schizophrenia to describe what he considered to be primarily a thought disorder resulting from loosening associations between mental content (Adityanjee et al., 1999). He distinguished between fundamental and accessory features of schizophrenia, viewing hallucinations, delusions, and catatonia to be secondary to more essential features like affective
flattening and ambivalence. This division of symptoms is fundamental to our current view of positive and negative features of schizophrenia and Bleuler was among the first to acknowledge the heterogeneity of schizophrenia (Adityanjee et al., 1999).

The work of Kurt Schneider, a German psychiatrist, was critical for the operational diagnostic criteria of schizophrenia through his description of first-rank symptoms that he considered to be particularly suggestive of the presence of schizophrenia (Kendler & Mishara, 2019). These symptoms include auditory and somatic hallucinations, delusional perception, thought withdrawal or broadcasting, and feelings of being influenced by external agents. These descriptions were fundamental to our understanding and diagnosis of psychosis.

1.1.2 Diagnostic Criteria

Schizophrenia is one diagnosis within a range of schizophrenia-spectrum disorders. This group of disorders is characterized by the presence of five key symptoms including delusions, hallucinations, disordered thought and movement, and negative symptoms (American Psychiatric Association, 2013). Delusions are fixed false beliefs that may be irrational or bizarre in nature and are resistant to change even when presented with conflicting evidence (American Psychiatric Association, 2013). Hallucinations are sensory perceptions that occur without a real external stimulus (American Psychiatric Association, 2013). They may be auditory, visual, olfactory, gustatory or even tactile. Disordered thought may manifest in derailment or loose associations between topics when speaking, incoherence, and generally impaired communication (American Psychiatric Association, 2013). Atypical motor behaviour may range from agitation and disorganized movements, to a marked decrease in movement known as catatonia. Individuals may adopt bizarre and rigid postures, or repeat stereotyped movements (American Psychiatric
Association, 2013). This collection of symptoms is known as positive symptoms and they can respond well to antipsychotic medication (Haddad & Correll, 2018). Negative symptoms are highly associated with morbidity in schizophrenia and are less receptive to antipsychotic treatment (Haddad & Correll, 2018). Diminished emotional expression, lack of motivation (amotivation), diminished speech (alogia), decreased ability to experience pleasure (anhedonia), and diminished interest in interacting with others, are all key negative symptoms of schizophrenia-spectrum disorders (American Psychiatric Association, 2013). Individuals with schizophrenia must experience at least two of the five key symptoms, one of which must be either delusions, hallucinations, or thought disorder. These symptoms must be present for at least six months and must be accompanied by marked impairment in interpersonal, academic, or occupational functioning (American Psychiatric Association, 2013).

Schizoaffective disorder requires concurrent psychosis and mood symptoms characterized by either major depressive or manic episodes (American Psychiatric Association, 2013). Diagnostic criteria for schizoaffective disorder also include a period of two or more weeks where delusions or hallucinations are present with the absence of major mood symptoms and that major mood symptoms be present for the majority of the duration of the illness. For both schizophrenia and schizoaffective disorder, symptoms cannot be related to a medical condition or the effects of a drug or medication (American Psychiatric Association, 2013). Either schizophrenia or schizoaffective disorder may be initially diagnosed as schizophreniform disorder, where symptoms must occur for a minimum of one month. Approximately 70% of individuals diagnosed with schizophreniform disorder will transition to a diagnosis of schizophrenia within one year (Haahr et al., 2008). First episode psychosis is a descriptor applied to any schizophrenia-spectrum disorder diagnosis to clarify the individual is experiencing their
first manifestation of their psychotic disorder (American Psychiatric Association, 2013). All of these diagnoses require that psychosis not be the result of substance use or some other medical condition.

### 1.1.3 Etiology of Schizophrenia

Schizophrenia has been referred to as the graveyard of neuropathology due to the lack of pathological findings over the first seventy years of research into this disorder (Roberts & Bruton, 1990). However, advancements in neuroimaging have led to an understanding of widespread neuroanatomic findings associated with schizophrenia. The neurodevelopmental hypothesis postulates that schizophrenia arises due to neuronal dysfunction during critical periods of development (Weinberger, Berman, & Zec, 1986). Schizophrenia-like symptoms can be observed in individuals with brain injury and neurodegeneration, and dysregulation of growth factors associated with maintaining neuronal health and promoting neurodevelopment have been observed in patients with schizophrenia (Iritani, 2007). Although no single genetic mutation has been found to be sufficient to cause schizophrenia, mutations in genes that play critical roles in neurodevelopment have been associated with a greater likelihood of developing schizophrenia (Iritani, 2007). Recent genome-wide association studies (GWAS) have identified risk genes in the AKT-mTOR signaling pathway that play a critical role in placental function, metabolism, and early brain development (Howell & Law, 2019). Existing genetic and environmental risk factors may interact through reductions in AKT/mTOR signaling leading to altered placentation that can impact fetal growth and nutrient delivery, while increasing the risk of birth complications. Reduced AKT/mTOR signaling can also lead to reduced neurogenesis and
maturation, cortical structural variations, dendritic reductions, and reduced neuronal connectivity, supporting the neurodevelopmental hypothesis of schizophrenia.

Schizophrenia is thought to arise due to dysconnectivity in the brain. Neuropathological findings of schizophrenia include atypical neuronal position associated with altered migration, and decreased dendritic spine density (Falkai et al., 2016; Muraki & Tanigaki, 2015; van den Heuvel, Scholtens, de Reus, & Kahn, 2016). Altered myelin and oligodendrocyte dysfunction have also been associated with schizophrenia (Falkai et al., 2016). Genes associated with myelin and oligodendrocytes have been shown to be downregulated in people with schizophrenia and alterations in white matter have been observed through diffusion tensor imaging in schizophrenia patients (Ren, Wang, & Xiao, 2013). These findings may indicate how cellular pathology associated with schizophrenia may result in altered brain connectivity.

Neurotransmitters play a critical role in our understanding of the neuropathology of schizophrenia, in particular the dysregulation of dopamine. Recent neuroimaging, using dopamine-precursor radiolabelling, has revealed that individuals with schizophrenia exhibit greatest dopaminergic dysfunction within the nigrostriatal pathway (Kegeles et al., 2010; McCutcheon, Beck, Jauhar, & Howes, 2018). Increased dopamine in the dorsal striatum has been observed even in prodromal schizophrenia (Howes et al., 2009). Cognitive deficits in schizophrenia have been linked with imbalance of dopamine D₁ and D₂ receptor activity in the prefrontal cortex (Goldman-Rakic, 1999; Sakurai et al., 2013). Alternations in other neurotransmitters including glutamate, serotonin, acetylcholine, and GABA have also been associated with schizophrenia (Yang & Tsai, 2017).

Onset of schizophrenia typically occurs in late adolescence and early adulthood, indicating that brain development during the adolescent period may play a critical role in the
emergence of this disorder (Uhlhaas, 2011). Adolescent brain development and maturation may be altered, with excessive synaptic pruning and disorganization of cortical networks observed in individuals who go on to develop schizophrenia. Alterations in neurotransmission during adolescence may result in disinhibition of the prefrontal cortex (Uhlhaas, 2011).

Risk factors for schizophrenia consist of both genetic and environmental influences. Although no one gene has been found to be causal, a number of susceptibility genes have been established and genetics or gene-environment interactions may explain up to 80% of the risk for schizophrenia (Tandon, Keshavan, & Nasrallah, 2008). Environmental factors associated with an elevated risk of schizophrenia include prenatal or perinatal complications (i.e. malnutrition or infection, obstetric complications, cannabis use, winter birth, urbanicity, and stress) (Tandon et al., 2008). Substance use and adverse events during adolescents can alter brain development and may increase risk for the development of schizophrenia (Hall, 2006; Stilo, Forti, & Murray, 2011). Many of these factors have been linked with inflammation (Yuii, Suzuki, & Kurachi, 2007).

This vulnerability-stress model postulates that exposure to stress during critical life periods of development, namely childhood and puberty, may alter dopamine and glutamate regulation in individuals with underlying genetic liability, increasing stress sensitization and altering brain development (Yuii et al., 2007). Changes in brain development and maturation may alter brain structure and function that, when coupled with environmental stressors, are associated with the emergence of psychotic disorders. Acute and chronic stress have been shown to decrease neuronal growth factor levels, namely BDNF (Brain-Derived Neurotrophic Factor), in the rat hippocampus resulting in dendritic atrophy and neuronal death potentially contributing
to the neuroanatomic findings associated with schizophrenia even at early stages of illness (Murakami, Imbe, Morikawa, Kubo, & Senba, 2005).

1.1.4 Prodromal Schizophrenia

As a neurodevelopmental disorder, the course of illness may begin prior to the presence of psychotic symptoms, considered the schizophrenia prodrome (George, Masheshwari, Chandran, Manohar, & Rao, 2017). The prodromal period lasts from the onset of first noticeable symptoms to the onset of the first psychotic symptoms (Beiser, Erickson, Fleming, & Iacono, 1993). Heterogeneity in the pattern and timing of symptoms can hinder diagnosis, yet early interventions have proved effective for improving social and occupational functioning (Shrivastava, 2010). Symptoms may include subthreshold or transient psychotic symptoms, social isolation or withdrawal, odd beliefs or peculiar behaviour, blunted affect, disordered or reduced speech, and lack of energy or initiative (George et al., 2017). Early neuroanatomic changes are also present including reductions in temporal, cingulate, and inferior frontal cortices (Pantelis et al., 2003). Individuals who go on to develop psychosis have significantly decreased parahippocampal, fusiform, orbitofrontal, cingulate, and cerebellar cortices. Cognitive deficits are common in the prodromal phase and can include impairment in working memory, verbal fluency, processing speed, and declarative verbal memory (Simon et al., 2007).

1.1.5 Cognitive Impairment

In addition, many patients experience cognitive impairment that may worsen over the course of the illness (Ohi et al., 2017). Cognitive impairment can have a significant negative impact on social, occupational, and educational functioning, particularly in domains of verbal
ability, verbal memory, and vigilance (Addington & Addington, 2000). Deficits in working memory and episodic memory encoding are evident even at early stages of illness (Pflueger et al., 2018). Cognitive deficits in schizophrenia patients has been associated with reductions in hippocampal volume and the orbitofrontal cortex, as well as a general reduction in brain volume (Czepielewski, Wang, Gama, & Barch, 2017; Guo et al., 2014; Van Rheenen et al., 2018). Decreased hippocampal volume and reductions in the medial temporal cortex have been linked with memory impairment, including visual, verbal, and episodic memory, in schizophrenia patients, even in the prodromal stage (Karnik-Henry et al., 2012; Vargas et al., 2018).

1.2 Neuroanatomy

1.2.1 Overview of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a valuable tool for non-invasive, detailed imaging of human tissue, including the brain. Within the constant magnetic field of the MRI scanner, free hydrogen protons, such as those within water and fat, will precess in alignment with the magnetic field (McRobbie, Moore, & Graves, 2006). The Larmor frequency is directly related to the strength of the magnetic field and refers to the rate of precession of protons around the magnetic field. An applied radiofrequency (RF) pulse, at the resonant Larmor frequency, excites protons within a target region and knocks them out of alignment with the static magnetic field, forcing them into phase with surrounding hydrogen protons (McRobbie et al., 2006). Hydrogen protons will gradually return to alignment with the static magnetic field as the energy from the RF pulse dissipates, falling out of phase with one another, generating an RF signal detected by the receiver coil (McRobbie et al., 2006). The rate of relaxation of protons back to their original state ($T_1$) and the rate of relaxation of protons out of phase with one another ($T_2$) vary depending
on the proton density within the tissue (McRobbie et al., 2006). This information is spatially arranged, impacting brightness within each voxel and generated an image.

Scanning parameters can vary to generate appropriate image contrast. Repetition time (TR) is the time between the applied excitation RF pulse and echo time (TE) refers to the time between the application of the excitation pulse and the peak signal induced in the coil (McRobbie et al., 2006). T₁-weighted scans are those with a short TR and short TE to enhance T₁ differences between tissue, resulting in high contrast and clear anatomical images (McRobbie et al., 2006). T₂-weighted scans require long TR and TE, resulting in high intensity fluid, potentially allowing for identification of pathological fluid accumulation (McRobbie et al., 2006). FLAIR (Fluid Attenuated Inversion Recovery) scans are a specific type of T₂-weighted scan that allows for the suppression of background CSF signal, for more subtle identification of fluid-filled lesions. Imaging parameters must balance the signal-to-noise (SNR) ratio and image resolution in order to produce a quality image (McRobbie et al., 2006).

1.2.2 Historical Perspective of Imaging in Schizophrenia

Since its clinical inception in the late 1970s and early 1980s, both computed tomography and CT and MRI have been used as powerful tools to tease apart and elucidate the underpinnings of psychiatric disorders. The first milestone psychiatry imaging study performed with CT by Johnstone, Frith, Crow, Husband, & Kreel, (1976) described the appearance of ventricular enlargement in patients with chronic schizophrenia. The observation of ventricular dilation in schizophrenia patients has now been clearly established as the most consistent and most replicated finding in this patient population (Shenton, Dickey, Frumin, & McCarley, 2001). As structural imaging resolution has improved over the intervening decades, researchers have also
observed loss of frontal and temporal grey matter volume, increased sulcal dilation, decreased amygdalo-hippocampal volumes, reduced thalamic volumes, reduced white matter integrity, and both increased and decreased basal ganglia volumes (Shenton et al., 2001). Such measures have been made possible because of improvements in scanner technology and the development of rapid, automated segmentation techniques (Despotović, Goossens, & Philips, 2015). While these more subtle parenchymal brain findings have been replicated across a number of studies, the consistency of these findings is lower than those for ventricular dilation. Similarly, metabolic and functional imaging, more technically challenging modalities, have also been developing and improving considerably over the last 2 decades (Birur, Kraguljac, Shelton, & Lahti, 2017). Newer modalities of image ascertainment, in conjunction with high-resolution capabilities mediates expanded opportunities to investigate the underlying cerebral physical and physiological mechanisms that characterize schizophrenia and offers the opportunity to more fully explore the relationships between, medications, cognitive functioning, cardiovascular health and the symptoms of schizophrenia.

1.2.3 Neuroanatomic Characteristics of Schizophrenia

Widespread volumetric reductions are prevalent throughout the brain in many patients with schizophrenia. The most consistent findings include enlargement of the lateral ventricles, decreased limbic subcortical volumes and cortical reductions, particularly in the frontal and temporal lobes (Van Erp et al., 2016; Van Erp et al., 2018; Van Rheenen et al., 2018). Of particular interest are reduced limbic volumes, which encompasses the hippocampal formation. The hippocampus, a central hub for memory and learning, is atrophied in patients with schizophrenia compared to matched healthy controls (Ebdrup et al., 2011). Hippocampal volume
reductions are present during the first episode of psychosis, prior to antipsychotic exposure and pre-date the onset of illness (Ho & Magnotta, 2010; Verma et al., 2014). Decreased hippocampal volume has been associated with greater severity of positive symptom severity and increased cognitive deficits in the domains of verbal learning and working memory (Antoniades et al., 2018; Guo et al., 2014). Relapse duration has been associated with decreased frontal and temporal white matter volume and total brain volume in schizophrenia patients (N. C. Andreasen, Liu, Ziebell, Vora, & Ho, 2013).

Dysfunction in the prefrontal-limbic network may be central to the pathophysiology of schizophrenia (Weinberger, Berman, Suddath, & Torrey, 1992). A critical component of this network is the entorhinal cortex, located within the medial temporal lobe, that serves as the primary intermediary between the hippocampus and the orbitofrontal cortex (Witter, Doan, Jacobsen, Nilssen, & Ohara, 2017). Decreased volume in the medial temporal lobe, including the entorhinal, fusiform, and parahippocampal cortices have been linked with greater positive symptom severity and cognitive impairment (Karnik-Henry et al., 2012; Prasad, Patel, Muddasani, Sweeney, & Keshavan, 2004). These neocortical regions involved in the prefrontal-limbic network, including the entorhinal, fusiform, parahippocampal, and orbitofrontal cortices, are outlined in Figure 1-1. Concomitantly, reduced frontal connectivity and loss of frontal grey matter volume and thickness in schizophrenia are thought to contribute to the emergence of the illness (Iritani, 2007). Frontal grey matter volume deficits in schizophrenia have been associated with affective flattening and poor semantic processing and are present at early stages of illness (Ohtani et al., 2014; Sprooten et al., 2013). Decreased orbitofrontal volume is associated with impaired executive functioning (Guo et al., 2014). Cortical deficits have been observed in treatment-naïve and chronically-medicated psychosis patients, but differentiating whether these
cortical differences are the result of medication or present at the onset of illness requires further investigation (Baiano et al., 2008).

**Figure 1.1 Cortical parcellation of neocortical regions of interest from the Desikan-Killiany atlas including entorhinal, fusiform, parahippocampal, and orbitofrontal cortices**

The entorhinal cortex is primarily divided into two functionally distinct regions: the lateral entorhinal cortex (LEC) and the medial entorhinal cortex (MEC) (Witter et al., 2017). Neurons in the LEC and MEC both project to the hippocampus and beyond to the neocortex. Domain specificity for the LEC and MEC has been observed in both humans and rodents (Reagh & Yassa, 2014; Rodo, Sargolini, & Save, 2017). The MEC contains spatially selective grid cells which are thought to play a role in processing spatial or context information, while the LEC is
more specialized in object or item processing due to a lack of grid cells (Hunsaker, Chen, Tran, & Kesner, 2013). The connecting of item and contextual information in episodic memory is one of the key roles of the hippocampus (Hargreaves, Rao, Lee, & Knierim, 2005). The layer II subregion in particular is the main source of entorhinal projections to the dentate gyrus and fields CA2 and CA3 of the hippocampus (Witter et al., 2017). Layer II neurons projecting to the hippocampus may play a key role in regulating temporal association in episodic memory (Kitamura et al., 2014). Episodic memory impairment is prevalent in individuals with schizophrenia and has been significantly linked with entorhinal thickness in these patients (Karnik-Henry et al., 2012).

### 1.2.4 Risk Factors for Cortical Deficits

The concept of schizophrenia as a progressive disorder with increasing neuroanatomic deficits over the course of illness has been a topic of debate due to confounding factors of duration of illness, age, disease severity, antipsychotic medication, and lifestyle factors. Neuroimaging investigations of patients at varying stages of illness have provided some insight. Cortical deficits have been observed in both early psychosis and chronic schizophrenia patients, with greater decrease in cortical grey matter associated with a longer duration of illness (Dietsche, Kircher, & Falkenberg, 2017). Individuals with prodromal symptoms have evidence of cortical thinning in similar regions to schizophrenia patients including frontal and temporal lobes, indicating that some neuroanatomic deficits are present early in the course of illness (Jung et al., 2011). Although still a topic of debate, some meta-analyses have shown that progressive grey matter volume loss, particularly in the frontal and temporal lobes, is related to antipsychotic treatment and not illness severity or chronicity (Fusar-Poli et al., 2015; Torres, Portela-Oliveira,
Borgwardt, & Busatto, 2013). Even in early psychosis patients, antipsychotic medication may contribute to reductions in cortical gray matter (Vita, De Peri, Deste, Barlati, & Sacchetti, 2015). Serum lipid levels have been found to influence the relationship between antipsychotic medication and cortical thickness across various cortical regions indicating that cardiovascular health and potentially even lipid/myelin interactions may be responsible (Gjerde et al., 2018).

Health risk factors common in individuals with schizophrenia have also been associated with cortical deficits. Cardiovascular and metabolic risk factors have been associated with cortical thinning across frontal and temporal regions (Krishnadas et al., 2013; Schwarz et al., 2018). Low physical activity has also been linked to decreased hippocampal volume and reduced cortical thickness in the orbitofrontal cortex (McEwen et al., 2015). Smoking, obesity, and cannabis use may also contribute to reduced cortical thickness in individuals with schizophrenia (Habets, Marcelis, Gronenschild, Drukker, & Van Os, 2011; K. N. Jørgensen et al., 2015; Medic et al., 2016). Disentangling the effects of illness chronicity, age, antipsychotic exposure, physical health and lifestyle factors on cortical thickness remains a significant challenge, requiring further focused investigation.

1.3 Current Treatment Paradigms

Antipsychotic medications, starting with the development of chlorpromazine in the 1950’s, are a crucial component of schizophrenia treatment (Shen, 1999). The first-generation of antipsychotic medications, also known as ‘typical’ antipsychotics, including haloperidol and chlorpromazine, act as dopamine receptor antagonists inhibiting dopamine neurotransmission (Gardner, Baldessarini, & Waraich, 2005). They act by blocking D2 dopamine receptors in the mesolimbic pathway, as well as inhibiting noradrenergic, cholinergic, and histaminergic
transmission. Second-generation antipsychotics, or ‘atypical’ antipsychotics, including risperidone, olanzapine, and clozapine, impact both serotonin and dopamine, blocking both the D₂ dopamine receptors and the 5-HT₂A serotonin receptors (Meltzer, 2013). Although still a dopamine antagonist, atypical antipsychotics tend to bind more loosely and more transiently to dopamine receptors, limiting the risk of motor side effects typically observed with first-generation antipsychotics (Gardner et al., 2005).

Antipsychotic medications are relatively effective at reducing positive symptoms, and over half of patients receiving them experience a reduction in their symptom severity (MacKenzie et al., 2018). Atypical antipsychotics like olanzapine may be better at treating negative symptoms and cognitive deficits compared to typical antipsychotics like haloperidol, but these effects are small (Keefe et al., 2004; Lieberman et al., 2003). Atypical antipsychotics, particularly clozapine, may increase BDNF levels in schizophrenia patients, while typical antipsychotic treatment has been associated with decreased serum BDNF (Chikama et al., 2017). This increase in BDNF may be associated with cognitive improvement following atypical antipsychotic treatment (Pedrini et al., 2011). Antipsychotic treatment is thought to alter synthesis or release of BDNF and other growth factors through interaction with the tyrosine receptor kinase B (TrkB) receptor on dopaminergic neurons, the primary receptor for BDNF (Angelucci, Mathé, & Aloe, 2000).

Typical antipsychotic treatment is highly associated with the development of extrapyramidal symptoms, including significant motor disorders like tardive dyskinesia (Shen, 1999). These symptoms can be highly debilitating and negatively impact quality of life for schizophrenia patients (Strejilevich et al., 2005). Second-generation antipsychotics can still cause extrapyramidal symptoms, but the incidence rate is low (Vallianatou, 2016). Cardio-metabolic
adverse effects including obesity, dyslipidemia, type 2 diabetes mellitus, and hypertension are primarily associated with atypical antipsychotics. Clozapine, risperidone, and olanzapine are particularly associated with these metabolic effects (De Hert et al., 2008). A meta-analysis of cardio-metabolic effects found differing rates of adverse effects over the course of illness with 9.9% of first episode patients with metabolic syndrome (1.2% with type 2 diabetes mellitus and 8.7% with hyperglycemia), 22% overweight, 19.6% hypertriglyceridemia, 21.9% low HDL, and 30.4% high blood pressure (Mitchell, Vancampfort, De Herdt, Yu, & De Hert, 2013). Rates for all cardio-metabolic effects were significantly increased for patients with chronic schizophrenia compared to first episode patients, with 52.7% overweight, 41.1% hypertriglyceridemia, 44.7% low HDL, and 39.7% high blood pressure. Forty one percent of chronic schizophrenia patients met criteria for metabolic syndrome (12.8% with type 2 diabetes mellitus and 27.8% with hyperglycemia) (Mitchell et al., 2013).

Some atypical antipsychotics are associated with lower rates of cardiometabolic side effects, primarily aripiprazole which has been associated with weight gain, but may not be associated with deteriorating metabolic health including lipid abnormalities and waist circumference (Correll et al., 2009). Other adverse effects include anticholinergic effects, such as dry mouth, sedation, constipation, and urinary retention, which are more common for first-generation antipsychotics (Vallianatou, 2016). Clozapine has been associated with an elevated risk of potentially fatal neutropenia or agranulocytosis, lowered white blood cell count, so regular monitoring is recommended (Gardner et al., 2005).
1.4 Cardiovascular Characteristics of Schizophrenia

Patients experiencing psychosis and schizophrenia have an elevated risk of cardiovascular disease, metabolic syndrome, and ultimately reduced life-expectancy (Addington & Addington, 2000; Fernandez-Egea et al., 2009). On average, schizophrenia is associated with a 10 to 20-year reduction in expected lifespan (Ringen, Engh, Birkenaes, Dieset, & Andreassen, 2014). There is a considerable burden of physical illness concomitant with schizophrenia, particularly conditions associated with neurovascular and cardiovascular risk factors, such as obesity, hypertension, and type 2 diabetes mellitus (De Hert, Detraux, van Winkel, Yu, & Correll, 2012; Protopopova, Masopust, Maly, Valis, & Bazant, 2012; Vancampfort, Stubbs, et al., 2015). Individuals with schizophrenia are thought to experience a 3-fold increased risk of cardiovascular disease and obesity. As a result, individuals with schizophrenia are at elevated risk of cardiovascular diseases, including coronary heart disease, cerebrovascular disease and congestive heart failure (Correll et al., 2017; Vancampfort et al., 2016). This metabolic dysfunction is associated with worse cognitive function in schizophrenia patients (MacKenzie et al., 2018). Prescribed antipsychotic medication and lifestyle factors increase these risks and cardiovascular disease is the main cause of premature mortality in patients with schizophrenia (Laursen, Munk-Olsen, & Vestergaard, 2012).

1.4.1 Cardiovascular Risk and Antipsychotics

Unfortunately, adverse side effects associated with antipsychotic medications, including rapid weight gain and unwanted cardiometabolic effects, are common (Bushe, Slooff, Haddad, & Karagianis, 2012; De Hert et al., 2012). Antipsychotics are strongly associated with significant and rapid weight gain, cardiotoxicity, impaired lipid and glucose metabolism, increased rates of
type 2 diabetes mellitus, and significantly increased rates of stroke and cardiac arrest (Layland, Liew, & Prior, 2009; Muench & Hamer, 2010). Both olanzapine and clozapine, two commonly prescribed antipsychotic medications for chronic patients, are strongly associated with weight gain and metabolic disorder (Fleischhaker et al., 2007; Riordan, Antonini, & Murphy, 2011). Exposure to clozapine has also been associated with reduced cardiovascular fitness due to interaction with alpha-adrenergic receptors (Kim et al., 2018). Moreover, treatment-resistant individuals with less than expected medication response are receiving higher doses of these antipsychotic medications and are frequently hospitalized for months to years. This results in more adverse medication side effects compared to other patients (Jeon & Kim, 2017). Interestingly, in a rodent model, exercise partially remediated some of the adverse effects of olanzapine (Barr et al., 2013; Ramos-Miguel et al., 2015).

### 1.4.2 Cardiovascular Risk and Genetics

Some metabolic disturbances may exist in drug-naïve early psychosis patients (Cohen & De Hert, 2011). Common underlying genetic risk factors for schizophrenia and cardiovascular disease have been found indicating potential shared pathological mechanisms (Andreassen et al., 2013). Lipid biology genes appear to be primary candidates for this shared mechanism, perhaps indicating a link between dyslipidemia and myelin dysfunction during neurodevelopment (Andreassen et al., 2013). Other genetic links include genes associated with inflammation and the immune system (So, Chau, Ao, Mo, & Sham, 2019). Chronic inflammation may trigger microglial activation in the brain and may serve as a key mediator between metabolic dysfunction and psychosis (Henderson, Vincenzi, Andrea, Ulloa, & Copeland, 2015).
1.4.3 Cardiovascular Risk and Lifestyle Factors

Several lifestyle behaviours such as lack of exercise, poor diet, psychosocial stress, and smoking may exacerbate psychiatric symptoms and increase the risk of comorbid medical illness commonly observed in schizophrenia (Gupta & Craig, 2009). Patients with schizophrenia are particularly sedentary and engage in markedly low rates of physical activity (Stubbs et al., 2016; Vancampfort, Firth, et al., 2017). Negative symptoms of anhedonia and amotivation may make self-motivated physical activity particularly challenging (Vancampfort, De Hert, et al., 2015). Individuals with schizophrenia consume more fast food than the general population and consistently fail to meet dietary requirements even for patients residing in hospital or care facilities (Gupta & Craig, 2009). Persistent psychosocial stress has been associated with increased risk of coronary heart disease, due to dysregulation of the cortisol stress response (De Hert, Detraux, & Vancampfort, 2018). Schizophrenia patients are far more likely to smoke than the general population and smokers with schizophrenia tend to smoke more cigarettes per day than smokers without psychosis (Bobes, Arango, Garcia-Garcia, & Rejas, 2010). Smoking is strongly linked with elevated cardiovascular risk in this population (Stolz et al., 2019).

A recent study has shown that despite a high prevalence of overweight and obesity in persons with mental illness, they are systematically excluded from weight loss and lifestyle interventions (Daumit et al., 2013). Weight gain and metabolic changes occur rapidly following antipsychotic exposure and have been associated with worse functional outcomes and medication noncompliance, highlighting early psychosis as a critical period for cardiovascular interventions (Foley & Morley, 2011). Given the high rates of obesity and weight-related disease among persons with serious mental illness, there is an urgent need for targeted behavioral weight-loss interventions in this high-risk population.
1.5 Exercise as a Non-Pharmacological Intervention

1.5.1 Cognitive Effects

Exercise and improved cardiorespiratory fitness have consistently shown benefits for cognitive and neuroanatomic decline associated with aging (Colcombe, Kramer, McAuley, Erickson, & Scalf, 2004). The hippocampus, critical for memory processing, is frequently atrophied in aging populations with cognitive impairment (Mueller et al., 2010). Aerobic exercise, in particular, has been associated with improved executive functioning and increased hippocampal volume in older women with mild cognitive impairment (Scarmeas et al., 2010; Ten Brinke et al., 2015). Greater cardiorespiratory fitness was also associated with increased grey matter volume in the prefrontal cortex in older adults (Erickson, Leckie, & Weinstein, 2014). Animal research has demonstrated that the cellular basis for improvements in memory after exercise are associated with exercise-induced hippocampal neurogenesis (Wolf, Melnik, & Kempermann, 2011). Exercise-induced hippocampal neuroplasticity and cognitive improvement have been observed in animal models of Alzheimer's disease (Nichol, Deeny, Seif, Camaclang, & Cotman, 2009).

Both experimental and clinical evidence suggests that regular aerobic exercise improves cognition in psychosis and schizophrenia, however this has not yet undergone systematic evaluation. Neurocognitive benefits of exercise interventions exist particularly in the domains of working memory, social cognition, and attention/vigilance for psychosis patients (Firth et al., 2017). Poor cognition, particularly deficits in learning, attention, memory, and problem solving are persistent, debilitating and are significant barriers to work, inter-personal relationships, and education for psychosis patients (Millan et al., 2012). A recent study by Oertel-Knochel and colleagues reported improved working memory and processing speed performance after 4 weeks
of regular aerobic exercise (3 times/week, 45 minutes/session) in chronic schizophrenia patients (Oertel-Knöchel et al., 2014). Post-exercise improvements in short-term memory in psychotic patients have been linked to exercise-mediated increases in hippocampal volume (Pajonk et al., 2010).

1.5.2 Clinical Effects

Exercise has been shown to increase functional performance, improve quality of life, and alleviate mood symptoms across a variety of psychiatric populations (Portugal et al., 2013). Individuals who exercise self-reported a lower mental health burden compared to those who do not (Chekroud et al., 2018). Physical activity has been associated with a reduction in depressive symptoms similar to that experienced with antidepressant medication for individuals with mild-to-moderate depression (Carek, Laibstain, & Carek, 2011). Aerobic and anaerobic exercise have both been shown to be a beneficial adjunct treatment for individuals with anxiety disorders (Jayakody, Gunadasa, & Hosker, 2014).

Both experimental and clinical evidence suggests that regular aerobic exercise reduces symptom severity in patients with schizophrenia, including psychosis, depression, and anxiety symptoms (Scheewe et al., 2013; Vancampfort et al., 2011). A systematic review of exercise interventions in psychosis patients confirmed reductions in the severity of co-morbid mood disorders and both positive and negative psychosis symptoms in response to exercise (Firth, Cotter, Elliott, French, & Yung, 2015). Exercise has also been associated with improved social functioning and quality of life across a number of psychiatric populations (Greer et al., 2016; Keating et al., 2019; Schuch et al., 2016).
1.5.3 Neuroanatomic Effects

The potential for exercise-mediated neuroanatomical growth in psychosis patients remains equivocal. Greater cardio-respiratory fitness has been associated with greater hippocampal volume, increased temporal cortical grey matter and elevated serum growth factor levels (Erickson et al., 2014; Whiteman, Young, Budson, Stern, & Schon, 2016). A study by Seifert and colleagues demonstrated enhanced release of BDNF in healthy humans after three months of aerobic endurance training and in mice after five weeks of treadmill running (Seifert et al., 2010). A 12% increase in hippocampal volume was found in chronic schizophrenia patients following a 3-month aerobic exercise intervention and a recent meta-analysis demonstrated exercise-induced retention of hippocampal volume in clinical patients compared to non-exercising controls (Firth, Stubbs, et al., 2018; Pajonk et al., 2010). Exercise-induced hippocampal neurogenesis is thought to be the basis for improvements in memory after exercise (Wolf et al., 2011). In some circumstances, exercise interventions appeared to increase temporal cortical grey matter in psychosis patients without a significant increase in hippocampal volume (Malchow et al., 2016). Other studies failed to find any changes in cortical or subcortical grey matter following six months of exercise therapy (Scheewe et al., 2013). However, the heterogeneity of patient populations and exercise programs indicates further research is required.

Variations in patient population, exercise protocols, and study duration may help explain conflicting evidence for hippocampal increase following an exercise intervention in psychosis patients. The Pajonk et al. (2010) study found a significant increase in hippocampal volume in male chronic schizophrenia patients who completed aerobic exercise three times per week for 12 weeks compared with a control group playing table football. Lin et al. (2015) demonstrated a small increase in female early psychosis patients who completed an identical aerobic exercise
intervention. However, Malchow et al. (2016) failed to observe a significant increase in hippocampal volume in chronic schizophrenia patients with the same exercise protocol. However, a significant decrease in hippocampal volume was observed for the table-top football control group over six months that was not observed in the aerobic exercise group, indicating that aerobic exercise may confer potential neuroprotective effects in schizophrenia patients. However further research is required to investigate this effect. A significant increase in medial temporal volume, including parts of the fusiform gyrus, was observed for schizophrenia patients following participation in the aerobic exercise intervention (Malchow et al., 2016).

Scheewe et al. (2013) included an exercise program that consisted of a combination of aerobic and resistance training once or twice per week for six months compared to an occupational therapy control. This lower frequency of exercise and lack of comparison with a treatment-as-usual control group may explain the lack of hippocampal findings observed in this study. Schizophrenia patients did exhibit a significant relationship between increased frontal and temporal cortical thickness and increased cardiorespiratory fitness (Scheewe et al., 2013).

1.5.4 Cerebrovascular and Cardiovascular Effects

It is postulated that vascular deficits in schizophrenia may be associated with components of the cognitive deficits observed as part of the illness (O’Brien et al., 2003). Hypo-perfusion of the frontal lobes in the inferior orbitofrontal region, has been observed in both early psychosis and chronic schizophrenia (Iwashiro et al., 2012; Kanahara et al., 2013). Reduced blood flow to the frontal and temporal regions has been observed when schizophrenia patients are at rest, and during cognitive activation (Hoshi, Shinba, Sato, & Doi, 2006). These observations do not necessarily represent frontal or temporal dysfunction per se, but may reflect potential anatomical
and/or functional alterations of neurovascular microcirculation. Post-mortem studies of capillaries and oligodendrocyte ultrastructure in schizophrenia demonstrated numerically reduced pericapillary oligodendrocytes in the prefrontal cortex compared to matched controls (Vostrikov, Orlovskaia, & Uranova, 2008).

Exercise interventions have been shown to improve cardiorespiratory fitness and markers of cardiometabolic health in schizophrenia patients (Vancampfort, Rosenbaum, et al., 2017). Regular aerobic exercise can confer significant physical benefits (i.e. reduction in cardiovascular disease risk, weight reduction) to psychotic patients in the presence of high-dose antipsychotic treatment (Knöchel et al., 2012). Routine exercise was found to improve olanzapine-induced glucose intolerance and insulin responsiveness in rats (Boyda et al., 2014). However, the impact of aerobic exercise programs on metabolic syndrome in schizophrenia patients remains equivocal (Schmitt et al., 2018). Exercise-induced increases in cerebral blood flow are thought to trigger a downstream neurometabolic response triggering hippocampal neuroplasticity (Seifert et al., 2010). Mitigation of cardio-metabolic risk factors, in conjunction with hippocampal remediation, in this population is key to reducing mortality and improving daily quality of life.

1.5.5 Cellular Mechanisms for Exercise-Mediated Neuroanatomical Changes

Exercise-induced hippocampal growth is thought to result from the upregulation of neuronal growth factors, including BDNF, triggering synaptic plasticity (Vivar & van Praag, 2017). Additionally, it has been suggested that exercise triggers the up-regulation of vascular endothelial growth factor (VEGF), and insulin-like growth factor 1 (IGF-1), promoting a downstream neurometabolic response to greater sub-regional blood flow (Seifert et al., 2010). The functional benefits of exercise may result from these changes, including increases in
neuronal proliferation, survival, and functioning, decreased inflammation, improved vascular function, and decreased stress-induced neuroendocrine response (Cotman, Berchtold, & Christie, 2007; van Praag, 2005).

While it is clear that exercise confers multiple health benefits and is likely to improve blood flow to all regions of the brain, the potential for exercise to induce growth of hippocampal vasculature is of particular interest. It is well established that the hippocampus is pivotal to effective brain functioning and that this region may be directly associated with cognitive deficits seen in schizophrenia (Boyer, Phillips, Rousseau, & Ilivitsky, 2007; Eisch et al., 2008). The animal data suggest that exercise-induced angiogenesis (new vascularization) is critical to improvements in hippocampal functioning (Kerr, Steuer, Pochtarev, & Swain, 2010). Increased cerebral vascular blood flow associated with exercise was positively related to increased neurogenesis of the dentate gyrus of the hippocampal formation (Pereira et al., 2007). The impact of exercise on hippocampal vascular volume in individuals with schizophrenia following an exercise intervention remains largely unexamined.

1.5.6 Exercise Type

To date, aerobic exercise, either treadmill running or stationary cycling, has been the most common intervention associated with neuroanatomical remediation in psychosis patients (Firth et al., 2015). In contrast, yoga training, typically consisting of a combination of breathing practice, body postures, and relaxation, has previously been shown to provide neurocognitive benefits to early psychosis patients, particularly in areas of working memory, verbal acquisition, and attention (Lin et al., 2015). Patients with psychosis who participated in yoga experienced improved psychotic and depressive symptoms (Lin et al., 2015; Varambally & Bangalore, 2012).
Experienced yoga practitioners have greater grey matter volumes throughout the brain, notably in frontal and temporal regions including the hippocampus and the orbitofrontal cortex (Villemure, Ceko, Cotton, & Bushnell, 2015). The ability of yoga to regulate stress and cortisol secretion may be critical. However, these neuroanatomic changes have not been replicated in psychosis patients (Lin et al., 2015).

Resistance training has been shown to confer a variety of benefits in randomized controlled trials of older adults including improved executive functioning, reduced depressive symptoms, and enhanced social functioning (Liu-Ambrose et al., 2010; Singh, Clements, & Fiatarone, 1997). Resistance training has not consistently been associated with neuroanatomic grey matter changes, as anaerobic exercise programs have not been shown to reliably increase BDNF levels (Jørgensen, Kjølhede, Dalgas, & Hvid, 2019; Szuhany, Bugatti, & Otto, 2015). The capacity for yoga and resistance training to remediate neuroanatomic deficits in psychosis patients requires further investigation.

1.6 Assessment Measures

1.6.1 Clinical Symptom Assessment Measures

The Positive and Negative Syndrome Scale (PANSS) was developed to measure symptom severity in patients with schizophrenia (Kay, Fiszbein, & Opler, 1987). The PANSS is a 30-item rating scale, with each item measured on a 7-point scale from 1 to 7. Scores for each item are based on a semi-structured clinical interview and symptoms are divided into three dimensions of positive, negative, and general psychopathology. Information can also be gathered from primary-care hospital staff, family members, and patient charts. The use of the PANSS to
assess psychosis symptoms has been validated in early psychosis and chronic schizophrenia patients (Fulford et al., 2014; Kay, Opler, & Lindenmayer, 1988).

The PANSS is divided into three subscales for positive, negative, and general psychopathology. However, due to the heterogeneous nature of schizophrenia, subsequent factor analyses have been conducted to assess the best fit for grouping symptoms (Wallwork, Fortgang, Hashimoto, Weinberger, & Dickinson, 2012). Particularly, a five-factor model including positive, negative, excitement, cognitive, and depression/anxiety domains has been frequently applied (Lindenmayer, Bernstein-Hyman, & Grochowski, 1994; Wallwork et al., 2012). However, consensus for an alternative factor model has not been reached and the three original subscales are still widely used in both clinical and academic settings. PANSS factorial analysis was not found to differ between treatment-response and treatment-resistant schizophrenia, however for treatment-resistant schizophrenia patients symptom improvement varied across domains for different atypical antipsychotic treatment (Freitas et al., 2019; Lindenmayer et al., 2004). While clozapine, olanzapine, and risperidone were all associated with improvement in positive, cognitive, and depression/anxiety domains, only clozapine and olanzapine were associate with improvement in the negative domain, and only clozapine was associated with improvement in the excitement domain (Lindenmayer et al., 2004).

Other clinical symptom assessments include the Calgary Depression Scale (CDS), a nine item, 4-point scale assessing depressive symptoms in psychotic patients from 0 (not present), to 4 (severe) (Addington, Addington, & Schissel, 1990). The Social and Occupational Functioning Assessment Scale (SOFAS) is designed to specifically address social and occupational functioning levels independent of psychological symptoms (Saraswat, Rao, Subbakkirshna, & Gangadhar, 2006). The SOFAS is a 100-point scale with a clear description for each 10-point
interval. Individuals with a score of 60 for example experience some difficulty in social, occupational, or school functioning, while individuals with a score 40 experience major impairment in these areas. The Hamilton Anxiety Rating Scale (HAM-A) is a 14-item scale used to assess severity of anxiety symptoms with each item being measured on a 4-point scale from 0 to 4 (Hamilton, 1959). This scale has been validated for the use of assessing anxiety symptoms in patients with schizophrenia (Seedat, Fritelli, Oosthuizen, Emsley, & Stein, 2007).

The Extrapyramidal Symptom Rating Scale (ESRS) allows for the assessment of drug-induced motor disorders, particularly parkinsonism, akathisia, dystonia, and tardive dyskinesia (Chouinard & Margolese, 2005). Parkinsonism describes movement patterns typically associated with Parkinson’s disease including resting tremor, rigidity, and slowed movement (bradykinesia) (Walther & Strik, 2012). Akathisia involves restlessness and an inability to stay still. Dystonia occurs when muscles contract uncontrollably, resulting in sustained and rigid postures or repetitive movements. Tardive dyskinesia is the presence of atypical, involuntary, and repetitive movements (Walther & Strik, 2012). These can originate from muscles in the face, limbs, or body. These movement disorders can occur as a result of antipsychotic treatment and can be highly distressing and uncomfortable for patients (Mathews et al., 2005).

### 1.6.2 Neurocognition Assessment Measures

The Wechsler Test of Adult Reading (WTAR) is a neuropsychological assessment used to assess cognitive function prior to the onset of illness (Venegas & Clark, 2011). As a measure of premorbid intelligence, it consists of 50 irregularly spelled English words and the participant is asked to read each word aloud. The assessment continues until the participant has given 12 consecutive incorrect pronunciations and a score of 1 is assigned for each correct pronunciation.
up to this point, for a maximum score of 50. The WTAR has been used to assess premorbid intelligence in a number of patient populations including traumatic brain injury, Alzheimer’s disease, and schizophrenia (Green et al., 2008; McFarlane, Welch, & Rodgers, 2006; Ohi et al., 2017).

The Kaufman Brief Intelligence Test (KBIT) is a brief measure of verbal and nonverbal intelligence used to assess current intelligence levels (Kaufman, 1990). The verbal scale consists of two tests, one where an individual is asked to name pictured objects, and another that requires the identification of words from a brief definition. The nonverbal scale consists of a multiple-choice task that requires the recognition of relationships among both meaningful and abstract visual stimuli. These scales can also be combined to form a composite measure of current intelligence.

1.7 Treatment-Resistant Schizophrenia

The efficacy of exercise as a non-pharmacological adjunct intervention to ameliorate anatomic and clinical deficits in treatment-resistant schizophrenia has not yet been clearly established. Approximately 30% of schizophrenia patients experience an insufficient response to treatment (Elkis & Buckley, 2013). Treatment-resistant patients typically have symptoms that have failed to respond to at least two antipsychotic medications and maintain high levels of psychopathology while being on high doses of antipsychotic medication. The Treatment Response and Resistance in Psychosis Working Group Consensus Guidelines established key elements necessary for diagnosis including confirmed diagnosis of schizophrenia, and persistence of significant symptoms despite adequate pharmacological treatment (Howes et al., 2017). Typically, an individual must have symptoms that have failed to response to at least two
different antipsychotic medications at adequate dosage and duration. Treatment response is considered to be a minimum of 20% reduction in psychosis symptom severity on the PANSS or \( \geq 2 \)-point change on the Clinical Global Impression scale (Howes et al., 2017).

Clozapine treatment is currently the primary recommendation for treatment-resistant patients and has been associated with improvement in psychopathology and functioning in these patients (Meltzer, 1997; Warnez & Alessi-Severini, 2014). While some studies have reported improvements in cognitive function following clozapine treatment, these results remain equivocal (Czepielewski et al., 2018; Hagger et al., 1993). Clozapine polypharmacy is also common for treatment-resistant schizophrenia patients and may result in excessively high dosing (Procyshyn et al., 2010). Like many second-generation antipsychotics, clozapine treatment has been associated with increased risk of metabolic syndrome with serious long-term health implications (Lamberti et al., 2006). Women, compared to men, and patients taking polypharmacy had an elevated risk for side effects including weight gain, sedation, and psychomotor dysfunction, namely akathisia, a movement disorder characterized by excessive movement (Iversen et al., 2018).

Treatment-resistant patients may exhibit unique clinical, neuroanatomical, and cognitive characteristics that differentiate them from treatment-responsive patients (Howes et al., 2017; Mouchlianitis, McCutcheon, & Howes, 2018). These differences include significantly decreased cortical grey matter volume and verbal memory deficits compared to treatment-responsive patients (Barry et al., 2019; Gillespie, Samanaite, Mill, Egerton, & MacCabe, 2017; Zugman et al., 2013). Treatment resistant patients also exhibit greater psychopathology, particularly driven by higher negative symptomatology (Iasevoli et al., 2018). Motivational deficits associated with
negative symptoms may make engaging in self-motivated exercise programs particularly difficult for treatment-resistant patients (Vancampfort, De Hert, et al., 2015).

1.8 Sex Differences

Sex differences in schizophrenia have been postulated since the time of Kraepelin who noted a higher age of first admission for women with dementia praecox compared with men (Häfner, 2005). The evidence for neuroanatomic sex differences in schizophrenia patients remains inconclusive. Men with schizophrenia may exhibit greater medial temporal and frontal volume reductions, however other studies have failed to find any frontal volumetric sex differences (Nancy C. Andreasen et al., 1994; Bogerts et al., 1990; Highley et al., 2001).

1.8.1 Clinical Differences

Some studies have noted sex differences in symptomatology with men typically experiencing greater negative symptoms and women exhibiting greater positive and affective symptoms (Køster, Matilde, Ae, Lindhardt, & Rosenbaum, 2008; Maric, Krabbendam, Vollebergh, De Graaf, & Van Os, 2003; Tang et al., 2007). While the level of cognitive impairment is similar between men and women, men may experience lower premorbid functioning and experience greater disability over the course of illness (Bozikas et al., 2010; Morgan, Castle, & Jablensky, 2008). While men appear to exhibit a higher incidence of psychosis symptoms at younger ages, overall lifetime incidence rates between men and women are comparable (Häfner, 2005).
1.8.2 Sex Differences and Exercise Interventions

Previous work investigating the impact of exercise interventions on psychosis patients have relied on samples of largely male participants (Malchow et al., 2016; Pajonk et al., 2010; Scheewe et al., 2013). However, women may actually be at greater risk for metabolic side effects of second-generation antipsychotics including weight gain and elevated cholesterol (Davey et al., 2012; Iversen et al., 2018). Exercise interventions for women may be more likely to produce positive findings. Physical activity was shown to have a greater effect for women in decreasing depressive symptoms (Zhang & Yen, 2015). Older women who complete aerobic exercise interventions show greater improvement in executive processing and larger volumetric increases in the prefrontal cortex compared to men (Barha et al., 2019; Barha, Davis, Falck, Nagamatsu, & Liu-Ambrose, 2017). These differences may be due to a greater efficacy of aerobic exercise in up-regulating BDNF in women than in men (Barha, Hsiung, et al., 2017). Further research to investigate the potential benefit for exercise interventions in female psychosis patients would be beneficial.

1.9 Overview and Research Goals

This dissertation examines the impact of exercise on brain volume and clinical symptoms in relation to psychosis across three different participant groups. First, given the elevated cardio-metabolic risk associated with second-generation antipsychotic medication, treatment-resistant schizophrenia patients, who frequently receive high doses of long-term treatment with these medications, may be particularly at risk for cardiovascular disease and cardiovascular-related death. These patients may also experience greater grey matter reduction. Chapter 2 will include
the evaluation of exercise-induced hippocampal changes and reductions in symptom severity in treatment-resistant patients.

While various studies have established that exercise promotes neuroplasticity within the hippocampus, the potential for exercise-induced parahippocampal or temporo-frontal cortical plasticity remains equivocal. Cortical loss can be observed in both chronic schizophrenia and early psychosis patients, although the pattern and extent of this loss may be distinct. Medial temporal regions including the entorhinal, fusiform, and parahippocampal cortices are valuable primary targets for investigation due to their proximity and connectivity with the hippocampus. Compared to early psychosis patients, chronic psychosis patients experience greater frontal cortical loss. The entorhinal cortex serves as a primary intermediary between the hippocampus and the neocortex, including the orbitofrontal cortex. This prefrontal-limbic pathway plays a critical role in episodic memory, a cognitive domain frequently impaired in individuals with schizophrenia. Investigating the efficacy of exercise, particularly aerobic exercise, to remediate cortical loss in both chronic and early psychosis patients would be beneficial to understanding the greater neuroplastic potential of exercise interventions for these patients. Evaluation of medial temporal regions and the orbitofrontal cortex allows for potential distinction between cortical areas impacted by different stages of illness. Chapter 2 will evaluate these cortical changes in chronic schizophrenia patients, while Chapter 3 will investigate the potential for cortical changes in early psychosis patients.

Clinical studies in psychosis patients face difficulty in disentangling the effects of ongoing antipsychotic treatment from the impact of exercise and the potential interactive nature of these two treatment paradigms. To further evaluate the impact of exercise-induced
neuroplasticity in cortical regions beyond the hippocampus, Chapter 4 includes an investigation of entorhinal cortical thickness in rats exposed to antipsychotic medication and exercise.

1.9.1 Specific Aims and Hypotheses

This dissertation seeks to address the following aims:

Aim 1: Evaluate the impact of exercise on hippocampal volume, hippocampal vascular volume, and symptom severity in treatment-resistant schizophrenia patients.

We expected participation in a 12-week exercise intervention to be associated with an increase in hippocampal volume and hippocampal venule volume in treatment-resistant psychosis patients. We also hypothesized a reduction in psychosis symptom severity and that this improvement would be associated with increased hippocampal volume.

Aim 2: Investigate the potential for exercise, particularly aerobic exercise, to promote cortical neuroplasticity in chronic schizophrenia and early psychosis patients.

We hypothesized that aerobic exercise specifically would be associated with cortical expansion in the medial temporal cortex and the orbitofrontal cortex. As orbitofrontal cortical deficits are more pronounced in chronic schizophrenia, we anticipated neuroremediation in this region specifically for patients with chronic schizophrenia. Cortical expansion was anticipated to be associated with reduction in psychosis symptom severity for both patient groups.

Aim 3: Determine the differential impact of olanzapine and exercise on entorhinal cortical thickness in an animal model (rats) and evaluate the relationship between entorhinal cortical change and metabolic indices.
We anticipated that olanzapine would be associated with decreased entorhinal cortical thickness, while exercise would increase entorhinal cortical thickness. Greater entorhinal cortical thickness was expected to be associated with greater amounts of activity, and improved metabolic indices, including lower fasting insulin and decreased glucose intolerance.
Chapter 2: Structural neuroimaging before and after exercise in treatment-resistant schizophrenia

2.1 Brief Introduction

Given the greater exposure to metabolically risky antipsychotic medications and the elevated frequency and severity of cardiovascular deficits in treatment-resistant patients, a clinical exercise intervention is expected to confer multiple clinical benefits and to induce a salutary neuroplastic response in the hippocampus. We conducted an in vivo investigation of the effects of regular exercise in a chronically medicated schizophrenia population. As described in Chapter 1, frontal and temporal volume loss is widely observed in chronic schizophrenia patients. Aerobic exercise, in particular, is thought to promote cortical plasticity. In combination with data collected from patients with treatment-resistant schizophrenia, we replicated this data collection in a cohort of age, gender, and education-matched healthy volunteers.

Potential effects on hippocampal plasticity and hippocampal vascular growth were evaluated. Effects of exercise type on cortical changes in medial temporal cortical regions including the entorhinal, fusiform, and parahippocampal cortices, and the orbitofrontal cortex were also assessed in comparison with healthy volunteers. It was hypothesized that 1) sustained regular exercise would induce hippocampal growth and hippocampal vascular expansion; and 2) hippocampal growth would be associated with improvements in symptoms and affect in treatment-resistant schizophrenia patients. It was anticipated that 3) healthy volunteers would demonstrate greater cortical volume and thickness compared to schizophrenia patients at baseline, 4) aerobic exercise in particular would promote cortical plasticity over the course of a
12-week exercise intervention, and 5) exercise-induced cortical expansion would be associated with improved symptom severity.

### 2.2 Methods

We conducted a longitudinal investigation of the effects of individualized exercise prescriptions (involving moderate intensity continuous aerobic and weight bearing exercise) on hippocampal volume and vascular volume, cortical volume and thickness, and clinical outcomes in chronic schizophrenia participants. Clinical, physical, neurocognitive and imaging data were ascertained at baseline and 12 weeks. All clinical data were collected by qualified trained clinicians. Data analysis was done by research staff independent of the data collection team.

#### 2.2.1 Participants

Ethics for this study were provided by the University of British Columbia (UBC) Clinical Research Ethics Board, in accordance with Tri-Council Policy. Chronically medicated inpatients between the ages of 19 and 50 years were recruited from the British Columbia (BC) Psychosis Program at UBC Hospital. Clinical diagnoses were based on DSM-IV criteria. Nine healthy volunteers were recruited through online advertising. Healthy volunteers were recruited to match to schizophrenia patients for age, sex, and years of education with an age range of 19-50 years and no post-secondary education. Exclusion criteria for both patients and healthy volunteers included history of developmental disorder, DSM diagnosis of substance abuse in the prior 6 months (excluding tobacco), history of angina, cardiac arrest or transient ischemia, non-independent mobility or limb prostheses, history of neurological disorder, history of head injury leading to loss of consciousness for greater than 5 minutes, or being currently enrolled in a
regular exercise program. Twenty-seven patients were recruited to the study. Twelve were diagnosed with schizophrenia and 15 were diagnosed with schizoaffective disorder. A total of 17 patient participants were able to complete the entire 12-week research protocol and had scans of sufficient quality for volumetric analysis at baseline and follow-up. Participants were lost due to symptom exacerbation preventing the participant from leaving the ward (N = 3), ward discharge back to community caretakers (N = 6), or the development of health issues identified as contraindications for the exercise intervention (N = 1). Analysis was completed using data from these seventeen participants. Participants who completed the exercise program did not differ significantly from participants who do not on any demographic measures of interest. All patient participants had been receiving treatment for psychosis for a minimum of 36 months at baseline. The atypical antipsychotics received included aripiprazole, clozapine, olanzapine, quetiapine and paliperidone. Additionally, 4 participants were also receiving typical antipsychotics (flupenthixol, perphenazine). Complete demographic and summary clinical data for participants are provided in Table 2-1.
### Table 2.1 Summary demographic and clinical measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N = 17)</th>
<th>Healthy Volunteers (N = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 Week Follow-up</td>
</tr>
<tr>
<td>Sex (%F)</td>
<td>M 11 / F 6 (35.3%)</td>
<td></td>
</tr>
<tr>
<td>Diagnosis (Schizophrenia/Schizoaffective)</td>
<td>7 SZ / 10 SA</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>31.8 ± 6.8</td>
<td>-</td>
</tr>
<tr>
<td>Years Education (years)</td>
<td>11.2 ± 2.0</td>
<td>-</td>
</tr>
<tr>
<td>Duration of Illness (years)</td>
<td>10.6 ± 5.8</td>
<td>-</td>
</tr>
<tr>
<td>Antipsychotic Dose (CPZ Equivalents mg/day)</td>
<td>570.1 ± 374.6</td>
<td>677.4 ± 363.0</td>
</tr>
<tr>
<td>Total PANSS Score</td>
<td>95.6 ± 13.0</td>
<td>78.8 ± 13.6</td>
</tr>
<tr>
<td>Calgary Depression Scale</td>
<td>5.8 ± 4.1</td>
<td>5.0 ± 4.6</td>
</tr>
<tr>
<td>Social/Occupational Functioning Scale</td>
<td>31.9 ± 4.1</td>
<td>37.3 ± 4.5</td>
</tr>
<tr>
<td>Hamilton Anxiety Scale</td>
<td>11.8 ± 8.4</td>
<td>7.7 ± 4.6</td>
</tr>
<tr>
<td>Extrapyramidal Symptoms Rating Scale</td>
<td>28.1 ± 12.8</td>
<td>25.4 ± 11.9</td>
</tr>
<tr>
<td>Resting Heart Rate (RHR)</td>
<td>89.9 ± 16.2</td>
<td>90.6 ± 12.8</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>28.3 ± 5.3</td>
<td>27.2 ± 4.9</td>
</tr>
<tr>
<td>VO\textsubscript{2} Max (mL/kg/min)</td>
<td>21.9 ± 11.8</td>
<td>21.5 ± 9.9</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.0 ± 1.7</td>
<td>1.2 ± 0.5</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.2 ± 0.7</td>
<td>3.9 ± 0.4</td>
</tr>
<tr>
<td>Blood Pressure (mmHg)</td>
<td>115/77</td>
<td>-</td>
</tr>
</tbody>
</table>

#### 2.2.2 Neuroimaging

All scans were acquired on a Philips Achieva 3.0 Tesla (3T) scanner, software version 3.2.3.1 with an 8-channel head coil. High-resolution anatomic and microvascular images were
acquired with the following protocols: Isotropic 3-dimensional T₁-weighted images (3D T₁-longitudinal relaxation time) in the sagittal plane, TR/TE (repetition time/echo time) = 6.6/3.0 ms, field of view (FOV) = 240 x 240, acquisition matrix = 240 x 240, recon matrix = 240 x 240, recon voxel size = 1 x 1 x 1 mm, slice thickness = 1 mm, 155 slices interleaved no gap, sensitivity encoding (SENSE) factor = 1, b-factor = 700, flip angle = 8 were acquired for volumetric analysis (scan time = 9:52.6); transverse susceptibility weighted images, repetition TR/TE = 34/6 ms, acquisition matrix 548 x 256, recon matrix = 640 x 640, recon voxel size 0.34 x 0.35 mm, slice thickness = 1 mm, 155 slices no gap, SENSE factor = 1, flip angle = 17°; 5 echoes were acquired for assessment of hippocampal vasculature (scan time = 7:02.6). Fluid-attenuated inversion recovery images (FLAIR) were acquired for clinical review to screen for the presence of significant brain injury or clinically relevant incidental findings (i.e. tumours, hemorrhage).

Post-processing of structural images was performed on a Mac Pro Dual Core Pentium Tower with Intel chips, which is housed at the BC Mental Health and Substance Use Research Institute. All structural scans (3D T₁-weighted) were processed using the FSL (Functional Magnetic Resonance Imaging of the Brain (FMRIB) Software Library) v5.0 shareware and matrix laboratory (MATLAB) software. Standard FSL FMRIB Automated Segmentation Tool (FAST) v2.0 eddy current correction was applied to all scans. Total brain volumes were extracted by FSL v5.0, after non-brain signal from subcutaneous fat and arachnoid spaces are removed using the FSL Brain Extraction Tool (BET) and tissue segmentation with FSL FAST. Extracted brain volumes were registered to MNI-152 (Montreal Neurological Institute) standard space after 12-degrees of freedom linear affine registration with FSL FLIRT v5.4.2 (FMRIB’s Linear Image Registration Tool) (Jenkinson, Bannister, Brady, & Smith, 2002). Subregional
extraction of hippocampal volumes was achieved by ANTS (Advanced Normalization Tools) v2.1 multi-atlas and manual segmentation based on 20 manually segmented templates from Neuromorphometrics (http://www.neuromorphometrics.com) to increase accuracy of hippocampal segmentation (Wang et al., 2013). This joint-label fusion technique improves the use of stand-alone atlas tools by accounting for small differences in segmentation results between individual atlas segmentations and improves segmentation accuracy. Additional exploratory hippocampal subfield segmentation with FreeSurfer v5.3 was performed (see Figure 2-1). Manual segmentation of left and right hippocampal volumes was conducted for all patient scans based on clear anatomic boundaries of the hippocampus (Duvernoy et al., 1999). Manual tracing was completed using ITK-SNAP v3.6.0 on contiguous coronal slices (Yushkevich et al., 2006). Additional FLAIR sequence T2 (transverse relaxation time) image sets were acquired for the purposes of clinical evaluation by the radiologist to rule out potential mass abnormalities (i.e., tumours), as these datasets would be excluded from analyses.
Figure 2.1 Sample segmentation of whole and subfield hippocampal volume (A: Axial plane, B: Coronal plane, C: Subfield segmentation)
Susceptibility weighted images (SWI) were used for the assessment of hippocampal vasculature. High spatial resolution of SWI allowed visualization of small veins, and also reduced SWI's sensitivity to background inhomogeneities of the static magnetic field. An automated segmentation protocol was applied to ensure reliability of the vascular volume assessment in the hippocampi. SWI venograms were co-registered to the anatomical scan with FSL v5.0 (see Figure 2-2 for a sample SWI image). A standard automated signal intensity-based segmentation protocol was applied to ensure reliability of the vascular volume assessment in the hippocampi. Prior to vascular segmentation, the SWI scans were co-registered to the 3D-T1 volumetric scans with FSL FLIRT v5.4.2 using a 12-degrees of freedom linear affine registration protocol. Neuromorphometric multi-atlas hippocampal masks were transformed from T1 space to SWI space. Bilateral hippocampal vessel volumes were then calculated based on the neuromorphometric hippocampal masks.
Figure 2.2 Sample of hippocampal venules segmentation from SWI (A: Raw axial SWI image, B: Segmented axial SWI image)

Structural magnetic resonance imaging (MRI) data was analyzed by Freesurfer v5.3 to calculate cortical thickness and volume measures using the Desikan-Killiany atlas for cortical parcellation (Desikan et al., 2006). To extract reliable thickness and volume estimates, images
were automatically processed with the longitudinal stream in Freesurfer (Reuter, Schmansky, Rosas, & Fischl, 2012). Only scans without significant motion artifact were included.

2.2.3 Clinical Assessments

All clinical assessments were conducted at baseline and 12 weeks. Symptom severity was assessed with the PANSS (Positive and Negative Syndrome Scale), the CDS (Calgary Depression Scale), and the HAM-A (Hamilton Anxiety Scale) (D. Addington et al., 1990; Hamilton, 1959; Kay et al., 1988). These scales have been specifically developed and validated for evaluation of symptoms in patients with psychosis. Level of social functioning was ascertained with the SOFAS (Social and Occupational Assessment Scale) (Rybarczyk, 2011). Extrapyramidal symptoms were assessed with the ESRS (Extrapyramidal Symptoms Rating Scale) (Chouinard & Margolese, 2005). Cardiovascular fitness, based on maximal aerobic power (VO\textsubscript{2}Max), resting blood pressure, resting heart rate, body mass index (BMI), blood cholesterol and triglyceride levels were measured at baseline and 12 weeks.

2.2.4 Cognitive Measures

In order to fully characterize this patient population, baseline premorbid intelligence quotient (IQ) was assessed with the full-scale Weschler Test of Adult Reading (WTAR), a highly validated test of crystallized IQ (Dykiert & Deary, 2013). Current IQ was assessed with the Kaufman Brief Intelligence Test (KBIT) (Kaufman, 1990). Means scores are shown in Table 2-2.
Table 2.2 Summary neurocognitive measures for schizophrenia patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (N = 17)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Mean Full Scale WTAR</td>
<td>97.5</td>
<td>9.0</td>
</tr>
<tr>
<td>Mean Full Scale KBIT</td>
<td>84.9</td>
<td>12.8</td>
</tr>
</tbody>
</table>

2.2.5 Exercise Intervention

Patients and healthy volunteers completed the same exercise program. Participants were randomly assigned using a random number generator to either a mainly aerobic (Patients: N = 9, Healthy Volunteers: N = 3) or mainly weight bearing (Patients: N = 8, Healthy Volunteers: N = 6) exercise program closely monitored by qualified exercise professionals. No significant demographic differences exist between participants assigned to the aerobic or resistance training programs. Participants participated in an individualized, 12-week, supervised program consisting of 30 minutes of moderate-intensity exercise (based on 40-59% of baseline heart rate reserve and baseline fitness level), three times per week using different exercise modalities (cycle ergometry, treadmill, elliptical training and weight training). Heart rate reserve was calculated from the common clinical Karvonen formula (Warburton, Nicol, & Bredin, 2006). Exercise intensity progression was based on heart rate changes (approximately 5% per week). Those who were randomized to the mainly weight-bearing program performed 30 minutes of weight training based on their individual muscular capacity of the major muscle groups. Progression was based on increased strength as monitored by the exercise professionals. All exercise sessions began with a standardized 10-minute warm-up (light aerobic exercise at 30% of heart rate reserve) and cool-down (gentle stretching) periods. Adherence rates were 83% ± 9.4% (Range 63.9%-97.2%) with 70% of patient participants completing the entire exercise program. For healthy volunteers,
75% of participants completed the program and those that did complete had adherence rates of 100%. The qualified exercise professionals monitored the progress of each participant on a weekly basis for the duration of the study.

2.2.6 Statistical Analysis

Antipsychotic dose was converted to chlorpromazine equivalents for each individual to facilitate dosage comparison and an average dose was calculated across time points (Prochysyn, Bezchlibnyk-Butler, & Jeffries, 2015). In patients, initial linear correlations (Pearson’s-r) were used to examine potential effects of age, total brain volume, average CPZ Equivalent (CPZE) dose, KBIT score and WTAR score on the outcome measures of percent change in hippocampal volume and hippocampal venule volume. These analyses did not reveal any statistically significant findings (all p-values > 0.1; see Table 2-3 for summary preliminary correlational results). Pearson’s-r correlations were also used to compare hippocampal volumes from automatic and manual segmentation. In accordance with previous findings, automatic and manual segmentation values for hippocampal volume were significantly related for both the left (r = 0.873, p < 0.001) and right (r = 0.708, p < 0.001) sides (Morey et al., 2009; Wenger et al., 2014). Hippocampal volumes from automatic segmentation are used for all further analysis. Percent change in hippocampal volume and venule volume were also not significantly correlate with percent change of antipsychotic dose or with antipsychotic dose at baseline. Pearson Chi-Square tests did not reveal any significant relationships between sex and percent change in hippocampal volume ($\chi^2 = 17.0, p = 0.386$) or percent change in hippocampal venule volume ($\chi^2 = 15.0, p = 0.378$). Subsequently, repeated measures models did not include age, sex, total brain volume, or average CPZE dose as covariates. Preliminary repeated measures t-tests of left-right
comparisons in hippocampal volume and hippocampal vascular volume at baseline and follow-up did not reveal significant side versus side differences (p-values > 0.07). For all subsequent comparisons, left and right volumes were summed to obtain a total hippocampal volume. Additionally, preliminary omnibus analysis of variance (ANOVA) models revealed that the rates of change in the PANSS, ESRS, HAM-A, SOFAS or CDS scores did not differ across the two exercise groups (all p-values > 0.40). Exploratory repeated-measures t-tests were conducted to compare baseline to follow-up clinical measures, cardiovascular fitness (VO\textsubscript{2}max), resting blood pressure and blood glucose levels. Subsequently, the baseline and follow-up comparisons of clinical measures included both the aerobic and weight-bearing exercise group. Additional exploratory relationships between clinical and hippocampal measures were investigated with linear correlation models.

Table 2.3 Preliminary correlational assessments of potential confounding factors for schizophrenia patients (N = 17)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hippocampal Volume Change</th>
<th>Hippocampal Venule Volume Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Total Brain Volume</td>
<td>-0.02</td>
<td>0.95</td>
</tr>
<tr>
<td>Age</td>
<td>0.03</td>
<td>0.90</td>
</tr>
<tr>
<td>Mean Antipsychotic Dose (Average CPZE)</td>
<td>0.36</td>
<td>0.15</td>
</tr>
<tr>
<td>KBIT score</td>
<td>0.01</td>
<td>0.98</td>
</tr>
<tr>
<td>WTAR score</td>
<td>0.09</td>
<td>0.74</td>
</tr>
</tbody>
</table>
2.2.6.1 Neocortical Analysis

No significant differences between left and right regional brain thickness and volumes were observed between groups using standard asymmetry index calculation (Pedraza, Bowers, & Gilmore, 2004). Left and right brain regional measures were subsequently summed, and percent change scores were calculated for all regions of interest and for all clinical measures. Both thickness and volume were evaluated as these measures have been shown to differ in psychosis populations and may address different underlying pathology (Kong et al., 2015). No significant correlation was observed for percent change in thickness or volume measures for the entorhinal, fusiform, orbitofrontal, and parahippocampal cortices in relation to total brain volume, age, average CPZE dose, KBIT score, or WTAR score (all p-values > 0.07). Chi-square tests indicated no significant differences in percent change of neocortical measures of interest related to sex (p > 0.07). Total brain volume, age, sex, and average antipsychotic dose were not included as covariates for repeated-measures analyses of neocortical regions. There was also no significant relationship between percent change in neocortical measures of interest and percent change in antipsychotic dose or antipsychotic dose at baseline (p > 0.07).

One-way ANOVA and Chi-square tests were used to compare baseline measures between groups. One-way analysis of covariance (ANCOVA), including age and total brain volume as covariates, was used to compare patient groups and healthy volunteers at baseline for cortical brain measures of interest including thickness and volume for entorhinal, fusiform, parahippocampal, and orbitofrontal cortices (see Figure 1-1). Patients and healthy volunteers were also compared for differences in hippocampal volume.

A 2x2 mixed ANOVA design was used to assess brain measure changes over time between patients and healthy volunteers. Subsequently, a 2x4 mixed ANOVA was used to assess
the impact of exercise type, by comparing brain measure changes over time between aerobic and resistance training exercise for both patients and healthy volunteers. Post-hoc tests were performed for all main effects and interactions, using the Tukey HSD (honestly significant difference) test for multiple group comparisons. The Tukey HSD test was chosen as it is a conservative test that is robust to unequal group sizes (McHugh, 2011). Simple linear regressions were conducted as secondary analyses to assess relationships between percent change in neocortical measures (independent variable) and percent change in hippocampal volume, and clinical measures of interest including PANSS total and subscale scores, CDS, HAMA-S, and ESRS (dependent variables). Assumptions for simple linear regressions were assessed and met for all analyses. All statistical analysis was conducted using SPSS (Statistical Package for the Social Sciences) v26.

2.3 Results

2.3.1 Clinical Measures

Our final analysis sample included 11 males and 6 females who had met DSM-IV criteria for schizophrenia or schizoaffective disorder for a minimum of 2 years at entry. The mean baseline total PANSS score at baseline was 95.3 and 79.7 at follow-up, a significant reduction from baseline \((t(16) = -6.35, p < 0.001)\). A strong trend for reduced depression based on the CDS was observed \((t(16) = -2.31, p = 0.06)\). At 12-week follow-up, participants had a significant improvement in social functioning as measured by the SOFAS \((t(16) = 4.78, p < 0.001)\). Both change in PANSS and SOFAS scores remained significant after standard Bonferroni correction.

We observed that average ward admission PANSS score between January 2012 and January 2015 was 96.4 \((N = 151)\) with an average discharge PANSS total of 77.4 \((N = 113)\) after
an average length of stay of 25.2 weeks for those not enrolled in the study. In contrast, patients enrolled in our exercise study, who entered the study with a mean PANSS score of 95.3, achieved a similar improvement (endpoint PANSS = 79.7) after 12 weeks of adjunct regular exercise. With respect to symptom severity, age (Ward mean 33.3) and sex (Ward group 63% M, 27% F), education level (Ward mean = 10.9 years) and antipsychotic treatments (mixed 1st and 2nd generation), no significant differences between the general ward population and our subsample were observed (all p-values > 0.05).

At follow-up, no statistically significant reduction in anxiety as measured by the HAM-A was observed (t(16) = -1.60, p = 0.13). Severity of extrapyramidal symptoms (ESRS score) remained stable over the course of the study (t(16) = -1.71, p = 0.11). Reductions in resting heart rate, resting blood pressure, BMI and blood triglyceride levels were seen after completion of the 12-week exercise intervention, however these reductions did not reach statistical significance (all p-values < 0.10). No statistically significant improvements in VO2max or blood cholesterol levels were observed (p-values > 0.10).

### 2.3.2 Hippocampal Measures

Summary volumetric data are provided in Table 2-4. A significant increase in total hippocampal volume was observed after 12 weeks of regular exercise (t(16) = -2.54, p = 0.02). Further exploratory comparisons of hippocampal subfield volumes revealed that hippocampal volume expansion after exercise was significant in the left CA1 field (t(16) = -2.33, p = 0.03), but not in other subfield regions (all p-values > 0.10). Percent change in hippocampal volume was not significantly related to percent change in antipsychotic dose, nor was baseline hippocampal volume significantly related to baseline antipsychotic dose, using linear regression.
analysis (all p-values > 0.20). The same was found for hippocampal venule volume percent change and baseline values. In contrast, hippocampal vascular volumes were unchanged after exercise (p-value > 0.20). At baseline, hippocampal volumes were positively correlated to hippocampal vascular volumes (r=0.56; F(2,15) = 6.66, p = 0.02). This correlation was not observed at follow-up (p > 0.40). Change in hippocampal volume and hippocampal vascular volume did not correlate with change in symptom severity (PANSS, ESRS) or affect scores (CDS, HAM-A) (p > 0.10).

**Table 2.4 Summary volumetric data (mm$^3$) for schizophrenia patients (N = 17)**

<table>
<thead>
<tr>
<th>Region of Interest Total (Left + Right)</th>
<th>Baseline</th>
<th>12 Week Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Hippocampus Volume</td>
<td>7249.9</td>
<td>678.8</td>
</tr>
<tr>
<td>CA-1 Field Volume</td>
<td>645.4</td>
<td>63.9</td>
</tr>
<tr>
<td>Hippocampal Venule Volume</td>
<td>1104.2</td>
<td>217.7</td>
</tr>
<tr>
<td>Total Brain Volume</td>
<td>1.41E6</td>
<td>1.36E5</td>
</tr>
</tbody>
</table>

### 2.3.3 Baseline Group Comparisons

No significant difference was observed between patients and healthy volunteers at baseline for age, years of education, or total brain volume. Table 2-5 contains baseline descriptive statistics for patients and healthy volunteers across the two exercise groups, aerobic and resistance training. Hippocampal volume and cortical volume and thickness for these four groups are included in Tables 2-6 and 2-7. At baseline patients exhibit a significantly smaller fusiform cortical thickness compared to healthy volunteers (F(1, 23) = 7.993, p = 0.010, $\eta^2 =$
0.258; see Figure 2-3). No other significant differences in brain measures, including hippocampal volume, were observed between patients and healthy volunteers at baseline.
Table 2.5 Baseline descriptive statistics

<table>
<thead>
<tr>
<th></th>
<th>Aerobic Patients (N = 9)</th>
<th>Resistance Patients (N = 8)</th>
<th>Aerobic Healthy Volunteers (N = 3)</th>
<th>Resistance Healthy Volunteers (N = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis (Schizophrenia/Schizoaffective)</td>
<td>4 SZ / 5 SA</td>
<td>3 SZ / 5 SA</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex (Male/Female)</td>
<td>5 M / 4 F</td>
<td>6 M / 2 F</td>
<td>1 M / 2 F</td>
<td>5 M / 1 F</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.2 7.47</td>
<td>31.3 6.41</td>
<td>34.7 12.4</td>
<td>27.7 8.71</td>
</tr>
<tr>
<td>Illness Duration (years)</td>
<td>9.56 5.48</td>
<td>11.8 6.34</td>
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<td>-</td>
</tr>
<tr>
<td>Education (years)</td>
<td>12.1 2.21</td>
<td>10.3 1.39</td>
<td>13.3 0.58</td>
<td>12.0 0.63</td>
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<tr>
<td>Mean Antipsychotic Dose (CPZ Equivalents)</td>
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<td>627.9 274.2</td>
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<td>-</td>
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<td>PANSS Total</td>
<td>99.0 15.0</td>
<td>91.8 9.98</td>
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<td>-</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.2 4.51</td>
<td>26.2 5.53</td>
<td>22.3 1.65</td>
<td>22.0 4.48</td>
</tr>
<tr>
<td>Total Brain Volume (mm³)</td>
<td>1.41E6 1.44E5</td>
<td>1.39E6 9.48E4</td>
<td>1.37E6 5.85E4</td>
<td>1.41E6 8.08E4</td>
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<tr>
<td>Groups</td>
<td>Hippocampal Volume</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>--------------------</td>
<td>--------------</td>
<td>--------------</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
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<td>Aerobic Patients (N = 9)</td>
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<td>186.2</td>
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<td>Resistance Healthy Volunteers (N = 6)</td>
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<td>793.0</td>
</tr>
<tr>
<td>Groups</td>
<td>Entorhinal thickness</td>
<td>Fusiform thickness</td>
<td>Orbitofrontal thickness</td>
<td>Parahippocampal thickness</td>
</tr>
<tr>
<td>--------</td>
<td>---------------------</td>
<td>-------------------</td>
<td>------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>A</td>
<td>7.11</td>
<td>0.758</td>
<td>5.41</td>
<td>0.244</td>
</tr>
<tr>
<td>B</td>
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<td>5.57</td>
<td>0.167</td>
</tr>
<tr>
<td>C</td>
<td>7.05</td>
<td>0.244</td>
<td>5.72</td>
<td>0.073</td>
</tr>
<tr>
<td>D</td>
<td>7.58</td>
<td>0.753</td>
<td>5.74</td>
<td>0.230</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Groups</th>
<th>Entorhinal volume</th>
<th>Fusiform volume</th>
<th>Orbitofrontal volume</th>
<th>Parahippocampal volume</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>A</td>
<td>3.43E3</td>
<td>677.8</td>
<td>2.05E4</td>
<td>2757.2</td>
</tr>
<tr>
<td>B</td>
<td>3.62E3</td>
<td>701.0</td>
<td>2.08E4</td>
<td>2476.4</td>
</tr>
<tr>
<td>C</td>
<td>3.13E3</td>
<td>493.8</td>
<td>1.97E4</td>
<td>2565.0</td>
</tr>
<tr>
<td>D</td>
<td>4.07E3</td>
<td>561.9</td>
<td>2.16E4</td>
<td>1867.7</td>
</tr>
</tbody>
</table>

Groups: A: Aerobic Patients (N = 9), B: Resistance Patients (N = 8), C: Aerobic Healthy Volunteers (N = 3), D: Resistance Healthy Volunteers (N = 6)
2.3.4 Follow-Up Group Comparisons

No significant differences in neocortical regions of interest were observed between baseline and 12-week follow-up for all patients. No significant differences in percent change of cortical thickness or volume were observed between patients and healthy volunteers. There was a significant main effect for Group for fusiform cortical thickness ($F(3, 22) = 4.163, p = 0.018, \eta^2 = 0.362$), with significant differences between the aerobic patient group and the resistance healthy volunteers groups ($p = 0.021$), following Tukey HSD correction for multiple
comparisons, with a smaller fusiform thickness for the patients compared to both groups of healthy volunteers. The significant difference between the aerobic patient group and the aerobic healthy volunteer group did not survive correction for multiple comparisons. No significant Group x Time interaction was observed for fusiform cortical thickness.

A significant Group x Time interaction was observed for orbitofrontal cortical thickness (F(3, 22) = 3.241, p = 0.042, η² = 0.306; see Figure 2-5). A greater increase in orbitofrontal cortical thickness was observed for the aerobic patient group compared to the resistance patient group (p = 0.027). No other significant group comparisons were observed. No significant main effects or interaction effects were observed for any other brain measure of interest.
Figure 2.4 Change in orbitofrontal cortical thickness across groups. Percent change in orbitofrontal cortical thickness with aerobic patients (N = 9), resistance patients (N = 8), aerobic healthy volunteers (N = 3) and resistance training healthy volunteers (N = 6). Error bars represent +/- 1 SE. * p < 0.05

A significant main effect of Group was observed for resting heart rate (F(3, 22) = 5.386, p = 0.006, η² = 0.423) with a lower resting heart rate for healthy volunteers in the aerobic group compared to patients in the aerobic group (p = 0.010) and patients in the resistance group (p = 0.029), following Tukey correction for multiple comparisons. A similar main effect of Group was observed for BMI (F(3, 19) = 3.189, p = 0.047, η² = 0.335) with a higher BMI observed for patients in the aerobic group compared to healthy volunteers in the aerobic and resistance groups, however these comparisons did not survive Tukey correction for multiple comparison.
Change in cortical regions of interest was not significantly associated with change in clinical measures, including PANSS total and subscale scores, CDS, HAMAS, and ESRS. A greater increase in hippocampal volume was significantly associated with a greater decrease in triglycerides ($\beta = -0.632$, $p = 0.003$).

### 2.4 Discussion

Patients had a significant increase in hippocampal volume and a statistically significant decrease in symptom severity following twelve weeks of exercise. The change in hippocampal volume was not associated with change in hippocampal venule volume. Significantly smaller fusiform cortical thickness was observed in patients compared to healthy volunteers at baseline. A greater increase in orbitofrontal cortical thickness was observed for aerobic patients compared to resistance patients. Healthy volunteers in the aerobic group demonstrated a lower resting heart rate and lower BMI compared to patients. Changes in hippocampal volume and cortical regions of interest were not significantly associated with changes in symptom severity across clinical measures.

The observation that participants enrolled in our exercise intervention had more rapid improvement in their symptoms and social functioning scores suggests that adjunct exercise may contribute to alleviation in a treatment-resistant population. A strong trend for change for reduction in severity of depression after completion of the exercise trial was observed ($p = 0.06$). Given the restricted sample size, it is posited that severity of depression in chronic patients would likely be ameliorated by regular exercise. These findings are consistent with previous work assessing symptom and functioning improvements following an exercise intervention in psychosis patients (Firth et al., 2015). Biochemical, physiological and psychological changes
have all been postulated as potential mechanisms for the link between physical activity and symptom reduction in schizophrenia (Gorczynski & Faulkner, 2010).

Anxiety and extrapyramidal symptoms did not decrease significantly following the exercise intervention. While some research has found that even a single session of aerobic exercise can reduce state anxiety in people with schizophrenia, a meta-analysis failed to find a significant effect of exercise in reducing anxiety symptoms (Bartley, Hay, & Bloch, 2013; Vancampfort et al., 2011). Extrapyramidal symptoms may be reduced in individuals who experience greater amounts of physical activity; however, this relationship requires further study as recent work has described the potential for exercise to increase extrapyramidal symptoms (Kim et al., 2017; Vancampfort et al., 2013). Further studies are required to understand the potential impact of exercise on anxiety and extrapyramidal symptoms.

### 2.4.1 Limitations

The longitudinal design of this study may serve as a potential limitation as patients were receiving continual ward care and antipsychotic treatment throughout the course of the exercise intervention. The participants who completed the exercise intervention observed a decrease in PANSS score in 12 weeks similar to those seen in patients who remain on the ward for an average of twenty-five weeks, indicating the exercise intervention may be contributing beyond the impact of antipsychotic medication and therapy. It is possible that the subsample enrolled in the exercise intervention were subject to sampling bias, however, no significant differences between the general ward population and our subsample were observed.

We observed a significant increase in hippocampal volumes after completion of the exercise intervention, whether the exercise was primarily weight-bearing or aerobic in nature.
Our data suggest that overall hippocampal volumetric increase after a 12-week exercise trial was not directly associated with readily measurable increased neurovascular volume. It should be noted that neuroimaging at 3T field strength does not offer sufficient resolution to directly determine cellular proliferation in the brain, and as such, the specific underlying mechanisms for the observed increases in hippocampal volumes in our sample are conjectural. Data from animal models of exercise have suggested that astrocytic up-regulation in response to exercise may contribute to volume increases after 3-6 weeks of regular exercise (Li et al., 2005). Further, exercise acts to support the restoration of presynaptic terminals in rat CA1, which was down-regulated by olanzapine (Ramos-Miguel et al., 2015). Concomitantly, the moderating effects of exercise on cortisol levels via stress amelioration may also contribute to hippocampal expansion in persons with psychosis (Mondelli et al., 2010). Animal data suggests that elevated cortisol levels may independently induce glutamate-mediated excitotoxicity associated with hippocampal volume loss (Schubert et al., 2008).

2.4.2 Conclusions

Increased hippocampal volume in response to aerobic exercise has been observed in older adults, persons with multiple sclerosis and psychoses, suggesting that salutary effects of exercise on hippocampal volume are universal across clinical populations (Leavitt et al., 2014; Maass et al., 2015; Pajonk et al., 2010). Salutary cognitive effects in early psychosis patients partaking in either aerobic exercise or yoga were observed, with improvements in memory and mood (Lin et al., 2015). The degree of hippocampal plasticity is moderated by age, exercise intensity and duration, medications, and type of illness, with volumetric gains being reported between 2-16% (Pajonk et al., 2010; Ten Brinke et al., 2015). The current data indicate that patients with
schizophrenia, even those receiving chronic antipsychotic treatments, experience hippocampal 
neuroplastic growth after 12 weeks of regular moderate intensity exercise. The persistence of the 
observed volume increases in our sample remains undetermined, as long-term follow-up data 
were not available. Whether a greater duration or intensity of exercise would provide a 
proportional increase either hippocampal volume or hippocampal vascular volume will require 
evaluation in a larger cohort of participants.
Chapter 3: Medial temporal lobe cortical changes in response to exercise interventions in early psychosis patients

3.1 Brief Introduction

We conducted an in vivo investigation of the effects of regular exercise in early psychosis patients to assess the potential effects on neuroanatomical plasticity beyond the hippocampus. It was hypothesized that patients who participated in an aerobic exercise intervention, compared to the yoga and waitlist interventions, would have increased orbitofrontal and medial temporal cortical grey matter, particularly in the entorhinal cortex. This exercise-induced increase in cortical grey matter was expected to be associated with decreased symptom severity. To elucidate the potential effects of exercise on the prefrontal-limbic network, analyses were conducted on the entorhinal, fusiform, parahippocampal, and orbitofrontal cortices.

3.2 Methods

3.2.1 Participants

A large multi-hospital randomized control trial of 140 female early psychosis patients was conducted in Hong Kong from Oct 2010 to May 2014. Participants were recruited from three outpatient clinics in Hong Kong following screening by a clinician. A full description of study recruitment and randomization procedure has been provided elsewhere (Lin et al., 2015). A sub-sample of 51 patients from this group completed successful MRI of the brain at both baseline and 12-week follow-up of an exercise intervention; all subsequent analysis included only these fifty-one patients. Additional scans were collected from eleven healthy volunteers recruited from community samples. Psychosis patients were diagnosed with a psychotic disorder.
(including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, psychosis not otherwise specified or delusional disorder) using the Structured Clinical Interview for DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th Edition) with onset within the past five years. Female patients aged 16 to 60, with stable psychotic symptoms, and fewer than ten hours of yoga or vigorous aerobic exercise (equivalent to jogging at 10km/hr) in the previous three months were eligible to participate. Exclusion criteria included severe physical disease as a contraindication for exercise, comorbid substance dependence, pregnancy or other MRI contraindications, a history of brain trauma or a history of diagnosed intellectual disability. Antipsychotic medications and outpatient clinical care were determined and maintained over the course of the study by psychiatrists blinded to study randomization. All participants provided written informed consent as required by the Institutional Review Board of the University of Hong Kong.

3.2.2 Intervention

Psychosis patients were randomized evenly into yoga therapy (N = 21 completed), aerobic exercise (walking and cycling) (N = 18 completed), or a waitlist control group (N = 12 completed). Yoga therapy consisted of basic breathing techniques and a series of body postures from Hatha yoga, followed by a brief relaxation. Each aerobic exercise session consisted of both walking on a treadmill and stationary cycling at moderate intensity as indicated by maintaining a heart rate of within 45-49% of heart rate reserve. One-hour exercise sessions occurred three times weekly for twelve consecutive weeks under the supervision of certified coaches. Participants who completed the program attended on average 51.4% (M = 18.5 ± 10.5) of the yoga sessions and 57.7% (M = 20.8 ± 11.3) of the aerobic exercise sessions. The percentage of
sessions attended did not differ significantly between exercise types (t(1, 82) = -0.942, p = 0.349). Assessments were conducted by research assistants blinded to the treatment group.

### 3.2.3 Measures

Psychosis patients completed clinical assessments and structural MRI scans at baseline and 12 weeks. Patients were assessed for symptom severity using the PANSS (Kay et al., 1988). VO2max test and BMI were used as assessments of physical fitness (Wolthuis et al., 1977). Healthy volunteers completed baseline MRI scans only.

### 3.2.4 Neuroimaging

Participants underwent structural MRI scanning on a 3T scanner (Philips Achieva 3T Quasar). A T1-weighted, MPRAGE (magnetization-prepared rapid acquisition with gradient echo) sequence (TE = 3.2ms, TR = 7.5ms, flip angle = 7°, FOV = 240mm x 240mm) of 155 consecutive slices were acquired at sagittal view with a voxel size of 1mm x 1mm x 1 mm. MRI data collected in Hong Kong were sent to UBC for post-image processing. Structural MRI data was analyzed by Freesurfer v5.3 to calculate cortical thickness and volume measures using the Desikan-Killiany atlas for cortical parcellation (Desikan et al., 2006). To extract reliable thickness and volume estimates, images were automatically processed with the longitudinal stream in Freesurfer (Reuter et al., 2012). Hippocampal volumes were produced using the ANTS v2.1 multi-atlas and manual segmentations from Neuromorphometrics Inc. (Wang et al., 2013). This joint-label fusion technique improves the use of stand-alone atlas tools by accounting for small differences in segmentation results between individual atlas segmentations and improves segmentation accuracy. Only scans without significant motion artifact were included.
3.2.5 Statistical Analysis

No significant differences between left and right regional brain thickness and volumes were observed between groups using standard asymmetry index calculation (Pedraza et al., 2004). Left and right brain regional measures were subsequently summed, and percent change scores were calculated for all regions of interest and for all clinical measures. Both thickness and volume were evaluated as these measures have been shown to differ in psychosis populations and may address different underlying pathology (Kong et al., 2015). Antipsychotic dose was converted to chlorpromazine equivalents for each individual to facilitate dosage comparison (Prochyshyn et al., 2015).

Within the patient sample, no significant correlations of age, antipsychotic dose, and total brain volume to our outcome measure of percent change thickness and volume measures for any region of interest (all p-values > 0.05, with Pearson r statistics ≤ 0.2). Subsequently, age, dose and total brain volume and were excluded from our repeated-measures omnibus analyses of change in cortical measures. These covariates were retained in our models for standard baseline comparisons. As education and duration of illness were strongly correlated with age in this sample (Age vs. Education: r = 0.463, p = 0.001; Age vs. Duration of Illness r = 0.414, p = 0.003), they were not included as co-variates in our within group repeated-measures models comparing change in volumes after exercise, but age as a factor was retained in our model.

3.2.5.1 Baseline Comparisons

One-way ANOVA and Chi-square tests were used to compare baseline measures between groups. One-way ANCOVA, including age and total brain volume as covariates, was used to compare patient groups and healthy volunteers at baseline for cortical brain measures of interest.
including thickness and volume for entorhinal, fusiform, parahippocampal, and orbitofrontal cortices (see Figure 2-3).

3.2.5.2 Follow-Up Comparisons

A 2x3 mixed ANCOVA design was used to assess brain measure changes over time across the three groups. Normalization for total brain volume was performed by including change in total brain volume as a covariate. Post-hoc tests were performed for all main effects and interactions, using the Tukey HSD test for multiple group comparisons. The Tukey HSD test was chosen as it is a conservative test that is robust to unequal group sizes (McHugh, 2011). Simple linear regressions were conducted as secondary analyses to assess relationships between percent change in cortical measures (independent variable) and other measures of interest including percent change in hippocampal volume, BMI and PANSS total and subscale scores (dependent variables). Differences in these relationships between patient groups were assessed by moderation analysis using the PROCESS macro (Hayes, 2017). This technique uses linear multiple regression to assess the significance of a categorical moderator (exercise group) on the relationship between the independent (percent change in brain measures) and dependent variable (percent change in clinical scores). Assumptions for simple and multiple linear regressions were assessed and met for all analyses. All statistical analysis was conducted using SPSS v26.

3.3 Results

3.3.1 Baseline Comparisons

Psychosis patients did not differ across groups at baseline for any demographic or clinical measures of interest including age, duration of illness, diagnosis, education, antipsychotic dose,
total PANSS, BMI, or VO$_2$max at baseline ($p > 0.05$) (see Table 3-1). Baseline cortical measurements for regions of interest for each patient group and healthy volunteers are listed in Table 3-2. At baseline, no differences in medial temporal cortical sub-regions (i.e. entorhinal, fusiform, parahippocampal) or orbitofrontal cortical thickness, or volume were observed between any groups (all $p$-values $> 0.05$).
Table 3.1 Baseline descriptive statistics

<table>
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<th>Yoga Patients</th>
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<th>Waitlist Patients</th>
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<td>(N = 18)</td>
<td>(N = 12)</td>
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<tr>
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<td></td>
</tr>
<tr>
<td></td>
<td>12.4</td>
<td>13.2</td>
<td>13.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.87</td>
<td>3.35</td>
<td>3.26</td>
<td></td>
</tr>
<tr>
<td><strong>CPZ Equivalent (mg/day)</strong></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>306.7</td>
<td>320.8</td>
<td>180.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>219.8</td>
<td>272.6</td>
<td>26.8</td>
<td></td>
</tr>
<tr>
<td><strong>PANSS Total</strong></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
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<tr>
<td></td>
<td>48.5</td>
<td>39.0</td>
<td>42.5</td>
<td></td>
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<tr>
<td></td>
<td>16.8</td>
<td>7.50</td>
<td>11.5</td>
<td></td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>24.0</td>
<td>24.3</td>
<td>24.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.17</td>
<td>4.31</td>
<td>5.46</td>
<td></td>
</tr>
<tr>
<td><strong>VO₂ max (mL/kg/min)</strong></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.1</td>
<td>28.4</td>
<td>27.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.77</td>
<td>5.04</td>
<td>4.38</td>
<td></td>
</tr>
<tr>
<td><strong>Total Brain Volume (mm³)</strong></td>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.30E6</td>
<td>1.29E6</td>
<td>1.31E6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7.39E4</td>
<td>9.41E4</td>
<td>6.65E4</td>
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</tbody>
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Table 3.2 Group brain volume (mm$^3$) and thickness (mm) measures at baseline and follow-up

<table>
<thead>
<tr>
<th></th>
<th>Entorhinal thickness</th>
<th>Fusiform thickness</th>
<th>Orbitofrontal thickness</th>
<th>Parahippocampal thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Yoga Patients (N = 21)</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
</tr>
<tr>
<td></td>
<td>7.33  0.709</td>
<td>7.28  0.686</td>
<td>5.55  0.280</td>
<td>5.51  0.218</td>
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<tr>
<td>Aerobic Patients (N = 18)</td>
<td>7.04  0.741</td>
<td>7.12  0.653</td>
<td>5.35  0.330</td>
<td>5.42  0.304</td>
</tr>
<tr>
<td>Waitlist Patients (N = 12)</td>
<td>7.00  0.540</td>
<td>7.05  0.466</td>
<td>5.42  0.260</td>
<td>5.37  0.343</td>
</tr>
<tr>
<td>Healthy Volunteers (N = 11)</td>
<td>7.50  0.547</td>
<td>-</td>
<td>5.50  0.148</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Entorhinal volume</th>
<th>Fusiform volume</th>
<th>Orbitofrontal volume</th>
<th>Parahippocampal volume</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Yoga Patients (N = 21)</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
<td>Mean  SD</td>
</tr>
<tr>
<td></td>
<td>2.69E3  500.4</td>
<td>2.69E3  522.1</td>
<td>1.94E4  2127.7</td>
<td>1.93E4  2062.0</td>
</tr>
<tr>
<td>Aerobic Patients (N = 18)</td>
<td>2.51E3  420.8</td>
<td>2.62E3  437.4</td>
<td>1.78E4  2260.0</td>
<td>1.80E4  2300.8</td>
</tr>
<tr>
<td>Waitlist Patients (N = 12)</td>
<td>2.74E3  451.1</td>
<td>2.80E3  384.0</td>
<td>1.86E4  2387.6</td>
<td>1.86E4  2373.2</td>
</tr>
<tr>
<td>Healthy Volunteers (N = 11)</td>
<td>2.74E3  536.5</td>
<td>-</td>
<td>1.94E4  1804.3</td>
<td>-</td>
</tr>
</tbody>
</table>
3.3.2 Follow-up Comparisons

There was a significant main effect of time on entorhinal cortical volume of psychosis patients \( F(2, 44) = 7.948, p = 0.007, \eta^2 = 0.142 \), indicating an increase in entorhinal cortical volume for psychosis patients across all three groups over the course of the twelve-week period. Psychosis patients had a significant Group x Time interaction for fusiform cortical thickness \( F(2, 48) = 4.221, p = 0.020, \eta^2 = 0.150 \) and fusiform cortical volume \( F(2, 48) = 3.521, p = 0.037, \eta^2 = 0.128 \), indicating that the change in fusiform cortex differed between exercise groups over the course of the twelve week period. No significant effects were observed for orbitofrontal and parahippocampal cortical regions.

A greater increase in fusiform cortical thickness was observed in the aerobic group compared to the yoga \( p = 0.017 \) and waitlist \( p = 0.019 \) groups. A similar pattern was observed for fusiform cortical volume with the aerobic group showing a greater increase compared to the yoga \( p = 0.040 \) and the waitlist \( p = 0.035 \) groups. The aerobic group had a larger increase compared to the yoga group for both entorhinal cortical thickness \( p = 0.031 \), and entorhinal cortical volume \( p = 0.021 \). Only the differences in fusiform cortical thickness survived the Tukey correction for multiple comparisons (see Figure 3-2). No other significant group comparisons were observed.
Figure 3.1 Change in fusiform cortical thickness across groups. Mean percent change in fusiform cortical thickness across yoga (N = 21), aerobic exercise (N = 18), and waitlist groups (N = 12). Error bars represent +/- 1 SE. * p < 0.05

There was a significant positive relationship between change in hippocampal volume and changes in fusiform thickness (β = 0.402, p = 0.003), parahippocampal thickness (β = 0.333, p = 0.017), fusiform volume (β = 0.353, p = 0.011), and orbitofrontal volume (β = 0.317, p = 0.024). Type of exercise did not impact the relationship between hippocampal and cortical measures when group was included in the model as a moderating variable. The greatest reduction in BMI was observed for the aerobic group, with a significant Group x Time effect (F(2, 31) = 3.396, p = 0.046, η² = 0.180). No significant difference was observed for VO₂max between groups over time (p > 0.05).
A significant interaction of exercise group was observed for the relationship between change in symptom severity and change in entorhinal thickness (Interaction: $b = -5.81$, $t = -2.46$, $p = 0.018$), indicating a greater increase in entorhinal thickness was associated with a greater decrease in total PANSS score for the aerobic group ($b = -3.25$, $t = -2.36$, $p = 0.023$), but not for the yoga or waitlist group ($p > 0.05$). A similar pattern exists where exercise group moderates the relationship between decreasing total PANSS score and increasing fusiform thickness (Interaction: $b = -4.51$, $t = -1.96$, $p = 0.056$). For the aerobic group only, increasing fusiform thickness ($b = -4.27$, $p = 0.020$) and volume ($b = -3.91$, $p = 0.022$) were significantly related to decreasing total PANSS scores. The relationship is not significant for the yoga or waitlist groups ($p > 0.05$).

Assessing PANSS subscale scores, exercise group moderates the relationship between change in entorhinal cortical thickness and change in PANSS General subscale (Interaction: $b = -7.77$, $t = -2.97$, $p = 0.005$), indicating that for the aerobic group, a greater increase in entorhinal thickness was associated with a greater decrease in PANSS General subscale scores ($b = -5.74$, $t = -3.44$, $p = 0.001$), but this relationship was not significant for the yoga or waitlist groups ($p > 0.05$). The same moderation of exercise group is observed for the relationship between change in fusiform thickness and PANSS General subscale scores (Interaction: $b = -7.51$, $t = -2.99$, $p = 0.005$) and fusiform volume (Interaction $b = -6.06$, $t = -2.53$, $p = 0.015$), with a significant relationship present only for the aerobic group between a decrease in PANSS General subscale scores and an increase in fusiform thickness ($b = -6.94$, $t = -3.70$, $p < 0.001$) and volume ($b = -5.96$, $t = -3.48$, $p = 0.001$) with no significant relationship for the yoga or waitlist groups ($p > 0.05$). No other significant interaction was observed between exercise group and the relationship between change in brain measures and change in PANSS subscale scores.
3.4 Discussion

Psychosis patients experienced an increase in entorhinal and fusiform cortical measures over a twelve-week exercise intervention. Aerobic exercise may induce neuroplasticity of the medial temporal cortex, particularly for the fusiform cortex, suggesting that exercise-induced synaptic plasticity exerts effects beyond the hippocampus. These changes may be linked with hippocampal synaptic plasticity as hippocampal volume increased in tandem with increases in fusiform, parahippocampal, and orbitofrontal cortices. Aerobic exercise-induced changes in entorhinal and fusiform cortices were associated with changes in psychosis symptom severity scores, particularly for the general symptom subscale.

The majority of research investigating the neuroremediation potential of exercise has focused on the hippocampus (Firth, Stubbs, et al., 2018). Running has been shown to increase input to the entorhinal cortex, promote synaptic plasticity of entorhinal cortex-dentate gyrus synapses, and increasing dendritic spine density in the entorhinal cortex (Vivar & van Praag, 2017) indicating the potential cellular mechanisms for remediation beyond the hippocampus. This study is one of the first to examine the different effects of aerobic versus yoga-based exercise on cortical grey matter changes following an exercise intervention in early psychosis patients.

The relationship between change in cortical measures and change in symptom severity scores was only observed for patients in the aerobic exercise group. Greater cardiovascular output, like that experienced during aerobic training, is associated with greater cerebral blood flow. Increased aerobic capacity has been associated with greater serum BDNF (Whiteman et al., 2014). Increased BDNF expression in the hippocampus and cerebral cortex is thought to be triggered by increased cerebral blood flow associated with aerobic exercise (Alomari, Khabour,
Maikano, & Alawneh, 2015). Lower intensity physical activity like resistance training and yoga may not increase cerebral blood flow sufficiently to trigger increased BDNF expression (Sanada et al., 2016). Increased BDNF levels in the brain is thought to promote neuronal survival and expansion, serving as a potential mechanism to explain increased cortical measures following aerobic exercise (Liu & Nusslock, 2018).

Increased cardiovascular conditioning is also associated with increased neurovascular capacity in key regions like frontal and medial temporal cortices, and the hippocampus (Maass et al., 2015). Greater neurovascular capacity is the result of neurovascular capillary expansion and branching triggered by increased expression of VEGF (Lucas, Cotter, Brassard, & Bailey, 2015). This neurovascular expansion may contribute to increases in cortical volume and thicknesses. We note the caveat that the scans obtained for this study were collected on a 3T MRI, which provides insufficient resolution to differentiate cortical microvascular volumes from surrounding tissue.

The relationship between change in entorhinal and fusiform cortices and PANSS scores in the aerobic exercise group further illuminates the mechanism behind previous findings showing exercise to be associated with decreasing symptom severity in schizophrenia patients (Scheewe et al., 2013; Woodward et al., 2018). Reduced medial temporal lobe volume has been associated with psychosis symptom severity including general symptoms of anxiety and depression (Satterthwaite et al., 2016). These findings are in agreement with previous work demonstrating aerobic exercise is associated with significant reductions in PANSS total and PANSS general subscales (Curcic et al., 2017). Targeting neuroremediation of medial temporal lobe cortical structures through aerobic exercise may lead to improved psychosis and depression.
symptom severity for psychosis patients and has strong implications for quality of life of these patients.

### 3.4.1 Limitations

While it is acknowledged that patients received antipsychotic treatments during the exercise intervention, we do not believe prescribed medications confounded the current results. We note that medications were kept stable in our patients throughout the intervention. Additionally, the inclusion of a waitlist group who did not exercise and were also maintained on antipsychotic treatments increased our confidence that the observed changes in cortical measures were exercise mediated. The waitlist group did appear to receive a lower dose of antipsychotic medication on average compared to the aerobic and yoga groups, however there were no significant differences between the yoga and waitlist groups throughout the analysis, supporting the argument that it is the aerobic exercise that is responsible for the observed changes. Antipsychotic treatments may also promote synaptic plasticity by increasing BDNF levels and promoting cell survival, however the role of antipsychotics with respect to remediation of grey matter deficits in psychotic disorders remains controversial. The exclusively female sample in this study may impact the generalizability of these findings. Sex differences in the impact of exercise on cortical grey matter is an area that requires further investigation.

### 3.4.2 Conclusion

Synaptic plasticity beyond the hippocampus is observable in psychosis patients and these changes are associated with improved psychosis symptom severity. Neuroremediation of medial temporal cortical thickness may have important implications for improvement of cognitive
impairment associated with psychosis, particularly within the domains of episodic memory and facial recognition. Aerobic exercise may be of particular benefit as it appears to induce beneficial structural neuroplasticity while simultaneously counteracting the negative cardiovascular impact of antipsychotic medications.
Chapter 4: Impact of olanzapine and exercise on the entorhinal cortex in rats

4.1 Brief Introduction

Differentiating the contribution of either exercise or antipsychotic exposure alone on regional volumes of interest in schizophrenia patients is difficult in the clinical setting. It is inappropriate to withhold medications for patients experiencing serious symptoms of psychosis to perform a case control study of exercise versus medication effects. In order to investigate the individual impact of antipsychotic drug treatment and exercise on entorhinal cortical thickness, adult rats were administered the second-generation antipsychotic drug olanzapine or vehicle for 9 weeks, and animals were either sedentary or able to exercise for 1 hour or 3 hours per day on a running wheel (Barr et al., 2013). Brain slices were Nissl stained and thickness measures were obtained for the entorhinal cortex and subregions including the lateral and medial entorhinal cortex and layer II. We anticipated that olanzapine would decrease entorhinal cortical thickness and exercise would increase entorhinal cortical thickness. Layer II neurons that project directly to the hippocampus would likely be the most impacted by exercise-induced plasticity. These exercise-induced entorhinal thickness changes will be associated with improved metabolic indices including decreased glucose intolerance and fasting insulin. Assessing the impact of antipsychotic medication and exercise on the entorhinal cortex and its subregions may provide further insight into the etiology of episodic memory impairments in psychosis patients.

4.2 Methods

We have previously published a description of the animals and drug administration involved in this study, which was primarily focused on examining the effects of chronic exercise
on metabolic side-effects associated with olanzapine, as well as the effects of chronic exercise and olanzapine administration on hippocampal volume. (Barr et al., 2013; Boyda et al., 2014). This current work assesses the impact of chronic exercise and olanzapine administration on entorhinal cortical thickness and thickness of sub-regions within the entorhinal cortex including the MEC, LEC, and layer II (LII).

4.2.1 Animals

Female, Sprague-Dawley rats (Charles River, Montreal, Canada) were acclimated at the UBC animal care facility for at least one week after delivery and housed in standard polycarbonate cages. Rats were maintained in a 22 ± 1 °C temperature-controlled colony with a 12-h light-dark cycle (lights on at 07:00h). Rats were group housed and weighted 250-275g at delivery; food (standard Purina rat chow) and water were available ad libitum. Animals were treated in accordance with the Canadian Council on Animal Care guidelines. All methods were approval by the University of British Columbia’s Animal Care and Use Committee.

4.2.2 Drug Administration

The dose of olanzapine (10 mg/kg) (Toronto Research Chemicals Inc, Canada) was established from previous work (Boyda, Procyshyn, Pang, et al., 2013; Boyda, Procyshyn, Tse, Hawkes, et al., 2012; Boyda, Procyshyn, Tse, Wong, et al., 2012; Boyda et al., 2010). Daily subcutaneous injection of olanzapine or vehicle (50% polyethylene-glycol 400, 40% distilled water and 10% ethanol, formulated daily) occurred every Monday to Friday for 9 consecutive weeks. The glucose tolerance test and olanzapine challenge was completed on Monday morning following a weekend “washout” period to clear olanzapine levels, as previously described
Subcutaneous administration of olanzapine and vehicle were done to minimize distress during daily injections (compared to repeated intravenous or intraperitoneal injection), however the drug was administered by intraperitoneal injection for the glucose tolerance test in order to provide a less variable glycemic response, based on prior observations in our laboratory. Eight weeks of olanzapine administration in rats has been posited to be equivalent to five years of exposure in humans (Vernon, Natesan, Modo, & Kapur, 2011).

4.2.3 Metabolic procedures

At baseline and once per week throughout the experiment, rats are administered an intraperitoneal glucose tolerance test (IGTT) as described previously (Barr et al., 2013; Boyda, Procyshyn, Tse, et al., 2013; Boyda et al., 2010). Animals received a full IGTT once per week starting at the end of the first week of drug administration. Glucose levels are documented every 15 min for 2 hours following an intraperitoneal glucose injection (1g/kg/ml). Plotting this time-series data produces an area-under-the-curve (AUC) value, with greater glucose intolerance indicated by larger AUC values.

Plasma samples for insulin analysis were taken from overnight fasted rats using a saphenous blood draw followed by centrifugation (10,000 RPM, 10 min, 4°C) and storage at -80°C. Insulin analysis was conducted using an ultra-sensitive rat insulin Enzyme-Linked ImmunoSorbent Assay (ELISA) kits (Crystal Chem Inc., IL, USA) as previously described (Boyda et al., 2010). On a 96 well plate, duplicate 5µl samples were added and incubated at 4°C for two hours followed by repeated washes. The samples were further incubation for 40 mins following addition of the substrate and then absorbance was measured at 450nl-630nm. Fasting
insulin concentrations were extrapolated from a calibration curve generated from samples within the kit.

### 4.2.4 Exercise

Rats were randomly assigned to either be administered olanzapine or vehicle and to one of three exercise conditions: sedentary (no exercise), 1-h exercise, and 3-h exercise, resulting in six treatment groups (n = 9-10 per group): olanzapine and no exercise (sedentary) (n = 10), olanzapine and 1-h exercise (n = 10), olanzapine and 3-h exercise (n = 9), vehicle and no exercise (n = 9), vehicle and 1-h exercise (n = 9), or vehicle and 3-h exercise (n = 10). Exercising rats were provided individual activity wheels for voluntary running [model ENV-046; Med-Associates, St. Albans, VT] every Monday to Friday for 9 weeks for 1 hour or 3 hours per day during the light phase. Animals were consistently placed in the same wheel each time, and wheels were thoroughly cleaned between sessions. Sedentary rats remained in their home cage and were not provided access to a running wheel but were handled. Rat activity was recorded as number of wheel rotations occurring during the exercise period using an external electronic counter. Using the wheel outer diameter of 36.83 cm, the number of wheel rotations was converted into a distance measure in meters for activity.

### 4.2.5 Nissl Staining

Following nine weeks of exercise, rats were sacrificed using sodium pentobarbital overdose and the brain was extracted and prepared as described previously (Barr et al., 2013). With one brain hemisphere frozen for proteomic analysis, the other hemisphere is fixed in 4% paraformaldehyde (Fisher)/phosphate-buffered saline solution and stored at room temperature for
two days followed by storage in Tris-buffered saline at 4°C. Hemisphere selection alternated for each rat following the initial selection by a random number generator. Agarose-embedded brains were coronally sectioned with a Leica VT 1200S vibratome at a thickness of 40µm and mounted onto 5% gelatin-coated slides (VWR Scientific SuperFrost Microslides) and Nissl stained using established procedures.

Nissl-stained sections were imaged using a Nikon Eclipse 80i light microscope and Prior ProScan II motorized stage system (X- and Y-axes), coupled with NIS-Elements Advanced Research software (version 3.0; Nikon Canada, Canada). Every 5th section was identified (-4.80mm to -7.30mm relative to bregma (Paxinos & Watson, 1986)) and a series of contiguous images of entorhinal cortex captured, from which a single composite image was formed. Following strict cytoarchitectural criteria (Paxinos & Watson, 1986), the entorhinal cortex lateral and medial subregions were manually outlined on all imaged sections using the software ImageJ (version 2.0; NIH Bethesda, Maryland) (see Figure 4-1). The lateral entorhinal cortex contains an easily distinguished cell-free zone between layers II and III, a zone which is not easily identified in the medial entorhinal cortex (van Groen, Miettinen, & Kadish, 2003). In addition, boundaries of cortical layer II were delineated within the lateral entorhinal cortex. Layer II thickness was not measured in the medial entorhinal cortex as layer II is not continuous in this region and therefore harder to distinguish from layer III (Insausti, Herrero, & Witter, 1997). Thickness measures were calculated using the BoneJ Macro (ImageJ) and the average thickness of entorhinal cortex and subregions of interest for each rat determined (Doube et al., 2010). Entorhinal cortical thickness was measured as the average of all measurements within the lateral and medial subregions. Lateral and medial entorhinal, and layer II thickness measures are the average of all thickness measures within the cytoarchitectural boundaries.
Figure 4.1 Sample manual segmentation of Nissl histology stains of rat entorhinal cortex indicating subdivisions of lateral (LEC) and medial (MEC) entorhinal cortex and layer II (LII). Scale bar indicates 100 µm.

4.2.6 Statistical Analysis

Consistent with previous analysis (Barr et al., 2013), no significant differences in outcome measures (total, lateral, and medial entorhinal thickness and layer II thickness) existed between 1hr and 3hr exercise groups so these groups were combined for all subsequent group analysis (p > 0.05). Significantly greater variability in average activity (wheel rotations) was observed for the 3hr group compared to the 1hr group (Levene’s test: F(1, 34) = 8.72, p = 0.006).
Therefore, average activity was used as a continuous measure of exercise to evaluate the relationship between exercise, metabolic indices, and entorhinal thickness measures.

Total entorhinal cortical thickness, as well as that of lateral and medial subregions, was analyzed by 2x2 analysis of variance (ANOVA) to test for main effects of olanzapine and exercise, and their interactions, with significance set at p < 0.05. Subsequent pairwise comparisons were tested with Bonferroni correction for multiple comparisons. One-way ANOVA with Welch’s test was conducted for layer II thickness as this measure violated the assumption of homogeneity of variance. Subsequent pairwise comparisons were performed with the Games-Howell non-equal variance correction for multiple comparisons.

Pearson correlations and linear regression were used for secondary analysis to assess the relationship between thickness measures, average activity (as measured by wheel rotations), and fasting insulin and glucose intolerance measured at week 9. Mediation analysis was conducted to assess if metabolic measures mediated the relationship between average activity and total entorhinal cortical thickness using the PROCESS method (Hayes, 2017). This technique uses hierarchical multiple regression to assess the significance of a continuous mediator (glucose intolerance/fasting insulin) on the relationship between the independent (average activity) and dependent variable (entorhinal cortical thickness).

4.3 Results

One rat was sacrificed prematurely due to development of illness, while three rats were excluded as the sections did not include sufficient coverage of the entorhinal cortex, leaving a total of 53 animals. See Table 4-1 for thickness measures across treatment groups. The mean number of sections per animal was 10.8 (+1.9) and number of sections did not differ between
groups. The mean coefficient of errors for entorhinal thickness estimates ranged between 0.010 and 0.018 (Gundersen, Jensen, Kieu, & Nielsen, 1999).

Table 4.1 Entorhinal cortical thickness and subregions (µm) in rats across olanzapine and exercise subgroups

<table>
<thead>
<tr>
<th>Groups</th>
<th>Entorhinal Cortical Thickness</th>
<th>Lateral EC Thickness</th>
<th>Medial EC Thickness</th>
<th>Layer II Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Vehicle + Sedentary (N = 7)</td>
<td>1084.7</td>
<td>74.9</td>
<td>1243.0</td>
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</tr>
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<td>Vehicle + Exercise (N = 18)</td>
<td>1063.0</td>
<td>95.4</td>
<td>1208.4</td>
<td>72.3</td>
</tr>
<tr>
<td>Olanzapine + Sedentary (N = 10)</td>
<td>1085.4</td>
<td>27.7</td>
<td>1250.5</td>
<td>105.8</td>
</tr>
<tr>
<td>Olanzapine + Exercise (N = 18)</td>
<td>1013.4</td>
<td>65.4</td>
<td>1171.6</td>
<td>98.6</td>
</tr>
</tbody>
</table>

4.3.1 Group Comparisons

A significant main effect of olanzapine treatment was observed for MEC thickness (F(1, 49) = 4.46, p = 0.040, η² = 0.083) with reduced thickness found in rats administered olanzapine compared to the vehicle-treated group. Exercise had a significant main effect for LEC thickness (F(1, 49) = 4.77, p = 0.034, η² = 0.089) with greater thickness in the sedentary group compared to the exercise group. A reverse effect was observed for layer II thickness (F(1, 49) = 6.48, p = 0.014, η² = 0.117) with greater thickness for the exercise group compared to the sedentary group.

A significant Treatment x Exercise interaction was found for layer II thickness (F(1, 50) = 5.194, p = 0.027, η² = 0.094), indicating that the effect of exercise differed between olanzapine
and vehicle-treated rats (see Figure 4-2). This interaction indicated that layer II thickness was greater in exercising rats compared to sedentary rats for vehicle-treated rats only. There was no impact of exercise on layer II thickness for rats treated with olanzapine. No significant interactions were observed for any other measures of total entorhinal cortical thickness.

Figure 4.2 Layer II thickness (µm) across olanzapine and exercise groups. Error bars represent +/- 1 SE. * p < 0.05

Layer II thickness was found to violate the assumption of homogeneity of variance for the 2x2 ANOVA analysis. Due to the robustness of 2x2 ANOVA for testing interaction effects under normality, these results were reported (Bao & Ananda, 2001). However, this is an
important consideration when interpreting the results of the interaction. A subsequent one-way ANOVA compared layer II thickness across all four groups and found a significant Welch statistic (F(3, 21.534) = 10.204, p = 0.000) indicating a significant difference between the four groups. Post-hoc testing, using the Games-Howell non-equal variance correction for multiple comparisons, indicated a significantly larger layer II thickness for vehicle-treated exercising rats compared to vehicle-treated sedentary rats (p < 0.001) and for olanzapine-treated exercising rats compared to vehicle-treated sedentary rats (p = 0.005). All other pairwise comparisons were not significant (p > 0.05).

4.3.2 Correlates

Descriptive statistics for all exercising rats are included in Table 4-2. A dosage effect was observed for rats in the exercise group, with increased average activity level (in meters) significantly associated with greater total entorhinal cortical thickness (r = 0.349, p = 0.037). LEC, MEC and layer II thickness were not associated with average activity level (p > 0.05) in the exercise group.
Table 4.2 Descriptive statistics for exercising rats (N = 36)

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
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<tbody>
<tr>
<td>Entorhinal Thickness (µm)</td>
<td>1038.2</td>
<td>84.4</td>
</tr>
<tr>
<td>LEC Thickness (µm)</td>
<td>1190.0</td>
<td>87.2</td>
</tr>
<tr>
<td>MEC Thickness (µm)</td>
<td>761.4</td>
<td>86.8</td>
</tr>
<tr>
<td>Layer II Thickness (µm)</td>
<td>104.9</td>
<td>10.3</td>
</tr>
<tr>
<td>Average Activity (meters)</td>
<td>1012.1</td>
<td>639.5</td>
</tr>
<tr>
<td>Glucose Intolerance (AUC) – Week 9</td>
<td>67.7</td>
<td>22.2</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml) – Week 9</td>
<td>25.2</td>
<td>16.5</td>
</tr>
</tbody>
</table>

SD: Standard Deviation; LEC: Lateral Entorhinal Cortex; MEC: Medial Entorhinal Cortex

In exercising rats, glucose intolerance, measured by the area-under-the-curve for the final glucose tolerance test, was negatively associated with total entorhinal cortical thickness (r = -0.361, p = 0.030), LEC thickness (r = -0.351, p = 0.036) and layer II thickness (r = -0.344, p = 0.040) indicating increased total entorhinal, LEC and layer II thickness in animals with decreased glucose intolerance. Fasting insulin levels were also negatively associated with total entorhinal cortical thickness (r = -0.408, p = 0.014), and layer II thickness (r = -0.336, p = 0.045), indicating that lower fasting insulin was associated with increased total entorhinal and layer II thickness. Average activity is negatively associated with both glucose intolerance (r = -0.483, p = 0.003) and fasting insulin (r = -0.356, p = 0.033). No significant correlations were observed in sedentary rats between entorhinal cortical and subregion thickness and metabolic measures.
4.3.3 Mediation Analysis

Mediation analysis was conducted to determine if metabolic measures mediated the relationship between average activity (as measured by wheel rotation) and entorhinal cortical thickness in exercising rats. The regression of average activity on entorhinal cortical thickness was significant (Path c': $\beta = 0.349$, t(34) = 2.169, $p = 0.033$). The regression of average activity on fasting insulin was significant (Path a: $\beta = -0.356$, t(34) = -2.222, $p = 0.033$). The regression of fasting insulin on entorhinal cortical thickness was not significant (Path b: $\beta = -0.325$, t(33) = -1.968, $p = 0.058$). Controlling for fasting insulin, average activity was not a significant predictor of entorhinal cortical thickness (Path c: $\beta = 0.233$, t(33) = 1.410, $p = 0.168$). A Sobel test was conducted and found significant mediation in the model ($z = 2.267$, $p = 0.023$). Reduced fasting insulin mediates the relationship between increased average activity and greater entorhinal cortical thickness in exercising rats. Glucose intolerance did not mediate the relationship between average activity and entorhinal cortical thickness.
Figure 4.3 Mediation analysis. Standardized regression coefficients for the relationship between average activity and entorhinal cortical thickness as mediated by reduced fasting insulin. The standardized regression coefficient between average activity and entorhinal cortical thickness, controlling for fasting insulin, is in parentheses. * p < 0.05

4.4 Discussion

Olanzapine-treated rats had decreased medial entorhinal cortical thickness compared to vehicle rats. A significant interaction between olanzapine and exercise was observed for layer II of the entorhinal cortex, with exercising rats having significantly greater thickness compared to sedentary rats in the vehicle group, but not in the olanzapine group. Greater total entorhinal and lateral entorhinal cortical thickness was associated with greater average activity. In exercising rats, lower glucose intolerance was associated with greater total entorhinal and layer II cortical thickness. Lower fasting insulin levels were also associated with increased total entorhinal, lateral entorhinal, and layer II cortical thickness. The relationship between increased activity and greater entorhinal cortical thickness was found to be mediated by lower fasting insulin, indicating that regulation of metabolic risk factors may be an important contributor to the impact of aerobic exercise on the entorhinal cortex.
Olanzapine-treated rats had decreased thickness in the MEC compared to vehicle-treated rats. Second-generation antipsychotics generally do not significantly contribute to cortical grey matter thinning (Vita et al., 2015), but some research suggests temporal cortical thinning may be associated with some atypical antipsychotics (Lesh et al., 2015). Previously, olanzapine-treatment in rats was associated with decreased hippocampal volume, primarily in the dentate gyrus and CA1 regions (Barr et al., 2013). The MEC-hippocampal circuit is largely responsible for temporal associations in episodic memory. Neurocognitive deficits have often been resistant to antipsychotic treatment and while second-generation antipsychotics show greater improvement than first-generation antipsychotics, these improvements can happen in different cognitive domains for different drugs (Flashman & Green, 2004). Further research is required to investigate the mechanism of antipsychotic treatment on entorhinal cortical thickness and how this might impact cognitive impairment in psychosis patients.

LEC thickness was larger in sedentary rats compared to exercising rats. There was no effect of exercise on total entorhinal cortical thickness or MEC thickness. These results appear to be in conflict with observed correlations between entorhinal cortical and LEC thickness and average activity, indicating an association between greater activity and increased thickness for both measures. As previously reported, rats treated with olanzapine had significantly lower mean average activity compared to vehicle-treated rats, therefore using average activity as a continuous variable of exercise may provide a more accurate understanding of the impact of exercise on the entorhinal cortex and its subregions.

A significant interaction between olanzapine and exercise was identified for layer II entorhinal cortical thickness. While a significant increase in layer II thickness was observed in exercising rats administered vehicle, olanzapine appears to diminish the effect of exercise on
layer II thickness. Layer II connects primarily to the dentate gyrus of the hippocampus. Exercise has previous been shown to selectively increase cerebral blood volume (CBV), primarily in the dentate gyrus in humans and rodents (Pereira et al., 2007). Increased CBV is thought to trigger neurogenesis and angiogenesis through the up-regulation of growth factors including BDNF and VEGF respectively (Pereira et al., 2007). This may give insight into the cellular mechanism behind exercise-induced layer II expansion, but further research is required. Olanzapine has previously been shown to increase BDNF and VEGF levels in the hippocampus (Kusumi, Boku, & Takahashi, 2015; Pillai & Mahadik, 2006). Further up-regulation of these growth factors through exercise may not be possible, which may explain why exercise significantly increased layer II thickness in vehicle-treated rats, but not in rats administered olanzapine.

Significant relationships between improved metabolic indices and increased thickness in the entorhinal cortex, LEC, and layer II were observed in exercising rats, with reduced fasting insulin mediating the relationship between average activity and entorhinal cortical thickness in this group. Elevated fasting insulin may be an indicator of insulin resistance and is a key feature of metabolic syndrome (Sung, Seo, Rhee, & Wilson, 2011). Insulin binding appears to be particularly elevated in the limbic system, including the entorhinal cortex, and insulin resistance has been associated with brain atrophy and decreased hippocampal volume (Hill, Lesniak, Pert, & Roth, 1986; Phillips, Onopa, Zaiko, & Singh, 2018; Rasgon et al., 2011). Higher average activity may prevent insulin resistance resulting in lower fasting insulin levels and increasing entorhinal cortical thickness.
4.4.1 Limitations

It is important to acknowledge certain limitations of this study. First, layer II thickness was found to violate the assumption of homogeneity of variance. This is thought to lower the power of an ANOVA analysis and any significant findings should be interpreted with caution (Bao & Ananda, 2001). To lend support to these findings a Welch unequal variance test was performed comparing the four groups, with significant findings of the Welch test corroborating the ANOVA results. Second, due to the combination of the 1-h and 3-h exercise groups, there were fewer rats in the sedentary groups, particularly for the vehicle-administered sedentary rats. This may introduce some bias in our statistical analysis. For the ANOVA, this unequal group size can impact the homogeneity of variance assumption. By testing for this assumption, and using appropriate alternative statistics when necessary, we helped limit any potential bias (Bao & Ananda, 2001). Third, although the entorhinal cortex shares many conserved structural characteristics between humans and rats, there may be key differences that impact the generalizability of this research to humans (Naumann et al., 2016). For example, human grid cells function in correspondence with grid cells in the cingulate and prefrontal cortices and may have wider localization variability than rodents (Jacobs et al., 2013). This may have key implications for episodic memory encoding and the potential for exercise interventions to address cognitive impairments in this area. Fourth, thickness variability along the anterior-posterior axes of the brain may impact thickness measures. Care was taken to measure average thickness throughout the entire entorhinal structure within specified anatomical bregma, in order to capture this variability within the average thickness measure. Finally, only female rats were used in this research. Female rats were utilized for this research as they show more consistent antipsychotic-induced metabolic changes than males (Boyda et al., 2010). While the majority of
research examining the impact of exercise interventions in psychosis has focused on samples comprising primarily male subjects, exercise-induced hippocampal volume increases have also been reported in female cohorts (Firth, Stubbs, et al., 2018; Lin et al., 2015; Pajonk et al., 2010). Further research is required to understand the potential impact of sex differences on the effects of antipsychotics and exercise in the entorhinal cortex.

4.4.2 Conclusion

In summary, the entorhinal cortex plays a key role in episodic memory processing and may have critical implications for the cognitive impairment observed in psychosis patients. Olanzapine was associated with lower medial entorhinal cortex thickness. While this was not ameliorated by exercise in this brain region, we previously reported an increase in hippocampal volume in rats administered olanzapine that were exposed to exercise. Evidence suggests that exercise may also help mitigate the cardio-metabolic side effects of antipsychotic medication, as such psychosis patients may benefit from exercise as a safe, non-pharmacological adjunct treatment to address both neuroanatomic and metabolic concerns.
Chapter 5: Discussion

5.1 Overview of Findings

This dissertation examined the impact of exercise on neuroplasticity and symptom severity for psychosis patients. Benefits of aerobic exercise interventions on hippocampal volume have been well established, but many other questions remained around the effectiveness of these interventions for treatment-resistant schizophrenia patients, the impact of alternative exercise types including resistance training and yoga, and the potential for exercise-induced cortical neuroplasticity, independent from the effects of antipsychotic medication.

5.1.1 Effects of Exercise in Treatment-Resistant Schizophrenia

We identified that a 12-week exercise intervention was associated with hippocampal volume increase and psychosis symptom severity decrease in a group of treatment-resistant schizophrenia patients. This is consistent with previous findings in chronic schizophrenia and early psychosis patients that demonstrated increased hippocampal volume and improved symptoms following 12 week exercise interventions (Lin et al., 2015; Pajonk et al., 2010). Treatment-resistant schizophrenia patients are typically prescribed higher doses of antipsychotic medications, experience more polypharmacy, and are at greater risk of metabolic dysfunction (Ijaz et al., 2018). Considering these factors and their likelihood to experience greater severity of negative symptoms including amotivation and anhedonia, investigating the capacity for treatment-resistant schizophrenia patients to participate in and benefit from an exercise intervention was highly valuable and has significant clinical implications (Vancampfort, De Hert, et al., 2015).
In the current investigation, change in hippocampal volume was not associated with change in symptom severity in treatment-resistant schizophrenia patients. Previous work has also failed to find a significant relationship between hippocampal neuroremediation and symptom improvement in chronic schizophrenia patients (Pajonk et al., 2010). However change in hippocampal volume was associated with change in cognitive measures. Antipsychotic treatment may be contributing to improvements in symptom severity while negatively impacting hippocampal volume, interfering with our ability to detect relationships between change in hippocampal volume and symptom severity (Barr et al., 2013). Larger sample sizes and studies with antipsychotic-naïve patients may help clarify the connection between hippocampal volume and psychosis symptom severity.

5.1.2 Effects of Exercise on Hippocampal Vascular Volume

We did not observe the anticipated change in hippocampal vascular volume following exercise. While acute bouts of exercise have been shown to upregulate angiogenic factors including VEGF, chronic exercise training may trigger a more complex temporal response (Olenich, Gutierrez-Reed, Audet, & Olfert, 2013). Anti-angiogenic factors, like endostatin, may also be up-regulated during exercise and the balance of these factors may serve as a feedback mechanism in humans and mouse models to limit angiogenic expansion over prolonged exercise training (Hoier et al., 2012; Olenich et al., 2013). Increases in cerebral blood flow associated with moderate-intensity aerobic exercise may be more associated with increased neuronal activity and metabolism as opposed to angiogenesis (Ogoh & Ainslie, 2009). In contrast, angiogenesis may be critical for exercise-induced cognitive benefits, as angiogenesis, not neurogenesis, was shown to be necessary for improved cognitive function in learning and
memory (Kerr et al., 2010). Further research into the mechanism behind exercise-induced cognitive benefits may provide further insight into the role of angiogenesis and its regulation.

Limitations of SWI resolution and its dependence on deoxygenated hemoglobin make it difficult to capture volume changes in capillaries, which may be more likely to change as a result of exercise (Liu et al., 2019; Swain et al., 2003). Previous studies looking at cerebrovascular plasticity following exercise have used gadolinium contrast-based perfusion imaging or arterial spin labeling (ASL) MRI (Maass et al., 2016, 2015; Steventon et al., 2019). SWI does not require injection of radioactive isotopes, nor does it require the long acquisition time of ASL, making it less susceptible to motion artifact, which may be especially likely in patients experiencing extrapyramidal symptoms (Verclytte et al., 2017). SWI offers a potentially ideal method for detecting vascular volume changes following exercise and further development of this technique could improve our capacity to detect these changes.

5.1.3 Baseline Neocortical Deficits in Chronic Schizophrenia Patients

While no baseline differences were observed between early psychosis patients and healthy volunteers in cortical regions of interest, chronically treated patients presented with decreased fusiform cortical thickness compared with healthy volunteers. Previous work with psychosis patients has found similar bilateral reduction in the fusiform cortex, without changes in other temporal cortical structures (Lee et al., 2002; Takahashi et al., 2006, 2011). The lack of fusiform reduction in early psychosis patients is in agreement with previous work suggesting progressive fusiform cortical loss over longer duration of psychosis (Bangalore et al., 2009; Takahashi et al., 2011).
Reduction in the fusiform cortex has been associated with negative symptom severity in people with schizophrenia, particularly the symptom of emotional withdrawal (Nestor et al., 2007). The fusiform gyrus plays a critical role in face perception and recognition. It has been hypothesized that the reduction of the fusiform cortex in psychosis patients may contribute to delusional misinterpretation experienced by individuals with schizophrenia (Lee et al., 2002).

Deficits in the fusiform cortex have been associated with difficulties in facial memory and emotional recognition common in schizophrenia (Nestor et al., 2007; Onitsuka et al., 2003). Deficits in facial emotional recognition is a likely contributor to social and occupational dysfunction in individuals with schizophrenia; as such, neuroremediation in this region may have significant clinical relevance (Behere, 2015).

Other differences between patients and healthy volunteers were noted including a lower resting heart rate and a lower BMI for healthy volunteers compared to patients. These findings were anticipated, especially for chronically treated patients who may experience greater cardiometabolic dysfunction associated with greater atypical antipsychotic exposure (Lappin et al., 2018). These cardiometabolic risk factors further support the need for exercise interventions for chronically treated schizophrenia patients.

5.1.4 Effect of Exercise on Neocortical Deficits in Psychosis Patients

Chronically treated patients who participated in the aerobic intervention had a greater increase in orbitofrontal cortical thickness compared to patients in the resistance training group. Change in orbitofrontal cortical thickness was not significantly associated with change in symptoms severity. Early psychosis patients who completed the aerobic intervention had neuroanatomical increases in the entorhinal and fusiform cortices and cortical increase in these
regions were associated with decreasing psychosis symptom severity, particularly for general psychopathology.

Orbitofrontal cortical deficits are more pronounced in patients with chronic schizophrenia compared to patients with early psychosis who may exhibit cortical deficits primarily in temporolimbic regions (Torres et al., 2016). Cortical areas with relatively greater deficits may be the first to benefit from exercise-induced neuroremediation. In early psychosis patients, the largest relative deficit is the temporal cortex, matching our findings that entorhinal and fusiform cortical thickness increased following exercise. In chronic schizophrenia patients, the greatest relative cortical deficits are in frontal regions, particularly for patients who are treatment-resistant, matching our finding that the orbitofrontal cortex benefitted from the exercise intervention (Quarantelli et al., 2014). It is important to note that these frontal cortical deficits may be the product of neuropathological differences in these regions that are not detected within the grey matter. Chronic schizophrenia patients demonstrate frontal dysconnectivity patterns associated with severity of cognitive impairment (Zhou, Fan, Qiu, & Jiang, 2015). Further research, with larger samples of patients and healthy volunteers, is required to confirm this hypothesis and investigate whether a longer duration of exercise could result in more widespread cortical expansion in psychosis patients.

It is interesting to note that change in orbitofrontal cortical thickness was not significantly associated with change in symptom severity in chronic schizophrenia patients, but increase in entorhinal and fusiform cortices was significantly associated with a decrease in psychosis symptom severity, specifically for the general subscale for early psychosis patients. Temporal lobe cortical thinning has been linked with psychosis symptom severity, particularly positive and general psychopathology (Mennigen et al., 2019; Padmanabhan et al., 2015; Turetsky et al.,
Frontal lobe deficits appear to be more closely tied with cognitive and social deficits (Yamada et al., 2007). The orbitofrontal cortex specifically has been linked with severity of negative symptoms, but also cognitive impairments and deficits in emotional processing (Bellani, Cerruti, & Brambilla, 2010). Cortical expansion in various brain regions may be associated with differential clinical and cognitive improvements. These differences may also interact with illness chronicity, antipsychotic treatment, and other factors that warrant further investigation.

5.1.5 Effect of Exercise and Olanzapine on Entorhinal Cortical Thickness

Olanzapine administration was associated with decreased thickness in the medial entorhinal cortex. While it was anticipated that olanzapine would decrease entorhinal cortical thickness, the specific effect on the medial region was unexpected. The LEC and MEC perform differential functions for memory encoding and receive information through projections from the parahippocampal and postrhinal cortices respectively. The response of the MEC to olanzapine administration may mean that this pathway specifically may be susceptible to the effects of antipsychotic medication. Antipsychotic treatment may be associated with the entorhinal cortical reductions observe in patients with schizophrenia and the MEC may be particularly sensitive to these effects.

Exercising rats had greater layer II entorhinal cortical thickness compared to sedentary rats, but only for those treated with vehicle. There was no effect of exercise observed for rats treated with olanzapine. Layer II neurons project to the dentate gyrus in the hippocampus and neuronal disturbances in layer II have been well documented in patients with schizophrenia (Falkai, Schneider-Axmann, & Honer, 2000). Exercise has been shown to increase dendritic
spine density and change dendritic arborization in both the entorhinal cortex and the hippocampus (Stranahan, Khalil, & Gould, 2007). Olanzapine administration may inhibit this increase in dendritic spine density and reduce dendritic arborization (Frost, Page, Carroll, & Kolb, 2010). Antipsychotic treatment may therefore inhibit the beneficial impacts of exercise on cortical thickness.

Greater entorhinal cortical thickness was associated with increased activity and improved fasting glucose and fasting insulin levels in rats. Fasting insulin was found to mediate the relationship between activity and entorhinal cortical thickness. These findings are similar to previous research finding cholesterol levels, another indicator of metabolic health, impacts the relationship between antipsychotic treatment and cortical thickness in humans (Gjerde et al., 2018). The impact of both antipsychotic medication and exercise on cortical thickness may be associated with their effects on cardio-metabolic systems. In individuals with metabolic syndrome, risk factors including obesity, dyslipidemia, and hyperglycemia were associated with reduced cortical thickness across various regions (Schwarz et al., 2018). These findings may indicate shared pathophysiology underlying metabolic dysfunction and neuroanatomic deficits. Inflammation and stress have been linked with both metabolic health and neuronal integrity (Habets et al., 2011; Krishnadas et al., 2013; Müller, Weidinger, Leitner, & Schwarz, 2015). Impaired cerebrovascular integrity may also be pathologically relevant (Schwarz et al., 2018). Insulin disturbances have been associated with vascular damage and impairing vasoreactivity (Lind, 2008). Reduced cerebral blood flow associated with insulin resistance may damage brain tissue and may impact cortical thickness (Hoscheidt et al., 2017). Antipsychotic medications and exercise may influence cortical thickness partially due to the exacerbation or regulation of metabolic risk factors, impacting vascular health.
5.2 Strengths and Limitations

The ability to investigate questions around the impact of exercise on neuroplasticity across various psychosis populations is a major strength of this dissertation. By investigating treatment-resistant chronic schizophrenia patients, early psychosis, and rats with and without olanzapine administration, we can begin to understand the differential impact of illness severity and duration, antipsychotic treatment, and exercise type on exercise-induced neuroplasticity. It would be unethical for psychosis patients to stop receiving clinical care from which they are benefitting, including antipsychotic medications. Therefore both psychosis patient populations maintained their treatments throughout the course of the exercise intervention. This is an important consideration in assessing the generalizability of these results, but also helps strengthen the validity of these interventions. An intervention that benefits patients in a setting that is unrealistic to their ongoing life is not one that has a likelihood of being implemented. However these findings indicate that exercise has a capacity to benefit patients above and beyond their ongoing clinical care and therefore could serve as an important adjunct treatment. Patients at different stages of illness, on different doses of antipsychotics may benefit differently from an exercise intervention, but generally can all experience neuroplastic expansion in the hippocampus and cortical regions, and experience improvement in psychosis symptom severity.

Another critical strength is the inclusion of female participants, across all three studies. Previous work on the impact of exercise for psychosis patients has included exclusively male participants (Pajonk et al., 2010; Scheewe et al., 2013). Establishing the benefits of exercise for female psychosis patients is critical as women may be more likely to experience metabolic side effects associated with antipsychotic medication (Kraal, Ward, & Ellingrod, 2017). Women may also be more likely to benefit from exercise interventions due to a greater sensitivity to exercise-
induced upregulation of BDNF (Barha, Hsiung, et al., 2017). While this may limit the
generalizability of these findings to male psychosis patients, these findings help to address a
current gap in the literature in establishing exercise-induced neuroplasticity for female psychosis
patients.

While most of the limitations of this work have already been described, a key limitation
for this research is the relatively small sample sizes across all three studies. Efforts were made to
establish sufficient sample sizes group analyses. However when separating groups by type of
exercise, sample sizes may no longer have been sufficient to detect group differences. However
the finding that aerobic exercise, but not resistance training or yoga, is associated with cortical
expansion in psychosis patients is consistent with the literature. Aerobic exercise has consistently
been associated with neuroremediation, while resistance training and yoga have shown benefits
for cognition and symptom severity, but do not impact neuroplasticity (Firth, Stubbs, et al., 2018;
Keller-Varady et al., 2018; Lin et al., 2015). Establishing consistent protocols for exercise
interventions could minimize the heterogeneity in the literature and further improve the ability to
draw conclusions from these findings.

The short-term nature of these exercise interventions is another important limitation. The
clinical benefits of an exercise program appear to be lost for psychosis patients who cease
exercising (Firth et al., 2018). The capacity for the maintenance of exercise-induced
neuroplasticity changes in psychosis patients who no longer exercise has not yet been
established. Maintaining a long-term exercise program is difficult, especially for individuals with
schizophrenia, and therefore ongoing support and supervision may be critical to receiving long-
term benefits (Firth, Carney, et al., 2018).
5.3 Clinical Implications

Psychosis patients can benefit from exercise as a safe, non-pharmacological adjunct treatment to address neuroanatomic, clinical, and metabolic concerns. Exercise programs promote global health benefits, remediation of hippocampal and cortical regions, and the potential for more rapid improvement in severity of symptoms in early psychosis and chronically treated schizophrenia patients. As a result, complimentary clinical exercise programs for this population are highly recommended for addressing both the adverse physical and cognitive sequelae of this illness.

Even treatment-resistant patients, who may face exceptional difficulty with amotivation and lack of energy, were able to participate in the majority of exercise sessions and maintain moderate intensity throughout the workout. Even without further lifestyle changes, these patients can experience metabolic and cardiovascular benefits from participating in a regular exercise program. Tailored programs, with enthusiastic staff, and a variety of exercise modalities available may have contributed to this success. For chronically medicated patients with high rates of metabolic and cardiovascular risk factors and severe clinical symptoms, the ability for exercise to address these concerns makes it a highly desirable and highly recommended part of any treatment plan.

Critical funding is needed to provide exercise programs to psychosis patients both in hospital and out in the community. Further research is required to understand the cost-benefit analysis of exercise programs. The cost of prolonged hospital care, ongoing medication, and high rates of cardiometabolic health issues may mean that integrating exercise programs into treatment may be a cost-effective strategy that could be useful when advocating for funding for patient exercise programs. Regardless, exercise provides a number of clear benefits for psychosis
patients who may face significant cognitive, social, and financial barriers to participating in community exercise programs. The lack of provincially funded exercise programs for patients with severe mental illness means that psychosis clinics and hospitals are often faced with inadequate resources to provide adequate exercise programs. Exercise programs that are available may not meet the intensity and frequency levels necessary for patients to experience cardiovascular, clinical, and neuroanatomic benefits so these requirements must be considered in the design of a patient exercise program.

Although aerobic exercise has been the most consistent form of exercise found to promote hippocampal and cortical neuroremediation in psychosis patients, other exercise modalities may also be beneficial. Both groups of patients who participated in resistance training and yoga experienced improvement in psychosis symptom severity. Cognitive benefits and quality of life improvements have previously been associated with these exercise methods (Lin et al., 2015; Nagamatsu, Handy, & Hsu, 2013). Alternative forms of exercise, like high-intensity interval training (HIIT), have also been beneficial for improving cardiometabolic health and symptom severity in chronic schizophrenia patients (Wu, Lee, Chieh Hsu, Chang, & Chen, 2015). HIIT may be especially beneficial for patients who find it difficult to maintain moderate intensity exercise for an extended period of time. Further research is required to determine the feasibility of high intensity exercise for chronically medicated patients and if short bursts of high intensity exercise can upregulate BDNF and produce neuroplastic changes. HIIT may be more engaging for patients than constant moderate intensity aerobic exercise on a treadmill or stationary bike and therefore patients may find the program more enjoyable and be more likely to attend regular exercise sessions. Similar alternatives like dance and other aerobic exercise classes could also be explored for this reason. Consultation with patients about the kinds of physical
activities they enjoy would also be critical. Providing a wider range of exercise choices may be key to increasing adherence rates for patients.

Adherence to a training program is key to experiencing these benefits. Psychosis patients have identified autonomy and social support as key factors for promoting participation in an exercise intervention (Firth et al., 2016). Providing patients with a variety of fully supported exercise options is critical to increasing the likelihood of long-term participation in exercise programs and ongoing health benefits. Participants were allowed to choose the exercise equipment they used (treadmill, elliptical, or stationary bike for the aerobic group) and the radio station they listened to throughout the exercise session. These choices promote a sense of autonomy for the participant and increase enjoyment. Enthusiastic support from the exercise trainer throughout the exercise session is also thought to be key to the success of the program. Providing patients with supervision that is positive and encouraging is also critical.

5.4 Conclusion

Cardiovascular-related death is the primary cause of reduced life expectancy in psychosis patients. While antipsychotic medication has been effective at treating positive symptoms, it does not properly address negative symptoms or cognitive deficits and may worsen frontal-limbic cortical deficits common in people with schizophrenia. Exercise interventions, particularly aerobic exercise, promotes neuroremediation of hippocampal volume while improving cardio-metabolic health and clinical symptoms including cognitive deficits. This dissertation highlighted the capacity for exercise to increase hippocampal volume and improve symptom severity in treatment-resistant schizophrenia patients. It also demonstrated changes in entorhinal, fusiform, and orbitofrontal cortical thickness following aerobic exercise and these changes were
associated with reduced symptom severity. Olanzapine treatment was associated with decreased medial entorhinal cortical thickness and exercise was associated with greater layer II entorhinal thickness in female rats. Change in fasting insulin was found to mediate the relationship between activity and entorhinal cortical thickness in rats. These findings provide key insight into the impact of exercise on neuroplasticity and symptom severity in schizophrenia patients at various stages of illness. Further areas of research include investigating the mechanistic relationship between metabolic dysfunction and neuroanatomic deficits in psychosis patients.

These findings lend support for exercise as a critical, adjunct treatment for psychosis patients at all stages of illness, including treatment-resistant patients. Aerobic exercise, in particular, is a safe, non-pharmacologic means of addressing physical, cognitive, and clinical sequelae of schizophrenia. The findings from this study indicate the clinical need and the clinical value of widespread adoption of clinical exercise programs for patients receiving psychotropic medications. The necessity and the utility of exercise interventions to truly support the physical and emotional health of a highly vulnerable patient population is clear.


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