THE EFFECTS OF EXERCISE ON WHITE MATTER IN THE BRAIN AND EMOTION RECOGNITION IN A TREATMENT RESISTANT SCHIZOPHRENIA POPULATION

by

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Abstract

Treatment-resistant schizophrenia is characterized by deficits in cognition, emotion recognition, cardiovascular health, and brain white matter (WM). Reductions in frontal-temporal white matter (WM) volumes in schizophrenia are associated with psychotic symptoms, cognitive deficits, poor emotional recognition, and cardiometabolic disorder. Regular exercise is posited to attenuate or restore functionality in multiple domains, but the efficacy of exercise as a non-pharmacological treatment for schizophrenia is unknown. Our goal was to examine the effects of exercise on WM in treatment-resistant schizophrenia.

Fifteen treatment-resistant schizophrenia patients and 10 age, gender and education matched healthy volunteers were included in a 12-week exercise intervention. At baseline, compared to healthy volunteers, patients had decreased myelin water fraction (MWF) in the genu, callosal body, splenium, external capsule, cingulum, superior longitudinal fasciculus, and forceps minor with corrected p-values ranging from 0.03 to 0.04 and hedges' g effect sizes ranging from -0.76 to -1.03. Patients also had decreased fractional anisotropy (FA) in the genu ($p = 0.03$, $g = -1.29$) and the forceps minor ($p = 0.03$, $g = -1.23$). Patients also had slower reaction times in emotion expression tasks ($p < 0.01$, $g = 1.30$), slower domain level speed of processing ($p < 0.01$, $g = -1.91$), and lower working memory ($p < 0.01$, $g = -1.52$), and executive function ($p < 0.01$, $g = -1.07$) tasks at baseline.

After exercise intervention, patients improved their reaction time, with corrected p-values and Cohen's d effect sizes, in correct emotion expression tasks ($p = 0.02$, $d = -1.0$) and domain level processing speed ($p = 0.03$, $d = -0.57$). Patients also had significantly improved social and occupation functioning ($p < 0.01$, $d = 0.92$), and reduced symptom severity ($p < 0.01$, $d = -1.0$). No detectable changes were seen in MWF, FA, or other cognitive tasks. Larger sample sizes or

longer periods of exercise intervention may be required to detect WM changes. In summary, exercise can be a safe and effective adjunct treatment for treatment resistant schizophrenia that reduces psychotic symptoms, improve social functioning, and improve processing speed.

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Lay Summary

Schizophrenia is a mental disorder with known deficits in the connective network that enables brain regions to communicate. This is thought to result in mental disorder, cognitive disabilities, cardiovascular abnormalities, and abnormal emotion perception in schizophrenia. These problems may be lessened with exercise. It is currently unclear if exercise will result in changes these four types of health deficits linked to connective network deficits in the brain. In our study people with schizophrenia and healthy volunteers took part in a 12-week exercise program. Before and after the exercise program participants were evaluated with MRI, cognitive tests, and emotion processing tests. The results linked exercise to improvements in mental health, the speed at which people with schizophrenia processed emotions, and overall processing speed. No specific changes to any areas of the connective network in the brain were found post exercise.

Preface

The research undertaken in this thesis was a part of the Brain Health and Exercise in Schizophrenia Study under the supervision of Dr. Donna Lang. This study is a longitudinal research project examining the effects of exercise in treatment resistant schizophrenia patients with study design by Dr. Donna Lang. Dr. Alan Thornton designed the neurocognitive test battery and supervised all data collecting using them. Dr. Darren Warburton created the individualized exercise programs and conducted all maximal oxygen consumption (VO_2max) assessments. Dr. Talia Vertinsky reviewed and provided clinical evaluations of all structural MRIs. Dr. Bill Honer led consensus diagnostic evaluations of patients. I conducted data collection for all healthy volunteer participants. Dr. Melissa Woodward and Dr. Randall White recruited all patients for the study. Processing of WM data in Advanced Normalization Tools software (ANTs) used code developed by Adam Dvorak. All patients recruited were from the BC Psychosis program at the UBC hospital in Vancouver, British Columbia. The Clinical Research Ethics Boards of the University of British Columbia provided ethical approval for the Brain Health and Exercise in Schizophrenia Study (certificate # H10-02919). This study was also a registered Clinical Trial (NCT01392885). I conducted all statistical analyses contained within this thesis.

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List of Abbreviations

3DT1 - Isotropic 3-dimensional T_1-weighted images

AD – Axial Diffusivity

Akt - Alpha serine/threonine-protein kinase

ANTs - Advanced Normalization Tools software

AT – Dr. Alan Thornton

ATV - Dr. AT Vertinsky

BMI – Body Mass Index

CDS – Calgary Depression Scale

CNV – Copy Number Variant

COWA - Control Oral Word Association Test

DEW – Dr. Darren E Warburton

DSM – Diagnostic and Statistical manual of mental disorders

DTI – Diffusion Tensor Imaging

ESRS – Extrapyramidal Symptoms Rating Scale

FA – Fractional Anisotropy

FDR – False Discovery Rate

fMRI - Functional magnetic resonance imaging

FOV – Field of View

FSL - FMRIB Software Library

GRASE – Gradient Spin Echo

HAM-A – Hamilton Anxiety Scale

HDL - High-density lipoprotein

HVLT-R - Hopkins Verbal Learning Test-Revised

IQ - Intelligence quotient

JHU – John Hopkins University

KBIT - Kaufman Brief Intelligence Test

LDL – Low-density lipoprotein

MATLAB – Matrix Laboratory

MD – Mean Diffusivity

MICE - Multivariate imputation by chained equations

MLD - Metachromatic leukodystrophy

MnM – Memory and Manipulation test

MRI – Magnetic Resonance Imaging

MS - Multiple Sclerosis

ms – millisecond

MTCF - Modified Taylor Complex Figure

MWF – Myelin Water Fraction

MWI – Myelin Water Imaging

NPC – Niemann-Pick Type C

PANSS – Positive and Negative Symptom Scale

PMM – Predictive Mean Matching

RD – Radial Diffusivity

ROI – Region of Interest

ROIs – Regions of Interest

SDMT - Symbol Digit Modalities Test

SENSE – Sensitivity Encoding Factor

SOFAS – Social and Occupational Functioning Scale

SPSS – Statistical Package for the Social Sciences

TE – Echo Time

TR – Repetition Time

VO_2max – maximal oxygen consumption

WM – White Matter

WTAR - Weschler Test of Adult Reading

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Dedication

This thesis is dedicated to the memories of my grandparents: Eugene & Gloria Senften and Charles & Ruth Cecil. Thank you for the love and guidance you gave me during your lives.

Chapter 1: Introduction

1.1 Schizophrenia

Schizophrenia is a devastating and complex psychiatric disorder that affects over 23 million people globally that has had a 14.3% increase in prevalence over a recent ten-year span (2005 – 2015) (Vos et al., 2016). In Canada, it has an overall prevalence rate of less than 1% (Smetanin et al., 2011). Onset is commonly from the teen years into early adulthood, with the age-standardized prevalence rate peaking females and males at approximately age 40 (Charlson et al., 2018). Schizophrenia is among the top causes of disability worldwide for persons aged 15 to 39 years of age (Vos et al., 2016) and in the top 15 across all age groups (Moreno-Küstner et al., 2018). The disorder is associated with significantly reduced life expectancy, reduced earning potential, decreased educational attainment, and is a significant economic burden on healthcare systems (Charlson et al., 2018).

A diagnosis of schizophrenia is made based on the criteria within the diagnostic and statistical manual of mental disorders (DSM), version 5, (DSM-5) (American Psychiatric Association, 2013). Schizophrenia is characterized by the decline of cognitive function, the presence of psychosis, negative symptoms, and concomitant psychopathologies for the majority of a one month period that persists continuously over at least six months (American Psychiatric Association, 2013). Psychosis is characterized by the presence of positive symptoms (i.e., delusions, hallucinations, disordered thoughts, and abnormal psychomotor behavior). Negative symptoms include reduced cognition and attention, decreased social functionality, avolition, and anhedonia. While many of the positive symptoms are amenable to treatment with antipsychotics, the negative symptoms are less responsive to pharmacological treatment. Most persistent are deficits in cognition that are identifiable at the earliest stage of the disorder and often worsen as

it becomes full-blown (Jahshan et al., 2010). Reductions in memory capacity, executive functioning, and attentional focus have also been identified as enduring traits of schizophrenia (Tripathi et al., 2018). Comparatively, schizophrenia disorders are the mental illnesses with the greatest personal, societal, and economic costs, accounting for over 40% of all long-term psychiatric hospital stays (Broder et al., 2018). The monetary costs are even higher for the one-third of patients with schizophrenia classified as treatment-resistant, as these people still experience psychotic episodes despite pharmacological treatment (Crocker & Tibbo, 2018). With the high level of disability for individuals with schizophrenia and high societal costs, there is a need to investigate potential new treatments for the disorder that will help ameliorate symptoms.

1.1.1 History of Schizophrenia

Eugen Bleuler coined the term 'schizophrenia' in 1908 to describe a condition of a 'split mind,' in which perception, memory, personality, and thinking occur as separate functions (Kraepelin, 1908; Kuhn, 2004). The disorder was first recorded in 1797 and 1809 (Heinrichs, 2003), with it first being thought of as an early form of dementia or degenerative disorder. With this belief it was called 'dementia praecox' ,or premature dementia, by psychiatrist Heinrich Schüle in 1886 (Laursen et al., 2014). Emil Kraepelin also used this term as early as 1893 but he later abandoned it for the better fitting term of schizophrenia (Laursen et al., 2014). As knowledge about schizophrenia progressed, Kurt Schneider separated the psychotic symptoms of schizophrenia into two major groups, hallucinations, and delusions. Schneider's work utilized what he called 'first-rank' symptoms that he believed characterized the disorder. According to Schneider, hallucinations were specific to audition and sight, with delusions described as being mainly thought-based. Until recently, these symptoms were used as diagnostic tests for the disorder and were required for a diagnosis of schizophrenia. However, these criteria changed

with the DSM-5 (American Psychiatric Association, 2013). They are now mainly used to aid differentiation between bipolar and schizophrenia and are not conclusive of one or the other as bipolar disorder with delusions is also a possible diagnosis (Picardi, 2019). Schizoaffective disorder is another diagnosis where psychotic symptoms occur. Schizoaffective disorder is notably different from schizophrenia with regard to symptoms related to mood. In schizophrenia mood symptoms do not co-occur with psychosis, whereas in schizoaffective disorder symptoms of psychosis may also occur while the person is experiencing a mood disorder, such as depression or mania (American Psychiatric Association, 2013). In research it is common to combine patients with schizophrenia and schizoaffective disorders as they are extremely similar in treatment and outcomes (Miller & Black, 2019).

1.1.2 Etiology of Schizophrenia

The etiology of schizophrenia and associated schizophrenia spectrum disorders remains elusive. Intensive clinical and laboratory-based research over the last three decades has begun to shed light on this complex, multi-factorial disorder. Risk factors for schizophrenia are varied and include both non-genetic and genetic factors. Non-genetic factors make up a minority of the risk of developing the disorder, but include obstetric complications, trauma in childhood or adulthood, social class, isolation, migration, living in an urban environment, and use of cannabis or psychostimulants (Stilo & Murray, 2019). Heritable genetic factors may explain up to 80% of the risk of developing schizophrenia (Marder & Cannon, 2019). Unfortunately, the heritable genetic risk does not come from a single gene but rather a polygenetic profile that interacts to increase the risk of developing this disorder (Ripke et al., 2014). Of the genetic risk factors, the 40% that are single genes have notable associations to the dopamine receptor D2 gene, which is the target for many of the antipsychotic drugs currently in use (Howes et al., 2012). These drugs

target dopamine dysfunction in the mesolimbic pathway of the brain which is believed to contribute to the emergence of psychosis (Howes et al., 2012; Yang & Tsai, 2017). The efficacy of these drugs to ameliorate psychotic symptoms in schizophrenia provides evidence in support of the dopamine hypothesis of schizophrenia. Sadly, dopamine abnormalities alone are unlikely to be sufficient as a causative agent (Yang & Tsai, 2017) with several other non-dopamine related genetic markers also implicated in schizophrenia (see Ripke et al., 2014). Taken all together, genetic and environmental factors likely lead to disrupted cortical networks in the brain. Disruption to cortical networks seen in first-episode psychosis (Lang et al., 2014), and other research (del Re et al., 2019; Kuswanto et al., 2012; Mwansisya et al., 2017; Zeng et al., 2016), suggest that changes in cortical networks, or WM microstructure, result in dysconnectivity in the brains of people with schizophrenia (Hummer et al., 2018). Support for the dysconnectivity hypothesis also comes from post-mortem examinations of myelination and oligodendrocytes (Aston et al., 2004), allele variations in patients that result in lower myelination (Deicken et al., 1994), and neuroimaging studies that also demonstrate lower overall WM volume in people with schizophrenia (Hummer et al., 2018).

1.1.3 Treatment-Resistant Schizophrenia

Treatment-resistant schizophrenia has recently undergone a significant review, under the Treatment Response and Resistance in Psychosis working group, to form consensus criteria to establish the diagnosis (Howes et al., 2017). The clinical evaluation to diagnose treatment-resistant schizophrenia must use an established tool such as the Positive and Negative Syndrome Scale (PANSS), show that the patient has moderate severity of symptoms in at least two categories with a less than 20% reduction in symptom severity over greater than or equal to 6 weeks, with a total duration of treatment greater than 12 weeks, and at least moderate functional

impairment on the Social and Occupational Assessment Scale (SOFAS) with adequate prior treatment. The requirements for adequate prior treatment requires information from the patient/carer reports, staff notes, pill counts, greater than six weeks of treatment of an antipsychotic at therapeutic dosage (greater than 600 mg chlorpromazine equivalents per day), two or more treatment episodes with different antipsychotic drugs with at least one being a long-lasting injectable antipsychotic (4-month minimum), with adherence rates established through serum levels of two weeks or a greater than 80% adherence rate to prior medications with pill counts, dispensing records, and staff reports, patient/carer reports (McCutcheon et al., 2018).

When a diagnosis of treatment-resistant schizophrenia is confirmed, the only pharmacological treatment approved is clozapine (Barnes, 2018). Unfortunately, clozapine is not an effective treatment for between 40%-70% of treatment-resistant schizophrenia cases (Miyamoto et al., 2014). In non-responders, patients who have persistent positive, negative, and cognitive deficits despite clozapine treatment the goal in continuing clozapine treatment becomes a reduction in positive symptoms, as efficacy for negative symptom remediation with clozapine is unclear (Souza et al., 2013). This lack of clear pharmacological agent to provide symptom relief results in non-responders being the most challenging schizophrenia patients to treat (Elkis & Buckley, 2016). While prescription of other antipsychotics to augment clozapine occurs on an individualized basis it is unclear which antipsychotics, if any, taken in conjunction with clozapine would benefit treatment-resistant schizophrenia patients or the clozapine non-responders subgroup of treatment-resistant schizophrenia patients (Miyamoto et al., 2014).

The use of clozapine is not without risk. Clozapine is associated with several adverse side effects, including weight gain, neuroleptic malignant syndrome, neutropenia, tardive dyskinesia, lethargy, dyslipidemia, and cardiometabolic disarray (Lamberti et al., 2006). It is also associated

with an increased risk of metabolic syndrome and a two- to three- fold increase in cardiovascular disorder mortality for this patient group (Lamberti et al., 2006). As such, treatment-resistant schizophrenia patients taking clozapine should have regular monitoring of weight, lipid levels, fasting blood glucose levels, and blood pressure. A potential intervention that may help ameliorate these side effects of clozapine is exercise. For treatment-resistant schizophrenia patients exercise may be a form of treatment for those with increased risk of metabolic disorder. Unfortunately, in treatment-resistant schizophrenia, negative symptoms often result in decreased motivation for physical activity making use of this treatment potentially difficult (Vancampfort et al., 2015).

1.2 White Matter Abnormalities in Schizophrenia

1.2.1 Fronto-Temporal White Matter and Psychosis

Psychotic symptoms in schizophrenia frequently correlate with deficits in fronto-temporal WM. Convergent evidence of the relationship between fronto-temporal WM abnormalities and psychosis comes from other demyelinating disorders such as Metachromatic leukodystrophy (MLD), Niemann-Pick Type C (NPC), and Multiple Sclerosis (MS). MLD is characterized by loss of sub-frontal and peri-ventricular WM (Mighdoll et al., 2015) with psychotic and cognitive symptoms similar to schizophrenia (Alves et al., 1986; Fukutani et al., 1999; Mighdoll et al., 2015). In the late-onset form of the disorder, ages 10-30, 53% of people diagnosed with MLD had an initial diagnosis of schizophrenia or a psychotic disorder (Hyde et al., 1992). This suggests that abnormal WM connections in the prefrontal region of the brain may initially trigger schizophrenia-like symptoms that are differentiable as MLD when it progresses and results in profound neurological deficits (Hyde et al., 1992). Given that the frontal areas are known to be the last regions to complete myelination during maturation, they may have

increased vulnerability to developmental derailment and impaired connectivity of fronto-temporal and fronto-medial regions. Consequently, in schizophrenia and MLD, non-normal fronto-medio-temporal connectivity is posited to contribute to a greater vulnerability to psychosis (Davis et al., 2003). In contrast, NPC is a demyelinating disorder that primarily affects the corpus callosum (German et al., 2002). Like MLD, NPC initially presents as schizophrenia-like in many cases (Walterfang et al., 2005). However, NPC eventually spreads to the grey matter of the brain resulting in a different set of symptoms from schizophrenia. Reduced WM volumes in the frontal lobes and corpus callosum are typical in NPC with psychosis, providing additional evidence that psychosis may be a problem of frontal WM dysconnectivity (Walterfang et al., 2005). While MS patients rarely present with psychotic symptoms, when they do, lesions are found in the fronto-temporal WM with an age of onset in adolescence to adulthood (Walterfang et al., 2005). In contrast, in MS, no psychotic symptoms are reported when affected brain areas are non-frontal/temporal (Mighdoll et al., 2015; Walterfang et al., 2005).

In schizophrenia, as with MLD, NPC, and MS, when psychosis does emerge, the timeframe is typically in late adolescence with a gradual onset of symptoms concomitant with changes in WM, suggesting a developmental trajectory of the disorder (Karlsgodt et al., 2012; Peters, Ikuta, et al., 2014). Additionally, post-mortem data indicate that schizophrenia patients have significantly reduced fiber counts in the corpus callosum, the primary region of inter-hemispheric connectivity (Highley et al., 1999) and in WM neuron density in dorsal-lateral prefrontal cortex and parahippocampal gyrus (Eastwood & Harrison, 2005). Observed associations between oligodendrocyte and myelin dysfunction to dopamine and glutamate abnormalities in schizophrenia further suggest that WM deficits contribute to the development the disorder (Takahashi et al., 2011).

Combining neuroimaging of WM and genetic analysis research has also linked schizophrenia and disruption of fronto-temporal WM. The largest oligodendrocyte and myelin related schizophrenia study found that there were multiple genes associated with an increased risk of someone developing schizophrenia (Ripke et al., 2013). The outcome measures of diffusion tensor imaging (DTI), an MRI modality that maps the diffusion of water in the brain, have been used in conjunction with genetic analysis to link changes in genes to changes in WM in the brain of people with schizophrenia. The most commonly used outcome measure of DTI is FA, a putative measure encompassing axon diameter, fiber coherence, and myelination in a single non-specific metric (Beaulieu, 2002). Another outcome measure is mean diffusivity (MD), which is the mean amount of water diffusion. Downregulation of WM related copy number variant (CNV) genes correlate with changes in FA and MD in a number of brain areas. These changes include decreased FA and MD in the striatum and the middle and superior temporal gyrus (Drakesmith et al., 2019; Maillard et al., 2015), lower FA in the cingulum, lower MD in the inferior longitudinal fasciculus (Roalf et al., 2017), and increased FA in the left inferior fronto-occipital fasciculus and overall right hemisphere FA. In particular, 25-30% of people with the WM altering CNV 22a11.2DS deletion develop schizophrenia (Drew et al., 2011). Deletion of this CNV results in increased left hemisphere FA, decreased radial diffusivity (RD), diffusivity that is orthogonal to axonal fibers in the left fronto-occipital fasciculus, increased FA in the right cingulum and right inferior longitudinal fasciculus, decreased RD in the right thalamo-frontal tract, and increased FA in the right cingulum (Olszewski et al., 2017). First-degree relatives of patients also provide additional insights into the genetic risk factors of schizophrenia, as these people likely carry a sizeable genetic risk of developing the disorder (Peters & Karlsgodt, 2015). First-degree relatives show reductions in FA in the prefrontal cortex,

cingulate, hippocampus, parietal lobe, and uncinate fasciculus, when compared to healthy age-matched volunteers. Though, the observed FA reductions in first-degree relative are not as severe as those seen in their affected family members (Hakak et al., 2001; Peters & Karlsgodt, 2015). In summary, genetic research has found alterations to a few CNVs that are associated with altered WM schizophrenia. Of note many of these CNVs, such as 22a11.2DS, appear to play a large part in the pathophysiology of schizophrenia as they are directly or indirectly responsible for myelination and oligodendrocytes (Mighdoll et al., 2015).

Overall, the converging evidence from patients with MLD, NPC, MS and psychosis suggests that fronto-temporal WM disruptions contribute to the emergence of psychotic symptoms in schizophrenia. Corollary evidence of frontal WM disruption in schizophrenia also comes from post-mortem and DTI research in schizophrenia. Deficits in frontal and temporal WM are posited to be a significant contributor to the emergence of psychosis, particularly during late adolescence to early adulthood, when critical phases of WM myelination and maturation are occurring in fronto-temporal regions (Yakovlev & Lecours, 1967).

1.2.2 Fronto-temporal White Matter in Schizophrenia

The majority of empirical evidence across imaging studies in schizophrenia has reliably established a burden of WM deficits in fronto-temporal regions that can both precede and result from exposure to antipsychotic medications (Lee et al., 2020; Lener et al., 2015; Stämpfli et al., 2019). The fronto-temporal WM includes several interhemispheric and intrahemispheric bundles that subserve cognitive functions known to be affected in schizophrenia, including attention, processing speed, and working memory (Karbasforoushan et al., 2015; Kubicki et al., 2009; Zeng et al., 2016b). Additionally, deficits in fronto-temporal WM may be associated with symptom severity (Kim & Jeong, 2015; Lener et al., 2015). Current imaging techniques include a

combination of informative approaches to probing the underlying physical properties of WM structure. In vivo deficits in WM may be measured by diffusion properties FA or with MWF, an index measure of myelin. Reduction in either FA or regional MWF is associated with slowed neural signaling between brain regions, mistiming of neural firings, or partial to complete loss of neural signal to and from grey matter regions (Kubicki et al., 2008). Many WM pathways in the brain have been correlated with the clinical symptoms of schizophrenia. Those implicated in schizophrenia, specifically in frontal and temporal regions of the brain, are reviewed below.

1.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imagining technology that can provide high-resolution spatial images of soft tissues in the body, along with functional and metabolic information, and more. It is based on the quantum mechanical intrinsic property called spin, which is inherent to all elementary particles (McRobbie et al., 2006). Most MRI machines will be tuned to be sensitive to hydrogen atoms within water molecules in tissue. When presenting a person or object in an MRI machine, a majority of hydrogen atoms in water align themselves in the direction of the MRI machine's magnetic field (Plewes & Kucharczyk, 2012). While the spins of most hydrogen protons will cancel each other out, enough of a signal will remain to allow manipulation and measurement of this property through disturbances in the magnetic field and receiver coils (McRobbie et al., 2006). Then a radio frequency (RF) pulse is sent from the MRI machine to the person or object in the MRI machine and subsequently displaces the protons of the hydrogen's atoms out of alignment with the MRI's main magnet. This displacement is detected by the MRI machine's receiver coils and the time it takes for the hydrogen atoms to return to their original alignment within the MRI machine is recorded as data. Once this RF excitation is completed there are two primary measurements one can make. The T_1, or

longitudinal relaxation time and the T_2, or transverse relaxation time (McRobbie et al., 2006). A T_1 signal measures the time it takes for the protons of the water molecule to have their spins return to normal after the RF pulse, whereas the T_2 signal represents the time it takes for the hydrogen protons to go out of phase with one another (McRobbie et al., 2006). Additionally, you can also repeat RF pulses to the same tissue area, known as the repetition time (TR), and alter the time between when you send an RF pulse and the time you receive it, called the time to echo (TE) (McRobbie et al., 2006). Creation of T_1-weighted images by the MRI machine use short TRs and short TEs. In contrast, creation of T2-weighted images requires long TR and long TE times (McRobbie et al., 2006). Other types of MRI sequences manipulate the TR and TE in T_1 and T_2-weighted images to create an image with different signal intensities. When looking at a T_1-weight image, fat will appear bright and Cerebrospinal fluid will be dark whereas with a T_2 image both fat and cerebrospinal fluid and water will appear bright (McMahon et al 2011).

1.3.1 Imaging White Matter with MRI

A technique known as diffusion weighted imaging is used to measure the directionality of water molecules within a voxel (Bammer et al., 2003). A physical characteristic of water molecules is that water is moving whether it is within a living tissue or not, also known as Brownian motion (Debenedetti & Klein, 2017). Diffusion imaging primarily assesses the movement of water along axonal pathways (McRobbie et al., 2006). This phenomenon of water molecules diffusing in a relatively constrained directional way is also known as anisotropy and is the basis for DTI. Directionality of water movement within the brain is based on local characteristics including tissue type, tissue density, tissue arrangement and cellular membrane integrity (Mori & Zhang, 2006). A useful measure produced by DTI is FA, or the preference for water to diffuse in a certain direction. It is a unitless measure with a value between 0 and 1 with

0 meaning water is diffusing in all directions, and approaching 1 shows that water is diffusing more so along one axis. (Assaf & Pasternak, 2008). WM tends to have a higher FA value than GM due to the lack of myelin in the latter. Calculation of FA uses diffusion tensor eigenvalues (λ) acquired from the three-axis measured: x, y, and z using the formula of $FA = \sqrt{\frac{1}{2}}\frac{\sqrt{(\lambda_1-\lambda_2)^2+(\lambda_2-\lambda_3)^2+(\lambda_3-\lambda_1)^2}}{\sqrt{\lambda_1^2+\lambda_2^2+\lambda_3^2}}$. Other DTI based metrics include RD, axial diffusivity (AD), and MD. RD represents the diffusion of water perpendicular to axonal fibers and may be the best DTI-based metric to evaluate myelin content or de-myelination. While higher RD values are thought to represent a loss of myelin, lower RD values likely represent greater WM integrity. AD values are thought to represent the amount of diffusion along the primary axon axis. Lower AD measures damage to the axon itself or a less cohesive orientation to the fibers. MD is a measure of the total diffusivity within a voxel.

DTI allows the tracking of WM in three dimensions but does have some limitations. First, as FA is made up of several different variables including myelin, axon diameter, fiber density, axon number, and axonal membrane density (Assaf & Pasternak, 2008; Vanes et al., 2018) and anisotropy in myelinated and unmyelinated axons may be similar (Beaulieu & Allen, 1994) it does not allow for the direct measurement of myelin. Second, areas where WM fibers cross each other are problematic for FA as it can only represent a single direction. As such, each different direction of fibers that is present in a voxel, after image processing, partially cancels out the direction of another set of fibers pushing the overall FA number closer to zero. This results in a reduction of signal strength in areas with crossing fibers that if severe enough can result in an area of WM being excluded from the FA map (Oouchi et al., 2007). Interpreting WM integrity using only FA may result in potentially missing important changes that occur in diseases and

treatments that target WM. Despite this FA remains useful in researching demyelinating disorders such as MS where reductions in FA can be seen in lesioned areas (Assaf & Pasternak, 2008).

Myelin water imaging (MWI) allows the examination of myelin using the T_2 MRI signal. In the 1990's it was demonstrated that the MWF from WM was greater than that found in grey matter (Mackay et al., 1994) and that T_2 decay times vary depending on the type of tissue restricting or containing the water, and hydrogen atoms contained therein. The T_2 decay from myelin occurs between 10 and 20 millisecond (ms) while intra/extracellular water has a T_2 decay time of 60 ms or longer (MacKay & Laule, 2016). In MWI the obtained T_2 decay curve, which is a plot of magnetic resonance signal vs TE (MacKay & Laule, 2016), is parsed out into its exponential components and then is set on a plot of the signal amplitude over T_2 time (Whittall & MacKay, 1989). MWF is calculated by taking the 10-40 ms signal from the T_2 decay curve time interval over all water of the entire T_2 distribution (0 – 2000 ms) plus the signal from the 10-40 ms timeframe or: $MWF = \frac{Myelin\ water}{All\ water}$ (MacKay & Laule, 2016). In the often utilized spin-echo method of MWI (Mackay et al., 1994), the T_2 decay curve is obtained using a 90 degree pulse followed by a series of 180 degree pulses with 32-echos collected every 10 ms (MacKay & Laule, 2016). MWF was histologically validated several years later in MS patients as an in-vivo measurement of myelin (Laule et al., 2006). This imaging modality, when contrasted with DTI metrics, results in a more accurate in-vivo representation of myelin distribution and allows us to observe changes to myelin over time. In contrast, the non-specificity of DTI metrics, such as FA, make it difficult to interpret the meaning of signal change from one time point to another. If a significant change in diffusion is observed, there is no certainty as to what component or characteristic of the WM has changed. It could be the myelin, the neurite, or

any other factor related to WM integrity. Given the physiological basis of the MWF index, it is more likely to accurately detect changes in the myelin component of WM than other imaging modalities. As a cautionary consideration, it has been observed that depletion of iron levels may lower MWF signal by 26%-28% (Birkl et al., 2019). Despite this limitation, MWF is an excellent method to investigate and evaluate de-myelinating disorders and interventions seeking to increase or change myelination.

1.3.2 History of White Matter Neuroimaging in Schizophrenia

While neuroimaging of the brain goes back to the 1970's with early computed tomography studies (Johnstone et al., 1976), specific WM-focused studies in schizophrenia did not occur until after the advent of DTI in 1994 (Basser et al., 1994). Subsequently, DTI has been the preferred MRI modality used to examine changes in WM, until the recent advent of MWF. A recent DTI based multi-site study with over four thousand psychosis patients reported deficits in many WM tracts (e.g. forceps minor, genu, body, splenium, anterior limb of the internal capsule, fornix, and sagittal stratum, and nine other areas) compared to healthy volunteers (Kelly et al., 2018). MWF investigations in these regions in schizophrenia have reported decreases in myelin content in the fronto-occipital fasciculi in the area of the striatum extending to the cerebellum (Vanes et al., 2018) and in the genu of the corpus callosum (Flynn et al., 2003). High RD values have been found in the forceps minor and superior longitudinal fasciculus in people with schizophrenia (Prasad et al., 2015), suggesting a tract-wide loss of myelin. Along with increased RD, reduced AD has been associated with the positive symptoms of schizophrenia (Park et al., 2014). Increased mean diffusivity in WM tracts have also been noted in the anterior thalamic radiation, forceps minor, bilateral inferior fronto-occipital fasciculus, and the superior longitudinal fasciculus (Clark et al., 2011). This increase in MD may also be specific to

schizophrenia and may represent subtle changes in myelination that occur in the disorder (Haigh et al., 2019).

1.4 Fronto-temporal White Matter Regions of Interest

1.4.1 Corpus Callosum

The largest bundle of interhemispheric WM is the corpus callosum, runs anteriorly from the frontal to the posterior extent of the parietal lobes, and is situated superiorly to the anterior ventricles. The corpus callosum is comprised of topographically organized bundles of WM, and reductions in either volume or structural integrity are associated with reduced cross-hemispheric communication (Kubicki et al., 2008). Reductions of FA in the body of the corpus callosum and forceps minor, a frontal WM fiber bundle that crosses at the genu, or anterior portion of the corpus callosum, are present in first-episode psychosis, suggesting WM abnormalities are present at early stages of the disorder (Keymer-Gausset et al., 2018). The genu connects the frontal lobes of the brain. The frontal lobes subserve higher-order thought, behavioral control, reasoning, and logic collectively known as executive functions (Anderson et al., 2008). Abnormal interhemispheric communication between the frontal regions may be responsible for some of the thought-based deficits typically seen in schizophrenia (e.g., jumbled or confused thoughts and speech). Disruption to this pathway is linked to integration deficits of non-verbal and verbal information to understand and adequately behave in social situations (McDonald et al., 2018). Decreased MWF, an indicator of reduced myelin integrity, has also been observed in the corpus callosum in schizophrenia and is correlated with lower cognitive control (Vanes et al., 2018). Additionally, deficits in the corpus callosum, anterior and superior coronal radiata (the superior-lateral frontal radial extensions of the anterior corpus callosum which funnel through the

midbrain) have been associated with symptom severity of chronic schizophrenia (Viher et al., 2016).

1.4.2 Superior Longitudinal Fasciculus:

The superior longitudinal fasciculus is a major WM pathway connecting the frontal, occipital, temporal, and parietal lobes, and is a main portion of the cortico-cortical attention network and critical to connecting the visuospatial attention network together. Superior longitudinal fasciculus deficits, as seen in schizophrenia, results in deficits in tasks that require sustained attention that utilize multiple sensory modalities (Chechlacz et al., 2013; Spalletta et al., 2015). The superior longitudinal fasciculus is associated with working memory performance in recent-onset schizophrenia (Karlsgodt et al., 2008) . Abnormalities in the WM network connecting to the superior longitudinal fasciculus, the coronal radiata, cingulum, and forceps minor, are correlated with a reduced ability to perceive and think about one's own thoughts (Spalletta et al., 2014). While the superior longitudinal fasciculus is associated with cognition in healthy volunteers, it does not seem to be directly linked to cognition in schizophrenia (Buchanan et al., 2005; Caprihan et al., 2015). Overall, deficits in the superior longitudinal fasciculus may be risk markers for schizophrenia.

1.4.3 Forceps Minor

The forceps minor connects the medial and lateral frontal lobes in each hemisphere together by crossing through the genu of the corpus callosum (Krebs, Weinberg, & Akesson, 2012). Lower FA and higher RD in the forceps minor is common in schizophrenia patients, with chronic patients having greater reductions in FA than first-episode psychosis patients (Friedman et al., 2008). These changes in the forceps minor are also correlated with a reduction in sustained

attention (Prasad et al., 2015) and executive functions for people with schizophrenia (Pérez-Iglesias et al., 2010).

1.4.4 Cingulum, Uncinate, & Arcuate Fasciculus

Deficits in shorter intra-hemispheric WM tracts such as the cingulum, uncinate, and arcuate fasciculus, have been implicated in the emergence of auditory hallucinations in schizophrenia (Seok et al., 2007). FA reductions in the uncinate have also been observed in schizophrenia (Hasan et al., 2009) and may be associated with changes in personality traits that occur in schizophrenia. These include elevation in ideas of reference and suspiciousness, reduced affect, reduced extraversion, increases in social anxiety (Hasan et al., 2009), and in one study, increased psychopathy (Nakamura et al., 2005).

Similarly, cingulum FA reductions are associated with increases in delusions of control in schizophrenia (Whitford et al., 2015). This association is hypothesized to be based in the cingulum's connection to the premotor cortex and the anterior portion of the cingulate gyrus, where hippocampal WM projections also reside (Whitford et al., 2015). The cingulum is also associated with the development of cognitive control, executive functions (Peters, Ikuta, et al., 2014), and positive symptom severity in schizophrenia (Whitford et al., 2015).

1.4.5 Fornix

The fornix is the major output tract of the hippocampus, connecting to the hypothalamus, and sends posterior afferent signals to the mamillary bodies and the anterior thalamic nuclei (Krebs et al., 2012). Anterior afferents diverge prior to the anterior commissure and connect to the nucleus accumbens (Cassel et al., 1997). Lower fornix FA values are associated with deficits in recall and recognition visual and verbal memory tests in schizophrenia patients. This suggests that lower FA values in the fornix are indicative of poorer visual and verbal memory

(Fitzsimmons et al., 2009). Disruption to this major output tract of the hippocampus may also play a role in short and long-term memory deficits in schizophrenia (Kelly et al., 2018).

1.4.6 Internal/External Capsules

The internal and external capsules are smaller midbrain WM bundles surrounding the lenticular nuclei (Krebs, 2012). External capsule deficits are associated with the negative symptoms of schizophrenia, i.e., avolition, flat affect, anhedonia, and decreased sociability along with increased severity in motor problems and prominent delusions (Viher et al., 2016)(Arnedo et al., 2015). Reported internal capsule FA reductions in schizophrenia may contribute to observed deficits in working memory in patients (Mamah et al., 2010). Whole capsular body FA reductions are also thought to be associated with lethargy in schizophrenia patients (Kelly et al., 2018).

1.4.7 Sagittal Striatum:

Sagittal stratum reductions in FA and MWF have been previously reported in schizophrenia in the inferior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and association fibers (Vanes et al., 2018). In schizophrenia, increased retention of visual information and attention is associated with greater FA in the fronto-occipital fasciculus, whereas damage to this region has been associated with spatial neglect and reduced attention to visual stimuli (Urbanski et al., 2008). FA in the inferior fronto-occipital fasciculus, which connects prefrontal and thalamic sensorimotor areas to subserve attention and vigilance (Subramaniam et al., 2018), in conjunction with inferior and superior longitudinal fasciculi, is associated with positive symptom severity in drug naïve first episode and chronic schizophrenia (Joo et al., 2018).

1.5 Developmental Trajectory of Myelin

Major epochs of myelination occur in infancy, middle childhood, adolescence, in the 20s-early 30s, and then continues more slowly into a person's mid-40s to early 50s (Yakovlev et al., 1967). Two of these phases, adolescence and the 20s- early 30s, correspond with the most common age of onset for schizophrenia, suggesting that aberrant myelination contributes to the emergence of schizophrenia. Structural MRI has revealed that over the lifespan, WM and myelin in the brain follow an inverted U shaped curve that peaks in the mid-forties in the frontal and temporal lobes (Arshad et al., 2016; G. Bartzokis et al., 2001). There is a region-specific trajectory for myelination and WM tracts that continues throughout childhood, through adolescence, and into adulthood (Karlsgodt et al., 2012). By the age of 10, myelination of the cerebral commissures and thalamic radiation is complete, with associated WM areas completing myelination in the adulthood years (Yakovlev & Lecours, 1967). Prior FA assessments have revealed that the corticospinal tract peaks earliest in the 20s, followed by the corpus callosum and association tracts with the cingulum peaking last in the late twenties through to the early forties in some cases (Peters et al., 2014). In sum, despite early post-mortem work suggesting regions such as the cingulum completed myelination within the first year of life (Lecours, 1967), modern research has confirmed that WM development and myelination continues into the mid-thirties and forties (George Bartzokis et al., 2012; Peters & Karlsgodt, 2015).

1.6 Emotion Deficits in Schizophrenia

1.6.1 History of Emotion Deficits in Schizophrenia

Schizophrenia patients experience flattened or inappropriate emotions, such as high emotional lability with outbursts or unexpected abnormal emotional reactions (Bleuler, 1911; Kraepelin, 1904). Klaus Conrad noted in the early to mid-1900s that people with schizophrenia

and psychoses often experienced a delusional mood episode prior to a psychotic episode (Mishara, 2010). More recent studies have also reported that a period of intense emotions does precede a sharp increase in psychotic episodes in schizophrenia with intense or overwhelming bouts of fear, anger, or happiness being noted (Bowers, 1974; Kavanagh, 1992). Emotional dysfunction in schizophrenia occurs not only in the expression of emotions but also in the ability to accurately recognize them. Impaired recognition of facial emotions in schizophrenia is a robust finding (Chan et al., 2010; Kohler et al., 2010). To date, researchers have focused on the deficits of recognition of universal emotions, including happiness, sadness, fear, disgust, surprise, and anger in schizophrenia (Goghari et al., 2011). Of note, deficits in emotion recognition in schizophrenia also appear to worsen as psychotic symptoms worsen (Won et al., 2019).

Tasks that assess emotion recognition and expression fall into two general categories. Either they focus on identifying a specific emotion that relies more on language and semantic skills or ask volunteers to determine the difference between various levels of expression, which is a judgment regarding emotions. Variables that affect patient performance on these two categories of emotion recognition tasks include a later age of onset for psychosis, increased age at the time of testing in general, treatment with first-generation antipsychotic medications, hospitalization at the time of assessment, and severity of negative and positive symptoms as measured with the Scheduled Assessment of Negative Symptoms and Scheduled Assessment of Positive Symptoms (Kohler et al., 2010). There is also an increase in accuracy for faces that match the cultural background of the person being tested (Kohler et al., 2010). Further, the level of education a patient has does not affect performance on emotion-based tasks (Kohler et al., 2010). As emotion perception and recognition are separate processes from neurocognitive

variables, it is possible to reliably study the hallmark impairment of emotion perception and recognition in schizophrenia and schizophreniform diseases except in cases with markedly severe cognitive deficits (Kohler et al., 2010).

1.6.2 Emotion Brain Network Disruptions in Schizophrenia

In-vivo structural studies have implicated WM deficits as a potential cause of impaired recognition of emotions in schizophrenia. In first-episode schizophrenia patients patient performance on a facial emotion perception task was correlated with reduced FA in the forceps major, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and the splenium of the corpus callosum (Zhao et al., 2017). A longitudinal study on populations at high risk for psychosis found lower FA in people who developed psychosis in the superior longitudinal fasciculus compared to those that did not (Karlsgodt et al., 2009). Additionally, lower FA in inferior longitudinal fasciculus and medial temporal lobe predicted deterioration in social functioning at a 15-month follow up which may be related to the recognition of emotions as well (Karlsgodt et al., 2009). Similarly, in primary progressive aphasia, loss of WM integrity in several regions correlates with emotion detection deficits. The WM areas associated with poor performance on emotion tasks in aphasia are primarily driven by the uncinate fasciculus, while also being associated with the superior longitudinal fasciculus and the inferior longitudinal fasciculus (Multani et al., 2017).

Studies utilizing functional magnetic resonance imaging (fMRI), an MRI protocol uses the hemodynamic response to track brain activity, have provided us with additional information regarding disruptions in emotion processing in schizophrenia. The most recent fMRI evidence of functional connectivity differences in people with schizophrenia comes from a network-based analysis fMRI study that directly examined emotional recognition (Goghari, Sanford, Spilka, &

Woodward, 2017). Compared to healthy volunteers, schizophrenia patients were observed to have hyper-deactivation during an emotion recognition task in the default mode network and increased activity in fear and anger trials, with intact visual attention network activity (Goghari, Sanford, Spilka, & Woodward, 2017). While these studies did not directly look at WM in the brain, one might infer potential WM tracts altered in schizophrenia that result in the impaired processing of facial emotions, such as the cingulum, forceps minor, superior longitudinal fasciculus, external capsule, genu, body, and splenium of the corpus callosum, internal capsule, fornix, tapetum, inferior, superior, and medial longitudinal fasciculi, occipitofrontal fasciculus.

1.7 The Effects of Exercise on White Matter in the Brain

It has been posited that exercise may have a salutary effect on WM deficits in schizophrenia, and could consequently improve symptom severity and cognitive functioning, based on observations from exercise-induced neuroplasticity in Alzheimer's disease and dementia (Perea et al., 2016). Several lines of evidence have emerged from both animal and human studies. Summary findings are presented below.

1.7.1 Animal Models

Exercise is associated with up-regulation of Brain Derived Neurotrophic Factor, decreased myelin-associated glycoprotein expression, and positive modulation of neuronal growth (Feter et al., 2018). In animal studies that look directly at myelination, exercise has been associated with either been increased myelin sheath thickness or increased numbers of myelinated fibers (Ahn et al., 2016). A meta-analysis on animal model studies found that low-intensity treadmill training and passive cycling increased the number of myelinated fibers with the treadmill training also increasing myelinated fiber diameter (Ahn et al., 2016). Endurance training also appears to increase the number of myelinated fibers and increased myelin sheath

thickness (Ahn et al., 2016). Animal work has demonstrated that long term treadmill exercise of four weeks in length restored myelin and microvessel damage after an ischemic stroke in gerbils (Ahn et al., 2016). Based on protein signaling pathways in neurons of animal models, demonstrated that Alpha serine/threonine-protein kinase (Akt) is an enzyme involved in upregulation of myelin that induces myelination in the both the central and peripheral nervous system (Domènech-Estévez et al., 2016; Flores et al., 2008). It is posited that exercise triggers Akt, up-regulation (Zang et al., 2017) and subsequently induces myelination. Additionally, deficits in of Akt it have been associated with smaller hippocampal volumes in schizophrenia (Szamosi et al., 2012). In totality, animal evidence supports the use of exercise as a potential treatment for myelin related disorders.

1.7.2 Human Studies

To examine the effects of exercise on white matter and myelin in humans, both DTI and MWF have been applied in-vivo to estimate measures of WM integrity. In healthy older adults, greater aerobic fitness has been associated with greater WM integrity in the frontal and temporal lobes based on diffusion findings (Voss et al., 2013). Similarly, aerobic fitness in young adults has also been associated with increased MWF in the right parahippocampal cingulum (Bracht et al., 2016). Additionally, in older adults, greater physical activity is negatively associated the DTI measures of MD, RD, AD, but not FA (Gons et al., 2013). In comparison, in schizophrenia patients, two DTI studies have reported that after six months of aerobic exercise, patients had increased FA in the left corticospinal tract, left superior longitudinal fasciculus, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left anterior thalamic radiation, and also the body and splenium of the corpus callosum (Scheewe et al., 2013; Svatkova et al., 2015).

1.7.3 Differences between Sexes in Exercise Interventions in Psychosis Patients

Prior work examining the effects of aerobic exercise in schizophrenia has primarily utilized primary male participants (Pajonk et al., 2010; Scheewe et al., 2013) or have not included MRI measures in their study protocol (Curcic et al., 2017). A systematic review on the effects of exercise in schizophrenia reported that of the total of 48 participants they were able to include there were only 6 women (Vancampfort et al., 2014). This highlights the need for future research to include women with schizophrenia in exercise research trials with MRI outcomes to illuminate potential effectiveness of exercise for females with treatment resistant schizophrenia.

1.7.4 Effects of Exercise on Clinical and Neuropsychological Variables

Aerobic fitness is associated with several improvements across several clinical and neuropsychological variables in schizophrenia. Increased volume of physical exercise may even be potentially protective against developing more severe psychosis (Brokmeier et al., 2019; Noordsy et al., 2018). Assessment of aerobic fitness may be based on a number of different metrics. VO_2max is a standard physiological metric of fitness and refers to maximal oxygen consumption during incremental exercise. It has been associated with increased mean hippocampal volumes with concomitant improvements in short-term memory, working memory PANSS total scores, and decreased severity of depression (Lin et al., 2015; Pajonk et al., 2010). A meta-analysis on the effects of exercise in schizophrenia demonstrated that higher levels of weekly exercise were associated with larger improvements in cognition, working memory, attention, social cognition (Firth et al., 2017). When combined with cognitive remediation therapy, it also reduced the severity of negative symptoms (Firth et al., 2017). A recent review article also stated that aerobic exercise improves cognitive deficits, working memory, and attention in schizophrenia but that the ideal method, type, and intensity of exercise to produce the

greatest effects have yet to be determined (Falkai et al., 2017). Of note, despite the potential clinical benefits of exercise, it is often challenging for a person with schizophrenia to engage in physical activity. Antipsychotic medication side effects, presence of existing cardio-metabolic comorbidity, negative symptoms, and lack of social support are each negatively correlated with physical activity in schizophrenia patients (Vancampfort et al., 2012).

1.8 Assessment Measures

1.8.1 Clinical Symptom Assessments

The measurement of psychiatric symptom severity in schizophrenia requires specialized and validated tools. For this body of work, the PANSS was used. The PANSS is a 30-item scale with a Positive, Negative, and General Psychopathology subscale is validated for evaluating severity of psychosis in chronic schizophrenia (Kay et al., 1988). A trained psychiatrist scores each item on a scale of 1 to 7. A score of 1 indicates absence of the symptom, whereas a score of 7 indicates the most extreme severity of the symptom. Information from a patient's medical chart, family, and hospital staff can also be incorporated into the PANSS. Along with psychosis, schizophrenia patients may also have clinically significant symptoms of anxiety, depression, impaired social and occupational functioning, and extrapyramidal movement disorders (Braga et al., 2013; Kavanagh, 1992; McCreadie et al., 2005; Mier & Kirsch, 2016; Myin-Germeys et al., 2000). Validated scales to measure these impairments in schizophrenia patients are the Hamilton Anxiety Scale (HAM-A), the Calgary Depression Scale (CDS), the SOFAS, and the Extrapyramidal Symptoms, Rating Scale (Addington et al., 1993; Chouinard & Margolese, 2005; Hamilton, 1959; Rybarczyk, 2011). The HAM-A is a fourteen-item questionnaire that assesses the severity of a variety of anxiety symptoms on a scale of zero to four while the CDS is a short nine-item scale with ratings for each question, ranging from zero to four (Addington et al., 1993;

Hamilton, 1959). The SOFAS is a 100-point scale with clear delineation for every ten points. A score of sixty or more indicates moderate social and occupational difficulties, while a score of forty or less indicates severe impairment in social and occupational domains (Rybarczyk, 2011). The presence and severity of extrapyramidal symptoms were assessed with the Extrapyramidal Symptoms Rating Scale (ESRS). This scale also has subscales for akathisia, parkinsonism, tardive dyskinesia, and dystonia (Chouinard & Margolese, 2005).

1.8.2 Neurocognitive Assessments

1.8.2.1 Cognitive Abilities

Aspects of cognitive ability, such as intelligence quotient (IQ), have been found to positively correlated with WM microstructure FA outcomes (Holleran et al., 2020). Additionally, positive relationships between myelin integrity and education, cognition, and IQ have been observed in healthy volunteers, but are attenuated or undetected in schizophrenia (Flynn et al 2003, Lang et al 2014). In healthy volunteers, MWF is positively correlated with age, years of education, and IQ, in frontal WM, the anterior and posterior internal capsules, and the genu and splenium of the corpus callosum. In contrast, these relationships are absent in chronic and early schizophrenia (Flynn et al., 2003, Lang et al., 2014), save for the splenium (Lang et al., 2014). These findings suggest that myelin abnormalities in schizophrenia are associated with multiple domains of low functioning in schizophrenia patients.

IQ can be determined using neurocognitive tests such as the Kaufman Brief Intelligence Test (KBIT) (Kaufman, 1990). The KBIT has three components: verbal IQ, a non-verbal IQ, and combined IQ. Another such measure of IQ is the full-scale Weschler Test of Adult Reading (WTAR) which is validated to measured pre-morbid IQ for people with schizophrenia (Dykiert & Drery, 2013). It consists of fifty words irregularly spelled words in English. The participant

receives a point for each irregularly spelled word that they can read correctly and can make up to twelve errors before reaching the ceiling of the test for that participant.

1.8.2.2 Memory

Memory performance has been positive correlated with FA measurements of WM in schizophrenia (Hanlon et al., 2012). The Hopkins Verbal Learning Test-Revised (HVLT-R) assesses verbal memory and learning performance and has alternative test versions to follow-up minimized practice effects (Belkonen, 2011). This assessment consists of three twelve-item word lists composed of four words each from three semantic categories and has been previously used to measure memory performance in schizophrenia patients (Zhou et al., 2012). Schizophrenia patients may also have problems with verbal fluency assessment that can be assessed with the Control Oral Word Association Test (COWA) (Spreen & Strauss, 1998). In the COWA, participants must name as many words as they can within a given time limit using pre-determined categories. This particular test has evaluated in schizophrenia and found to positive correlated with greater connectivity between brain regions in an fMRI task (Lynall et al., 2010). Verbal working memory was evaluated with the Digit Span subtest from the Weschler memory scale (Wilde et al., 2004). This task requires participants to listen to a list of numbers and then repeat them back to the assessor in three different trials and has been successfully used to assess working memory in schizophrenia patients. The Digit Span Test has been found to be negatively correlated to hospitalization rates in schizophrenia patients (Chen et al., 2018). Visual memory is also impaired in schizophrenia, particularly in chronic cases (Silverstein et al., 1998), and can be measured with the Modified Taylor Complex figure (MTCF) and has multiple versions to prevent practice effects (Casarotti et al., 2014). Additionally, a newer computerized working memory and manipulation (MnM) task is also able to assess visual working memory in people

with schizophrenia. This particular task allows the differentiation between the ability to hold information and to hold & manipulate it (Cassetta & Goghari, 2016) which may or may not be equally impaired in schizophrenia patients.

1.8.2.3 Processing Speed and Attention

Speed of processing (a measure of cognitive agility) and attentional capacity are both associated with reductions in FA based WM integrity in schizophrenia and may be amenable to improvements with exercise (Firth et al., 2017; Zeng et al., 2016). These are assessable using the Symbol Digit Modalities Test (SDMT) (Smith, 1995) along with the Trails A and Trails B tasks (Reitan, 1958). Both SDMT and Trails A/B tasks are standardized, highly validated tests that have been widely used across populations including schizophrenia patients. In schizophrenia, better performance on SDMT and Trails tests have been positively correlated with FA measures of WM (Lee et al., 2011; Subramaniam et al., 2018; Tombaugh, 2004).

1.8.3 Emotion Assessments

A number of studies have examined the impaired emotion recognition in schizophrenia using FA (Zhao et al., 2017) and fMRI (Goghari et al., 2017; Spilka & Goghari, 2017), but none have used MWF in their studies. Specifically, the aforementioned studies found reduced WM connectivity in schizophrenia, either with FA or fMRI-based network connectivity, and was concomitantly correlated with decreased performance in emotion processing tasks.

1.8.3.1 Emotion Recognition Task

One way to measure the processing of emotions is through a computerized task that requires participants to discriminate between of four facial emotions (anger, fear, happy, sad) and a trial based on age discrimination (e.g. “Is this person over 30? or under 30?”), to check for non-emotion processing deficits. In these ‘emotion recognition’ style tasks each trial block has two

options, a target (e.g., happy) and non-target (not happy) that participants can choose from to determine how accurate and quickly people can recognize facial emotions. Many of these tasks use faces with no background or contextual information from the Pennsylvania faces database as it consists of male and female facial images from various cultural backgrounds, and ages ranging from ten to eighty-five (Gur et al., 2002). This particular approach has been used successfully in fMRI research studies (Goghari et al., 2017; Spilka & Goghari, 2017).

1.8.3.2 Emotional Expression Task

Another way to test emotion processing in humans is to vary the amount of emotion a face is expressing. These 'emotion expression' measures a person's ability to identify the various facial emotions, of different cultural background and sexes, at different levels of expression, ranging from 10% to 100% of the emotion. Prior research examining abnormal facial emotion recognition has demonstrated this type of task is able to measure both accuracy and reaction time for the processing facial emotions in schizophrenia patients (Bediou et al., 2005) and healthy volunteers (Diaz, Wong, Hodgins, Chiu, & Goghari, 2016).

1.9 Overview and Research Goals

This thesis is an examination of how exercise affects WM pathways in the brain and the recognition of facial emotions with additional analyses of clinical symptoms and neuropsychological outcomes in treatment-resistant schizophrenia. Current evidence suggests that WM deficits are a core feature of schizophrenia. The efficacy of exercise to induce WM plasticity in schizophrenia has been demonstrated in non-treatment resistant populations over a six-month period (Scheewe et al., 2013; Svatkova et al., 2015; Vancampfort et al., 2012), but whether or not it is feasible in a treatment resistant population over a shorter time period has not been examined. For treatment-resistant patients that are at increased cardiometabolic risk due to

atypical antipsychotic treatments like clozapine, the utility of exercise as a potentially safe and clinically beneficial intervention is of great interest. This study was designed to extend the findings of Pajonk et al. in 2010 where they utilized a 12-week exercise intervention, consisting of 3 30-minute sessions per week, to increase hippocampal volume size in schizophrenia patients (Pajonk et al., 2010).

The second chapter examines the effects of exercise on the myelin, measured with MWF, and WM integrity, measured with FA, in the genu, body, and splenium of the corpus callosum, superior longitudinal fasciculus, sagittal stratum, forceps minor, forceps, major, and the external capsule, along with changes in symptom severity for the patient group and physical outcome measures such as Body Mass Index (BMI), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and others. To date, few studies have examined the effects of exercise on WM in treatment-resistant schizophrenia. Prior studies on the effects of exercise on grey matter regions, such as the hippocampus, have established positive results from exercise as an adjunct treatment in schizophrenia (Woodward et al., 2018). Given the established deficits in WM integrity in treatment-resistant schizophrenia, it is expected that the patient group will have lower MWF and DTI based values in all regions of interest (ROIs) compared to healthy volunteers at baseline.

The third chapter examines the effects of exercise on the accuracy and reaction time of facial emotion recognition in treatment-resistant schizophrenia along with neurocognitive test outcomes. It will also examine potential correlations between task performance in the facial emotion recognition and expression tasks with MWF and FA in in the genu, body, and splenium of the corpus callosum, superior longitudinal fasciculus, sagittal stratum, forceps minor, forceps, major, and the external capsule.

1.9.1 Specific Aims and Hypotheses

This thesis seeks to address the following aims:

Aim 1: Assess the effects of exercise on the genu, body, splenium of the corpus callosum, external capsule, sagittal stratum, superior longitudinal fasciculus, forceps minor, and forceps major in treatment-resistant psychosis patients.

- **Primary Hypothesis:** At baseline, healthy volunteers will have greater MWF and FA scores in fronto-temporal WM ROIs compared to treatment resistant schizophrenia patients.
- **Secondary Hypothesis 1**: Exercise will be associated with increased MWF and FA in WM pathways in fronto-temporal regions.
- **Secondary Hypothesis 2 (Exploratory)**: Psychosis symptom severity will be inversely associated with WM integrity, as measured by MWF and FA.
- **Exploratory Analyses**
    - A) Relationships between psychosis and clinical measures with RD, AD, and MD
    - B). Potential differences between healthy volunteers and patients in RD, AD, and MD
    - C) Changes in RD, AD, and MD after 12-weeks of exercise
    - D) Relationships between VO_2max and MWF, FA, RD, AD, and MD

Aim 2: Probe the effects of exercise on facial emotion recognition in treatment-resistant psychosis patients.

- **Primary Hypothesis**: treatment resistant schizophrenia patients will have deficits in accuracy and reaction time for facial emotion recognition compared to healthy volunteers at baseline.

- **Secondary Hypothesis:** Schizophrenia patients will have improvements in accuracy and reaction time for facial emotion recognitions after completing a 12-week trial of exercise.
- **Exploratory Hypotheses:**
    - A) Improvements in facial emotional recognition will be related to increased WM integrity as measured by MWF and FA.
    - B) Improvements in facial emotional recognition will be positively associated with improvements in working memory and processing speed.
    - C) Improvements in the cognitive domains of executive functions, speed of processing, and working memory will be related to increased WM integrity as measured by MWF and FA.
- **Exploratory Analyses**
    - A) Relationships between MWF, FA, RD, MD, AD and domain level cognitive measures will be explored with linear models.

Chapter 2: White Matter Neuroimaging Before and After an Exercise Intervention in Treatment-Resistant Schizophrenia

2.1 White Matter Imaging before and after a 12-week Exercise Intervention in Treatment-Resistant Schizophrenia

A pre-/post exercise trial was conducted to examine the effects of exercise on WM, symptom severity, and cognition in a cohort of treatment-resistant schizophrenia patients. As stated, an increase in physical activity and fitness may help mitigate the increased cardiometabolic risk, provide increased neurocognitive abilities, and increase the integrity of the compromised fronto-temporal WM networks in treatment-resistant schizophrenia. Corollary data from healthy volunteers matched on age, sex, and education were also obtained.

The primary hypothesis was that at baseline, healthy volunteers will have greater MWF and FA scores in fronto-temporal WM ROIs compared to treatment resistant schizophrenia patients. Additional secondary exploratory hypotheses were that 1) the exercise intervention would result in a significant increase in WM integrity in the genu, body, splenium of the corpus callosum, external capsule, sagittal stratum, superior longitudinal fasciculus, forceps minor, and forceps major; and 2) that this increase in WM integrity would be associated with a reduction in clinical symptoms in the patient group. Exploratory analyses with RD, AD, and MD and psychosis, differences between healthy volunteers and patients, changes over the exercise intervention, and with VO_2max are also explored. See figure 2.1 for a visualization of the ROIs and figure 2.2 for a visualization of the MWF, FA, MD, RD, and AD images obtained during this study.

Figure 2-1 Visualization of white matter regions examined for MWF and DTI based analyses

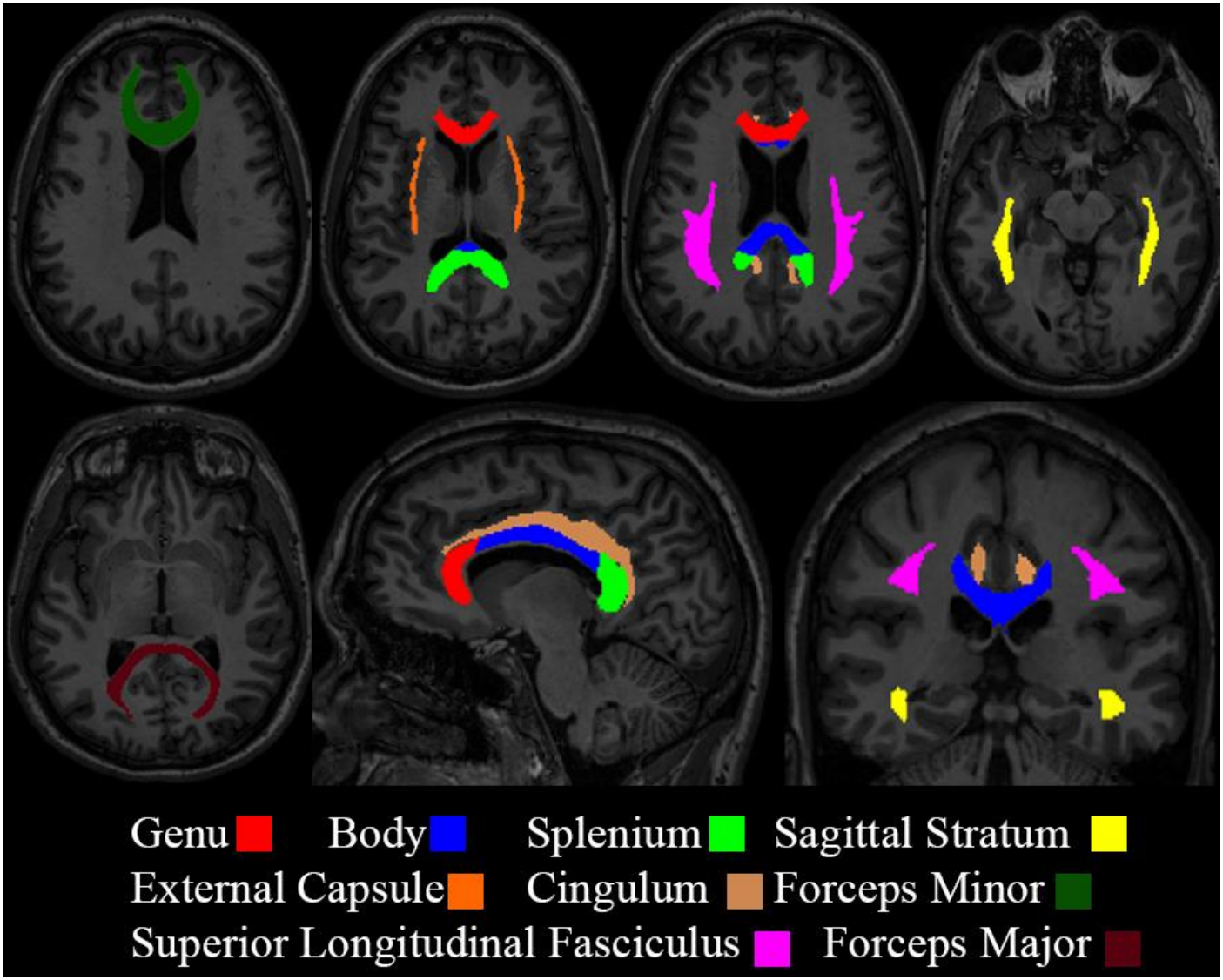
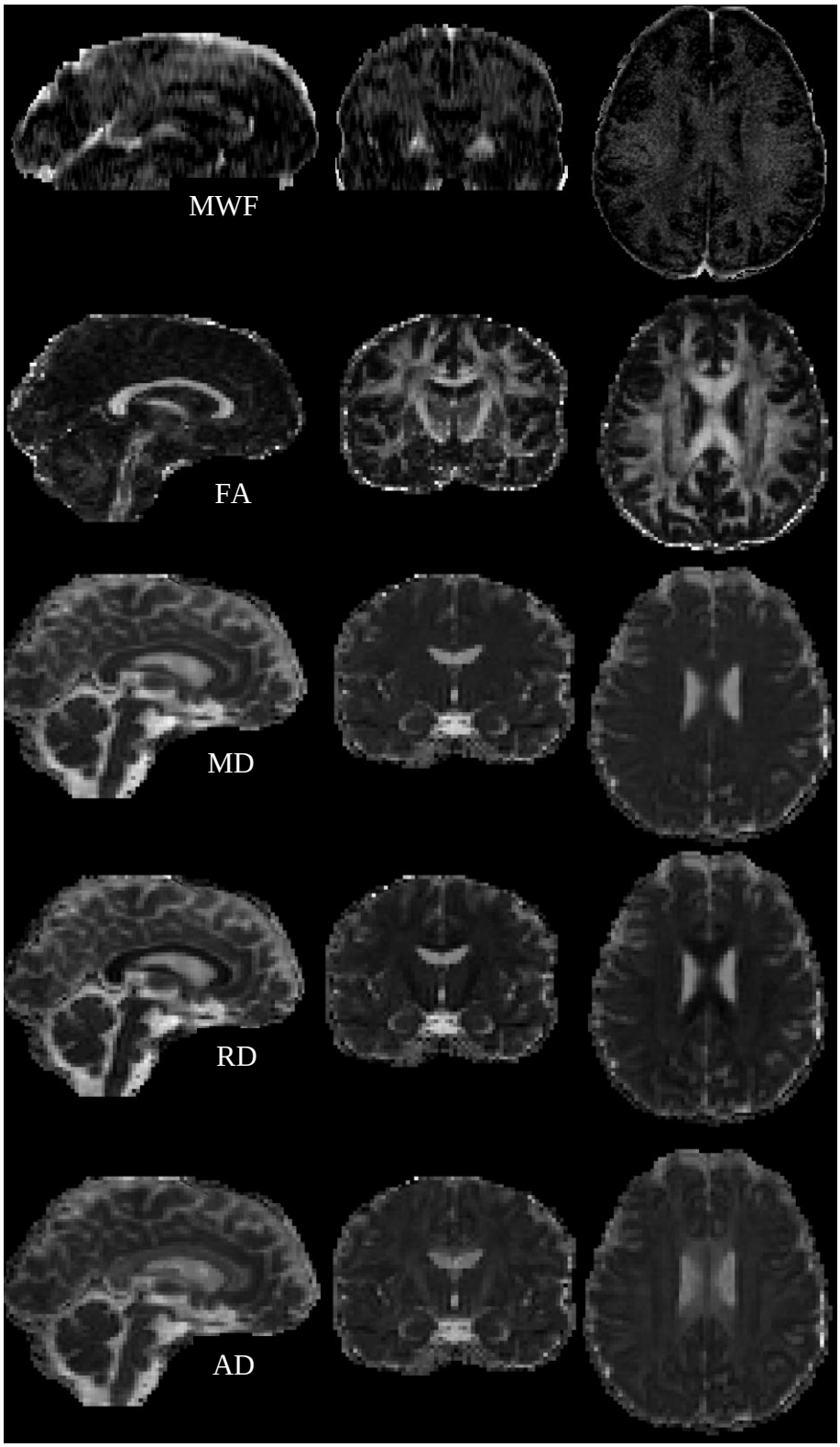


Figure 2-2 Visualization of MRI data obtained for the study using FSLeyes (from top to bottom) for MWF, FA, MD, RD, AD - Brighter pixels represent a stronger signal for that specific imaging.



2.2 Methods

We undertook a longitudinal study examining the effects of physical exercise on WM plasticity using either weight-bearing or aerobic exercise. Assessment of neurocognitive, clinical, physical, and neuroimaging (i.e., MRI) measures occurred at baseline and after completing the 12 weeks of exercise. In-vivo MRI assessment of the following ROIs were acquired: genu, body, and splenium of the corpus callosum, external capsule, sagittal stratum, superior longitudinal fasciculus, forceps minor, and forceps major. Qualified and trained clinicians completed all assessments of clinical psychiatric symptoms. Qualified Kinesiology trainees who were overseen by their supervisor (DEW) collected all exercise data. A fully qualified cardiovascular kinesiologist (DEW) completed the preliminary physiological data analysis. Ten male and 5 female DSM-IV schizophrenia/schizoaffective patients were included in the WM analysis. Patients had been diagnosed for a minimum of two years before entering the study. All patients received pharmacological treatment during the study. Antipsychotic medication dosages were converted to chlorpromazine equivalents to allow for quantitative comparisons (Prochyshyn, Bezchlibnyk-Butler, & Jeffries, 2015). Six males and four female healthy volunteers, matched to patients on age, sex, and level of education, were recruited as a comparison group.

2.2.1 Participants

The Clinical Research Ethics Board at the University of British Columbia provided ethical approval for the study in compliance with Canada Tri-council policies. Patient recruitment consisted of 27 (age range 19-50) treatment-resistant schizophrenia patients into the study from the British Columbia Psychosis Program at the University of British Columbia Hospital. Twelve had a diagnosis of schizophrenia, while fifteen had a diagnosis of schizoaffective disorder. Of the twenty-seven total patients recruited, twenty-four had usable

MRI scans at baseline, and fifteen participants completed the exercise program along with having MRI data of sufficient quality for analysis. Participants in the patient group were lost for the following reasons: discharged from the British Columbia Psychosis Program (n=6), unable to leave the ward due to increased symptom severity (n=3), excessive movement during either the baseline or post-intervention MRI WM related sequences resulting in unusable scan data (n=2), participants unable to exercise due to contraindications (recent surgery, or metal implant) uncovered during prescreening (n=1). All patients had been in treatment for psychosis for at least thirty-six months before the baseline assessment and beginning of the exercise intervention. Prescribed antipsychotic medications included: Clozapine (n=7), Olanzapine (n=2), Aripiprazole (n=1), Quetiapine (n=1), Olanzapine + Haloperidol (n=1), Olanzapine + Paliperidone (n=1), Flupentixol + Quetiapine (n=1), Clozapine, Paliperidone, and Quetiapine (n=1). Recruitment of healthy volunteer participants was from the community at large, using online advertisements on Craigslist and Twitter with an age range of 16 to 50 years. Sex of patients in the study was 40% female (n = 6) and 60% male (n = 9). Matching of healthy volunteers to patients, who had completed the study protocol and had usable WM MRI data at both time points, occurred using the variables of age, sex, and level of education. In total, ten healthy volunteers were recruited to the study maximizing the financial resources available. Sex of healthy volunteers was 40% female (n = 40), male 60% (n=6) matching the sex ratio in the patient group. All ten healthy participants were able to complete the exercise intervention and had good quality MRI data scans, with only one participant requiring a re-scan of a single MRI sequence due to motion during the Gradient and Spin echo (GRASE) sequence. The criteria for exclusion from the study were similar for both groups. Exclusionary criteria included any history of angina, cardiac arrest, transient ischemia, non-independent mobility or limb prostheses, neurological disorder, head

injury leading to a loss of consciousness of five minutes or greater, developmental disorders, any history of DSM diagnoses of mood, anxiety, or substance disorder in the past twelve months (tobacco excluded), IQ < 85, or if a person was currently engaging in any type of regular or semi-regular exercise regime.

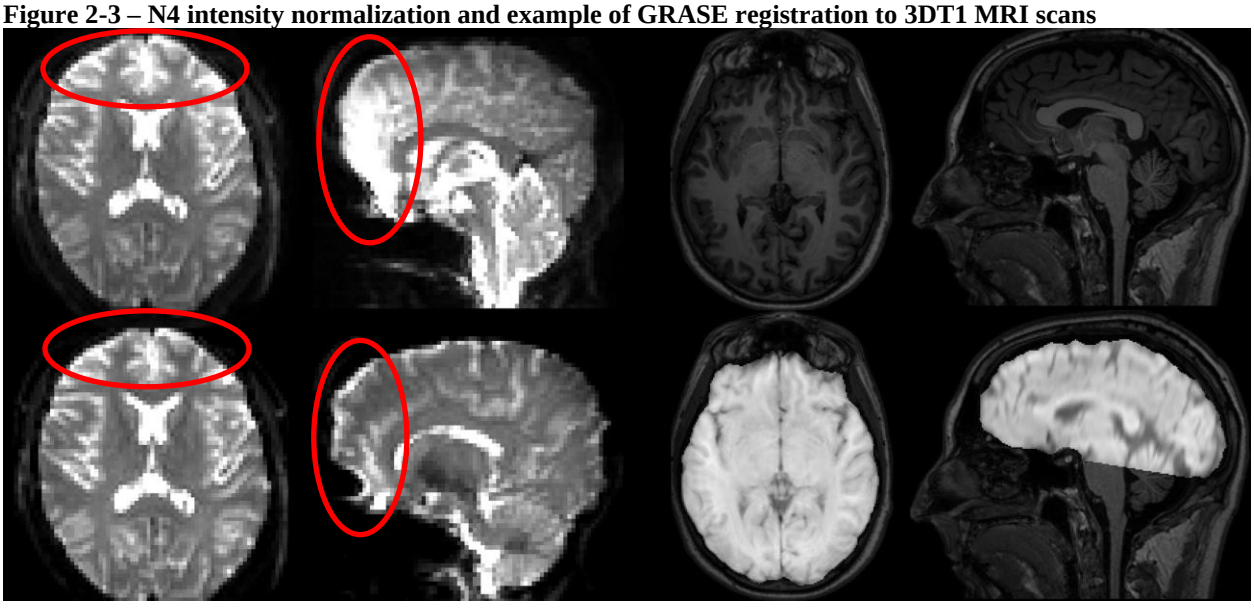
2.2.2 Neuroimaging

Acquisition of MRI scans was performed on a Philips Achieva 3.0 Tesla (3T) scanner with an 8-channel head coil utilizing software version 3.2.3.1. Isotropic 3-dimensional T_1-weighted images (3DT1) in the sagittal plane, TR/TE = 6.6/3.0 ms, field of view (FOV) = 240 x 240 x 155 mm^3, acquisition matrix = 240 x 240, recon matrix = 240 x 240, recon voxel size = 1 x 1 x 1 mm^3, slice thickness = 1 mm, 155 slices interleaved with no gap, sensitivity encoding factor (SENSE) = 1, b-factor = 700, flip angle = 8, scan time = 9:52.6 min:sec). Computation of MWF values used GRASE T_2 weighted images with the following parameters: TR/TE 1000/10 ms, FOV = 230 x 100 x 190 mm^3, acquisition matrix = 232 x 232, 32-echo, 40 slices, water fat shift 2.865 [pixels], scan time = 14:22.0 min:sec. High angular resolution diffusion images (HARDI) acquired used 61 gradient directions, b=700 s/mm^2 TR/TE = 6120/60 ms, voxel size = 2.3x2.3x2.3 mm^3 FOV 256 x 256 x 138 mm^3, acquisition matrix 112 x 108, EPI factor = 55, flip angle = 90°, scan time 6:25.6 min:sec. Additional collection of clinical T2-weighted fluid-attenuated inversion recovery images for clinical evaluation by a qualified neuroradiologist (ATV) for potential unknown brain injury or congenital dysmorphology and clinically significant incidental findings such as a tumor or hemorrhage. The clinical FLAIR images uncovered no incidental findings, resulting in no need to exclude any participant for this potential reason.

Post-acquisition processing of the MRI images for WM analysis used ANTs, FMRIB Software Library (FSL), matrix laboratory (MATLAB), and dcm2niix software packages. For

the 3DT1 MRI scan sequences, ANTs was used to normalize the intensity using an N4 bias correction, extract brain masks, and segmented the brain. N4 bias correction was chosen over N3 occurred as N4 provided increased accuracy and reliability in the data and helped ensure the inclusion of all appropriate voxels for analysis (Tustison et al., 2010). The software package dcm2niix was used to convert the .par and .rec MRI image files to .nii files for post-processing in ANTs and FSL. GRASE MRI sequences used ANTs to normalize the intensity of the images, and extract region of interest (ROI) values (Tustison et al., 2010, 2014). ANTs was also used to register the GRASE sequences to the 3DT1 scan utilizing a SyN model (Tustison et al., 2014). FSL was used to replicate T1 weight in the GRASE images, apply ROIs to GRASE sequence data, and warp a 3DT1-based mask to the GRASE data to increase mask accuracy (see figure 2.3). Extraction of MWF values from the processed GRASE sequence MRI data using custom in house MATLAB code with ROI locations based on the John Hopkins University (JHU) WM atlas (Mori et al., 2008).

Figure 2-3 – N4 intensity normalization and example of GRASE registration to 3DT1 MRI scans



Left four images: before(left) and after(right) N4 intensity normalization of DTI data.
Right four images 3DT1 scan images with GRASE data overlayed the lower two images

N4 bias field correction using ANTs for the DTI data used the b0 image as reference for the extraction of DTI brain masks. Motion correction used FSL MCFLIRT (Motion Correction FMRIB's Linear Image Registration Tool) (Jenkinson, Bannister, Brady, & Smith, 2002). This method uses spline interpolation to correct for motion in images on the order of a single voxel. DTI metrics of FA and MD were calculated with FSL's DTIFIT with AD and RD maps calculated using fslmaths (Jenkinson et al., 2012). Manual verification of all DTI masks used FSL-view with adjustments to DTI masks made on an as-needed basis.

Verification of ROI registration was done manually for each participant, at both time points, using the genu, body, and splenium of the corpus callosum and the longitudinal fasciculus as reference ROIs. After manual JHU WM atlas fit checks, two participants required minor ROI correction due to over-inclusion.

2.2.3 Clinical Assessments

In the patient group, assessment of clinical psychiatric symptom severity occurred at baseline and post 12-weeks of exercise. The severity of schizophrenia symptoms assessment utilized the PANSS, anxiety with the HAM-A, and depressive symptoms with the CDS. These scales are specific and validated to accurately measure the positive, negative, anxiety, and depressive symptoms in patients with psychosis (Addington et al., 1990: Hamilton, 1959, Kay et al., 1988). The presence and severity of extrapyramidal symptoms assessment used the ESRS (Chouinard & Margolese, 2005). Social functioning was assessed with the SOFAS (Rybarczyk, 2011).

Patient and healthy volunteer participants had cardiovascular fitness assessed using VO_2max at baseline and week 12. It is a measurement of the maximum rate of oxygen consumption during exercise that increases the intensity and is a metric of cardiovascular fitness.

Calculation of VO_2max requires monitoring the volume of oxygen consumed during maximal effort exercise by trained personnel. The protocol involves using an exercise bike hooked up to a metabolic cart with a mask covering the airways of each participant to measure O_2 output while monitoring resting heart rate and resting blood pressure. Lipid assessment (HDL, LDL), and triglyceride levels occurred with blood work done at the UBC Hospital Pathology laboratory. Measurements of the participant's weight and height allowed for the calculation of BMI.

All participants in the study completed twelve weeks of exercise consisting of three exercise sessions per week. Sessions consisted of 30 minutes of monitored exercise followed by a 10-minute cool-down stretch period. Randomization to either an aerobic or weight-bearing condition occurred using a random number generator for the schizophrenia participants. All healthy volunteers engaged in the same exercise condition that their matched patient participant did. Participants in the aerobic condition (Patients, n=8, Healthy Volunteers, n=5) completed a supervised program using either a treadmill, elliptical trainer, or cycle ergometry. Participants in the weight-bearing condition (Patients, n=7, Healthy Volunteers, n=5) performed supervised weight-bearing exercises. Exercises were either upper or lower body exercises for each session. Balancing of upper and lower body exercise sessions ensured equal use of that all major upper and lower body muscles over the intervention. All participant's heart rates maintained a rate between 40%-59% of their baseline heart rate reserve to ensure a moderate level of effort during exercises. Confirmation of moderate effort used a qualitative perceived effort rating on a 10-point scale given by each participant in 3- or 5-minute time intervals depending on the condition (weight-bearing = 3-minute intervals; aerobic = 5-minute intervals). Exercise progression was based on changes in heart rate of approximately 5% per week, with the heart rate reserve being calculated upon the clinical Karvonen formula (Karvonen & Vuorimaa, 1988). Qualified

exercise physiologists monitored the progress of all participants during every session for the duration of the study to ensure 1) safety, proper progressive levels of intensity, 2) maintenance of effort at moderate levels of 40-59% of baseline heart rate, and 3) that participant's perceived effort levels stayed in a moderate zone.

Table 2-1 Participant demographics and clinical measures summary at baseline

Variable	Patients (N = 15)		Healthy Volunteers (N = 10)	
Sex (% F)	M 9 / 6 F (40%)		M 6 / 4 F (40%)	
Handedness (%L)	12 R / 3 L (20%)		9 R / 1 L (10%)	
Diagnosis (Schizophrenia/Schizoaffective)	6 Schizophrenia 9 Schizoaffective		-	
	Mean	SD	Mean	SD
Age	31.09	6.8	29.7	9.32
Years of Education	11.40	0.51	12.70	1.25
Duration of Illness (years)	9.94	6.01	-	-
Antipsychotic Dose CPZ Equivalents: mg/day)	677.47	351.5	-	-
Total PANSS Score	93.73	12.10	-	-
Social/Occupational Functioning Scale	32.87	4.16	-	-
Calgary Depression Scale	5.933	4.30	-	-
Hamilton Anxiety Scale	10.53	7.68	-	-
Extrapyramidal Symptoms Rating Scale	28.27	13.67	-	-
Resting Heart Rate (RHR)*	91.2	15.76	72.27	15.38
Resting Blood Pressure (systolic)	116.4	14.53	115.79	9.0
Resting Blood Pressure (diastolic)	77.06	10.64	76.96	7.43
Body Mass Index (BMI)*	28.49	5.58	21.9	3.48
Cholesterol (mmol/L)	4.23	0.77	4.43	0.48
Triglycerides (mmol/L)*	2.03	1.769	0.81	0.27
High-density lipoprotein (HDL)	1.2	0.64	1.6	0.36
Low-density lipoprotein (LDL)	2.23	0.91	2.46	0.47
V02max (mL/kg min)*	20.79	11.52	42.61	12.01
* **significantly different between groups at baseline**				

2.2.4 Statistical Analysis

Baseline comparisons between groups were done with welch t-tests, bivariate correlations, and multivariate general linear models. The welch t-test was selected as it is superior to the student t-test in several ways. First, it allows for unequal variances between groups and performs identically to the student t-test when variances are equal. Second, when compared against first conducting Levene's test followed by a student or welch t-test, a welch t-test prevents the type 1 error rate from increasing. Third, a welch t test offers more accurate results with small samples sizes and or unequal group sizes (Zimmerman, 2004). The adjustment for the standard deviation in welch's t-test results in non-integer degrees of freedom. Given the well-established literature on WM deficits in schizophrenia, and previously established reduced WM volumes and integrity in treatment-resistant schizophrenia, baseline comparisons between groups in MWF, FA, MD, and RD were one-tailed Welch t-tests. Presently, AD findings in schizophrenia are not conclusive enough to warrant a 1-sided t-test. Subsequently, the analyses done for this study were two-sided welch t-tests. MWF and DTI were co-registered to 3DT1 images to ensure accuracy of anatomic ROIs. Preliminary comparison of individual ROI MWF values did not reveal side to side differences, aside from the external capsule, which in our cohort were larger on the left in both the patient and healthy volunteers. Subsequently, left and right values were averaged to increase power. Associations between ROIs and emotional and cognitive tasks were explored with bi-variate correlations. The type of exercise, weight-bearing or aerobic, was not entered as a covariate as it did not exert significant effects on any measures of interest. Longitudinal within group analyses were conducted with paired t-tests to compare the mean differences in variables examined from the start to the end of the exercise intervention. The rates of change for measures of interest in each group over time were examined using regression

model interactions (timepoint*Group). A significant interaction in timepoint*Group for a variable indicates that the slope of the regression line is different for each group. If found, it shows that the groups changed at different rates over the intervention. Effect sizes reported include Hedges' g (Ellis, 2010) for baseline between group comparison, to control for unequal group size differences. Cohen's d was used for within group baseline to week 12 comparisons and Pearson r for the relationship between two continuous variables (Cohen, 1988). Effect sizes for Hedges' g and Cohen's d are interpreted as follows: small effect (0.2 – 0.49), intermediate effect (0.5 – 0.79), large effect (0.8 - >1.0) (Cohen, 1988). Effect sizes for Pearson 'r' values are interpreted as follows: small (0.1 – 0.29), medium (0.3 – 0.49), large (0.5 – 1.0) (Cohen, 1988). Use of Hedges' g for between group comparisons and Cohen's d for repeated measures effect sizes was done in accordance with recommended guidelines from statistical literature (Ellis, 2010; Fritz et al., 2012; Morris, 2008; Sexton et al., 2016; Vacha-Haase & Thompson, 2004).

The False Discovery Rate (FDR) using the Benjamini-Hochberg method (Benjamini & Hochberg, 1995) was used to correction for multiple comparisons. FDR represents the probability that a null hypothesis is true if the null hypothesis is rejected (Benjamini & Hochberg, 1995). FDR offers several advantages over the well-known Bonferroni correction for multiple comparisons. First, Bonferroni corrects for a study-wide error rate and not at an individual test level. It examines two populations are the same on all variables and does not offer insight into which, or how many variables, differ between groups despite Bonferroni correction commonly being used in this manner (Perneger, 1998). Second, the multiple comparison correction done by the Bonferroni test is dependent on the number of tests completed, whereas FDR scales with the number of tests done. Also, Bonferroni correction does not control false discovery rates, but rather only limits false positives. By using FDR to correct for multiple

comparisons, we also increase our power to detect significant findings. When it is set at 0.05, FDR tells us that a variable which remains significant after FDR correction is only a false discovery 5% of the time (Glickman et al., 2014).

2.3 Results at Baseline

2.3.1 Demographic Variables at Baseline

There were no significant differences between patient and healthy volunteer groups in age, years of education, or handedness. Years of education did approach significance ($t(15.28) = 0.40$, $p = 0.069$), but exploratory analyses did not reveal any effect on measures of interest when years of education were included in models for clinical and cognitive variables. Subsequently, years of education is not included as a covariate in the analyses. Exercise type, either weight-bearing or aerobic, was not associated with age, sex, or years of education for the patients nor the healthy volunteers.

2.3.2 Physical Health Measures at Baseline

Welch t-test baseline between-group comparisons of BMI, cholesterol, triglycerides, HDL, LDL, resting heart rate, systolic blood pressure, diastolic blood pressure, and VO_2max revealed only a few differences. The patient group had significantly higher BMI ($t(22.95) = 3.58$, $p < 0.01$; $g = 1.29$), triglycerides ($t(13.83) = 2.53$, $p = 0.02$; $g = 0.86$) and resting heart rate ($t(19.79) = 2.98$, $p = 0.007$; $g = 1.17$) than the healthy volunteer group. The patient group VO_2max measurement was significantly lower at baseline compared to the healthy volunteer group ($t(18.86) = -4.52$, $p < 0.01$; $g = 4.01$). No significant differences between groups at baseline occurred in the HDL, LDL, Cholesterol, systolic blood pressure, or diastolic blood pressure variables. Exercise type was not significantly associated with any variables, and analysis of physical health variables is across both exercise types (all p-values > 0.05). The 15

participants in the patient group had total exercise adherence rates of 83.2% (±8.3, range 66.67%-97.2%). Healthy volunteers had an exercise adherence rate of 100%.

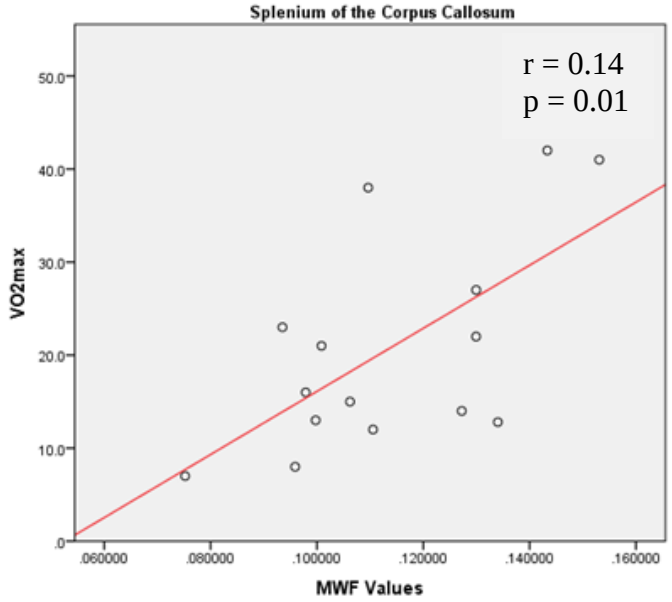
2.3.2.1 VO_2max Exploratory Findings with White Matter ROIs

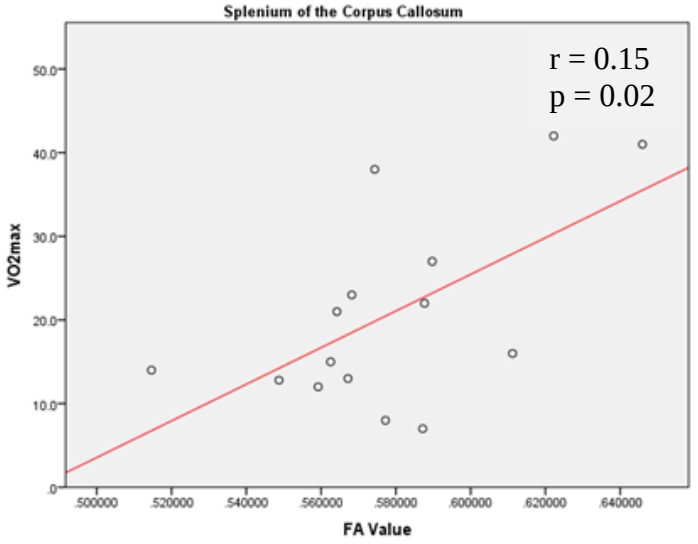
In the patient group at baseline VO_2max was positively associated with MWF values in the genu (t (15) = 0.615, p = 0.01, r = 0.14), splenium (t (15) = 0.632, p = 0.01; r = 0.16), Bilateral cingulum (t (15) = 0.543, p = 0.04; r = 0.14), bilateral superior longitudinal fasciculus (t (15) = 0.621, p = 0.01; r = 0.16), and the forceps minor (t (15) = 0.601, p = 0.02; r = 0.15) (see figures 2.3 and 2.4). There were no correlations between MWF values and VO_2max in the healthy volunteer group at baseline.

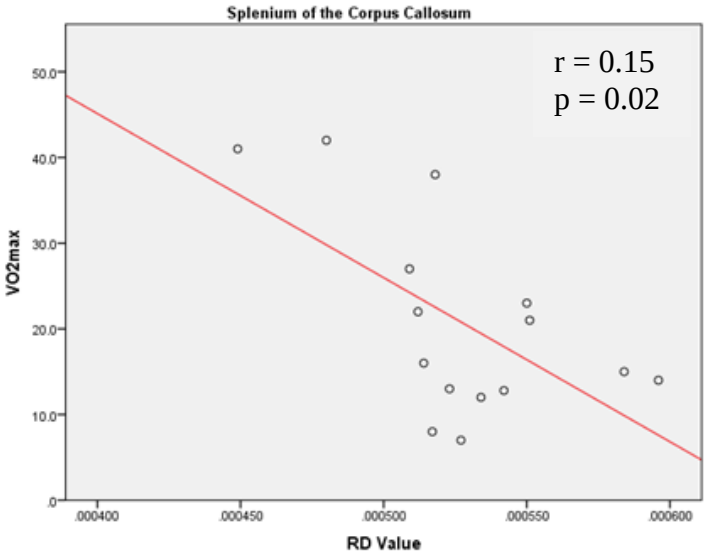
At baseline, FA and VO_2max were positively correlated in the splenium (t (15) = 0.598, p = 0.02; r = 0.15) and bilateral sagittal stratum (t (15) = 0.533, p = 0.02; r = 0.14) for the patient group. (see figures 2.4 and 2.5). The healthy volunteer group had no significant correlations between FA and VO_2max at baseline.

RD baseline correlations in patients revealed a negative correlation between VO_2ma_x and RD in the splenium (t (15) = -0.606, p = 0.02; r = 0.15) (see figure 2.4). There were no significant correlations between VO_2max and AD or MD ROIs in patients at baseline. Healthy volunteers had no significant baseline correlations between VO_2max and RD or MD. Healthy volunteers did have a positive correlation between VO_2max and AD in the splenium (t (10) = 0.718, p = 0.02; r = 0.22) at baseline.

Figure 2-4 Patient relationships between VO_2max and MWF & FA ROIs - 1







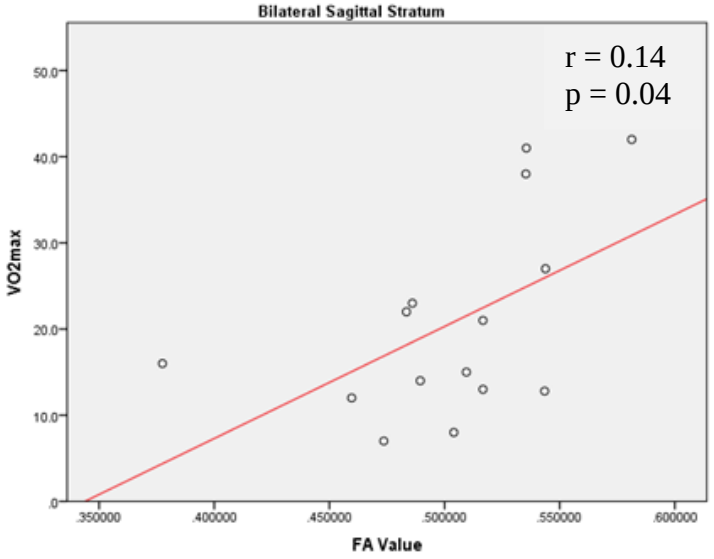
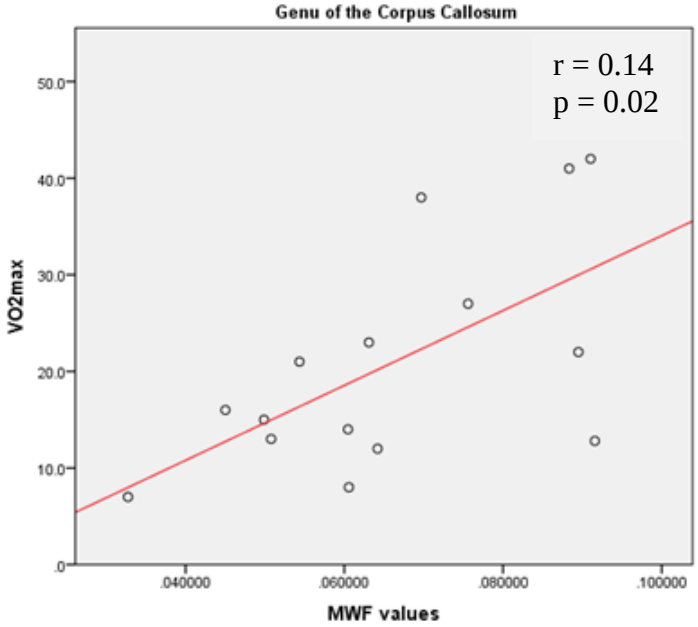
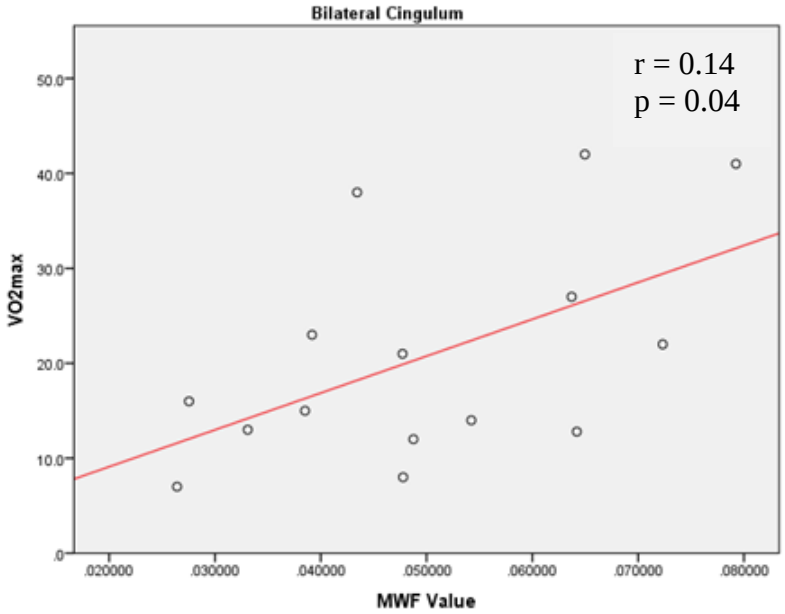
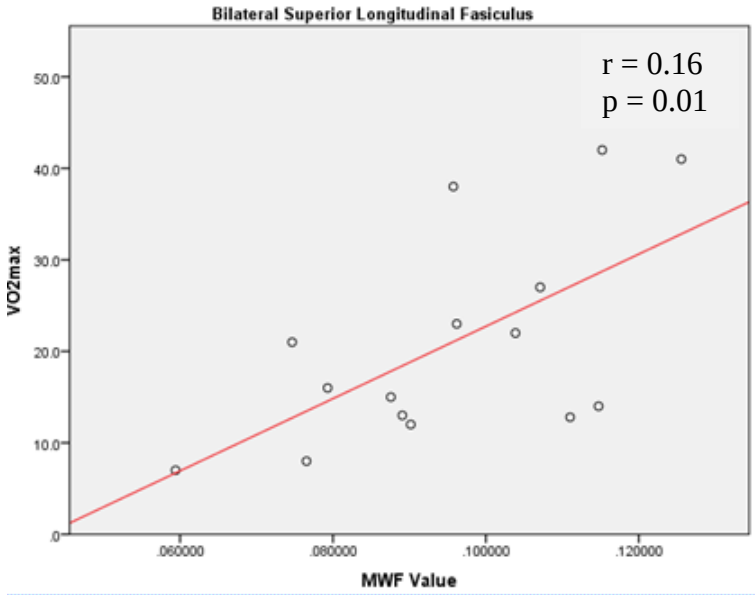
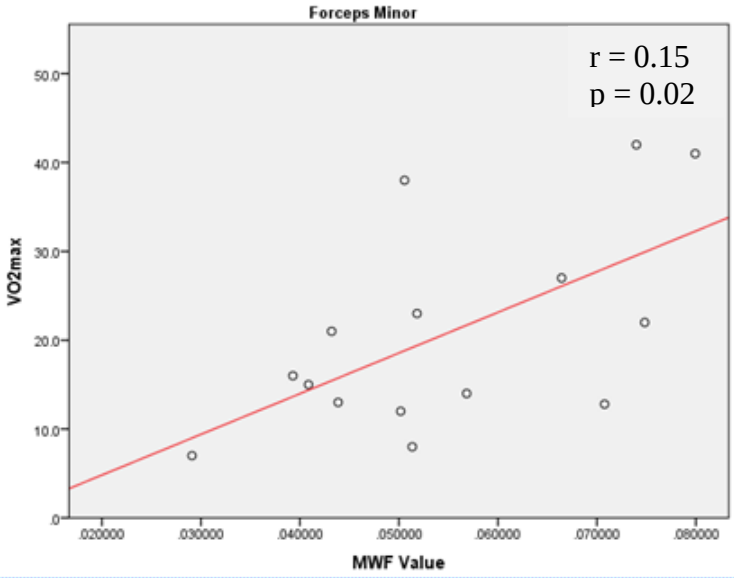


Figure 2-5 Patient relationships between VO_2max and MWF ROIs - 2









2.3.3 Baseline Clinical Measures Findings

Patient's scores on the PANSS, SOFAS, CDS, and HAM-A did not differ between the aerobic and weight-bearing exercise groups (p-values all > 0.2). There was no association between PANSS scores and any of the MWF or DTI based measures at baseline.

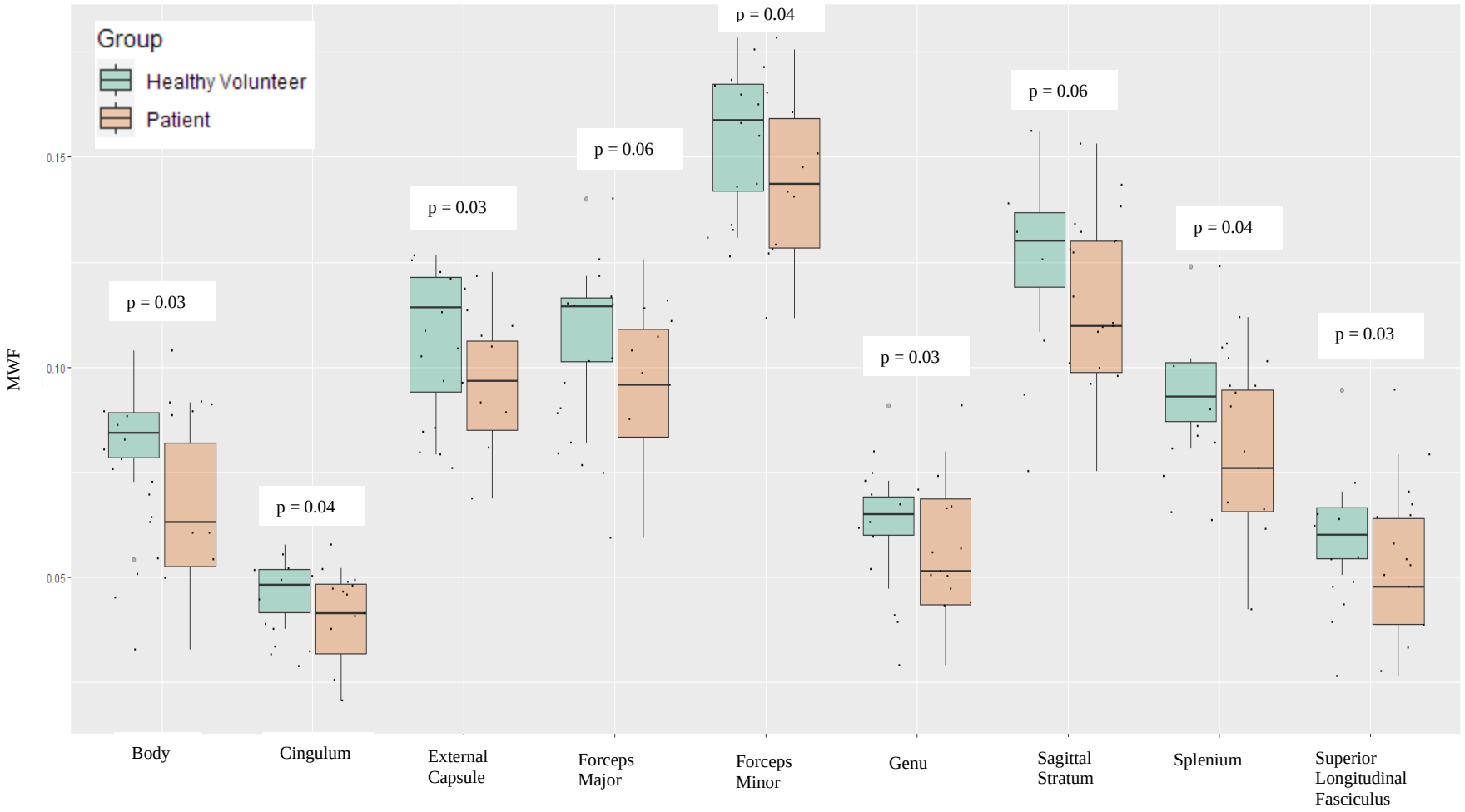
2.3.4 Myelin Water Fraction baseline comparison between patients and healthy volunteers

MWF indices in several ROIs were significantly lower in patients compared to healthy volunteers at baseline. Welch's one-sided t tests revealed that the genu ($t(22.78) = -2.69$, $p < 0.01$; $g = -1.03$), the callosal body ($t(22.99) = -2.51$, $p < 0.01$; $g = -0.98$), and splenium ($t(22.97) = -2.05$, $p = 0.02$; $g = -0.78$) were significantly lower in the patients at baseline. Additionally, MWF was lower in patients in the bilateral external capsules ($t(22.88) = -2.27$, $p = 0.01$; $g = -0.86$), bilateral cingulum ($t(22.07) = -2.19$, $p = 0.02$), bilateral superior longitudinal fasciculus ($t(21.29) = -2.29$, $p = 0.01$; $g = -0.91$), and forceps minor ($t(22.46) = -1.98$, $p = 0.03$; $g = -0.76$) compared to healthy volunteers at baseline. These results survived FDR correction for multiple comparisons. There was a non-significant trend in patients for lower MWF scores in bilateral sagittal stratum ($t(16.74) = -1.62$, $p = 0.06$; $g = -0.69$) and the forceps major ($t(21.48) = -1.70$, $p = 0.051$; $g = -0.67$) (see table 2.2 and figure 2.6).

Table 2-2 Summary MWF ROI differences between groups at baseline

MWF ROI	MWF Mean – Patients	MWF Mean – Healthy Volunteers	% difference between group mean scores	DF	t	p-value	FDR p-value	Hedges' g
Genu of the corpus callosum	0.066	0.083	11.44%	22.78	-2.69	< 0.01	**0.03**	-1.03
Body of the corpus callosum	0.079	0.095	9.21%	22.99	-2.51	< 0.01	**0.03**	-0.94
Splenium of the corpus callosum	0.114	0.129	6.10%	22.97	-2.05	0.03	**0.04**	-0.78
Bilateral Sagittal Stratum	0.097	0.108	5.59%	16.74	-1.62	0.06	0.06	-0.69
Bilateral External Capsule	0.039	0.047	9.01%	22.88	-2.27	0.02	**0.03**	-0.86
Bilateral Cingulum	0.050	0.063	11.32%	22.07	-2.19	0.02	**0.03**	-0.86
Bilateral Superior Longitudinal Fasciculus	0.095	0.111	7.58%	21.28	-2.29	0.02	**0.03**	-0.91
Forceps Minor	.055	0.065	8.80%	22.46	-1.98	0.03	**0.04**	-0.76
Forceps Major	.144	0.156	3.96%	21.48	-1.70	0.05	0.06	-0.67
Results in blue remained significant after FDR correction for multiple comparisons								

Figure 2-6 MWF values of patients and healthy volunteers at baseline with FDR corrected p-values



2.3.5 Summary Diffusion Tensor Imaging Findings Between Groups at Baseline

One-sided Welch t-tests revealed that patients had significantly lower FA than in healthy volunteers in the genu ($t(22.73) = -3.36$, $p < 0.01$; $g = -1.29$), and the callosal body ($t(20.97) = -2.39$, $p = 0.01$; $g = -0.95$). The patients also had significantly lower FA than healthy volunteers in the bilateral sagittal stratum ($t(22.69) = -2.136$, $p = 0.02$; $g = -0.82$), bilateral external capsule ($t(19.61) = -3.00$, $p < 0.01$; $g = -1.05$), forceps minor ($t(22.61) = -3.19$, $p < 0.01$; $g = -1.23$), and the forceps major ($t(17.61) = -2.32$, $p = 0.02$; $g = -0.97$). After FDR correction only the findings for the genu and forceps minor remained significant, while the body, external capsule, and forceps minor strongly trended towards significance. No baseline differences in FA were seen between patients and healthy volunteers in the splenium, bilateral cingulum, and superior longitudinal fasciculus. See figure 2.7 for visualized FDR corrected results.

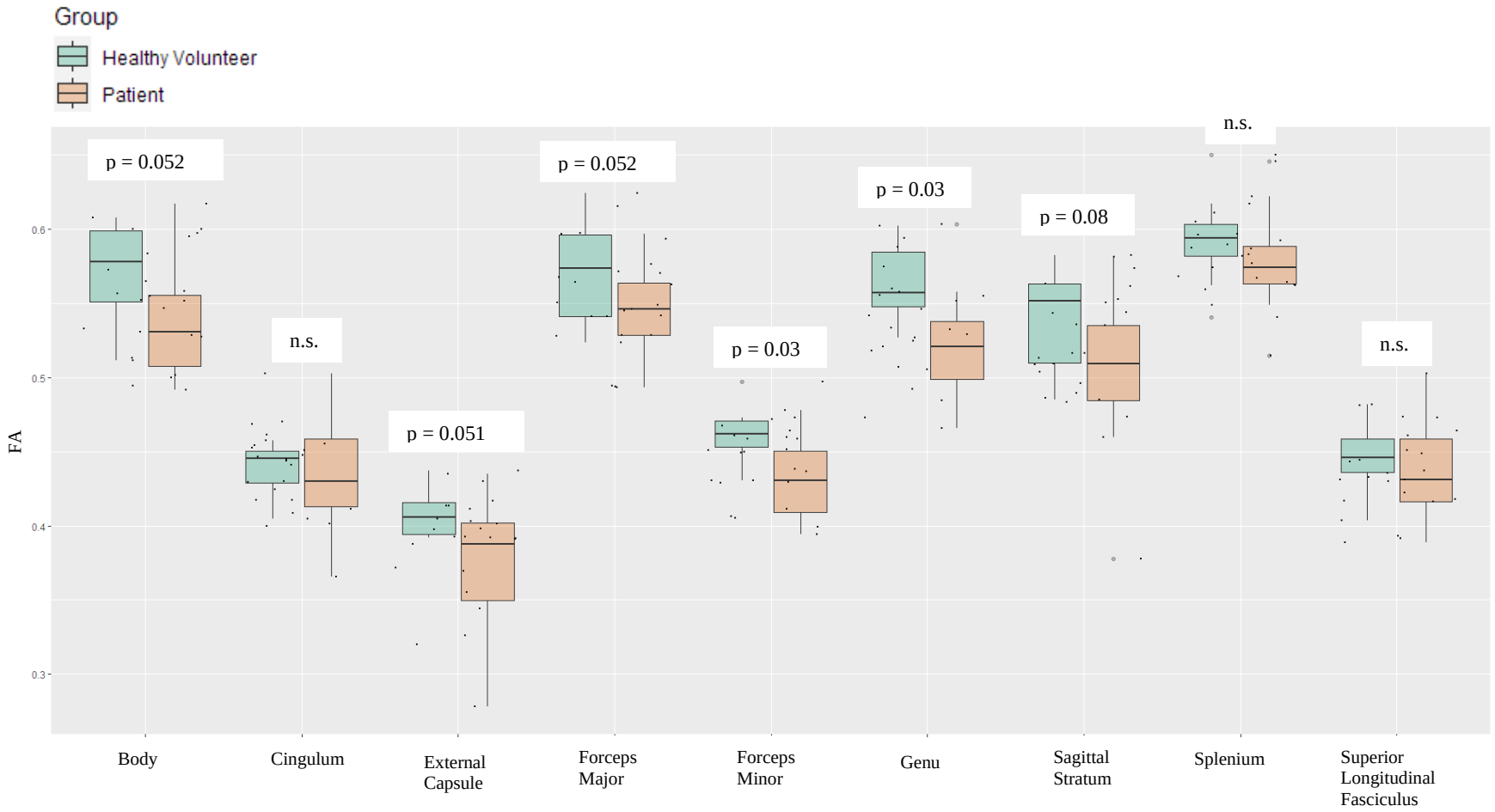
One-sided welch t-tests were used to analyze RD. At baseline the patient group had significantly high RD than the healthy volunteers in the genu ($t(22.63) = 3.80$, $p < 0.01$; $g = 1.39$), body ($t(22.99) = 3.44$, $p < 0.01$; $g = 1.29$), bilateral external capsule ($t(22.5) = 2.36$, $p = 0.01$; $g = 0.86$), forceps minor ($t(22.95) = 3.69$, $p < 0.01$; $g = 1.4$). These results remained significant after FDR correction. Additionally, there was a trend for greater bilateral sagittal stratum RD in patients compared to healthy volunteers ($t(18.72) = 1.65$, $p = 0.06$; $g = 0.57$). At baseline, patients' RD was not different in the splenium, bilateral cingulum, bilateral longitudinal fasciculus, and forceps major compared to the healthy volunteers.

At baseline, two-sided welch t-tests revealed that AD between groups was significantly different in the bilateral superior longitudinal fasciculus ($t = (20.11) = -2.77$, $p = 0.01$; $g = -0.98$) and the forceps major ($t(18.49) = -2.26$, $p = 0.03$; $g = -0.94$) while the bilateral external capsule approached significance ($t(21.08) = -2.06$, $p = 0.052$; $g = -0.73$). The genu, body, and splenium

of the corpus callosum, bilateral sagittal stratum, bilateral cingulum, and forceps minor did not differ significantly between groups at baseline. None of the significant findings for AD survived FDR correction for multiple comparisons.

At baseline, the MD for the patient group was significantly greater than the healthy volunteers in the genu ($t(21.06) = 3.58$, $p < 0.01$; $g = 1.28$) and body ($t(20.3) = 3.21$, $p < 0.01$; $g = 1.13$) of the corpus callosum, the bilateral superior longitudinal fasciculus ($t(22.49) = 2.27$, $p = 0.01$; $g = 0.83$), and forceps minor ($t(22.92) = 3.43$, $p < 0.01$; $g = 1.31$). All four of the significant differences at baseline in MD survived FDR correction for multiple comparisons. ROIs not significantly greater at baseline in MD in the patient group compared to the healthy volunteer group were the splenium of the corpus callosum, bilateral sagittal stratum, bilateral external capsule, bilateral cingulum, and forceps major.

Figure 2-7 Patient and healthy volunteers FA values at baseline with FDR corrected p-values



2.4 Post-exercise Intervention Findings

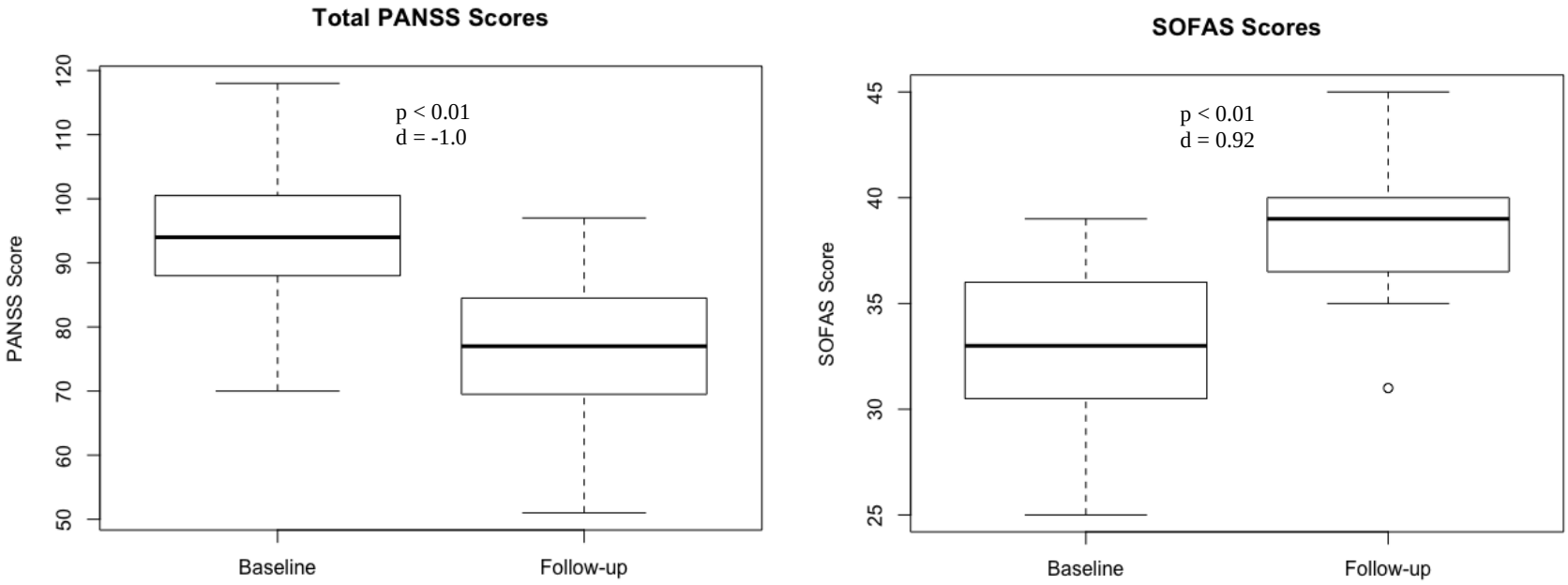
2.4.1 Clinical Variables at Follow-up

After 12 weeks of moderate-intensity exercise, the schizophrenia group did not have a statistically significant reduction in total antipsychotic dose, CDS, or HAM-A scores. The PANSS scores did show a significant decrease ($t(14) = 6.00$, $p < 0.01$; $d = -1.00$) along with a significant improvement in SOFAS scores ($t(14) = -4.65$, $p < 0.01$; $d = 0.92$) (see figure 2.8). These both remained significant after FDR correction.

2.4.2 Physical Health Measures at Follow-up

A non-significant trend for reduction was seen in patient's BMI ($t(12) = 1.98$, $p = 0.07$; $d = -0.13$). Cholesterol, triglycerides, resting heart rate, systolic blood pressure, diastolic blood pressure, and VO_2max were unchanged after exercise for patients (all p-values > 0.05). Similarly, BMI, cholesterol, triglycerides, HDL, LDL, resting heart rate, systolic blood pressure, diastolic blood pressure, and VO_2max were unchanged after exercise in healthy volunteers (all p-values > 0.05). The two groups did have significantly different rates of change in VO_2max over the intervention that did not survive FDR correction. In this case, the healthy volunteers improved and patients declined slightly with uncorrected results as ($F(1,24) = 4.5$, $p = 0.04$, $d = -0.5$).

Figure 2-8 Total PANSS scores and SOFAS from baseline to week 12 (note: these assessments are patient group only)



A decrease in PANSS scores represents a decrease in symptom severity. An increase in SOFAS indicates improved ability for a patient to successfully function in social and occupational situations.

2.4.3 MWF ROIs: Baseline to Follow-up Comparisons for Each Group

There were no statistically significant changes in MWF ROI scores between baseline and week 12 for the patient group or the healthy volunteers, as measured with paired t-tests (all p-values > 0.05). Time x ROI linear regression models did not reveal differences in the rate of change between groups for any of the MWF ROI scores between groups.

2.4.4 DTI ROIs: Baseline to Follow-up Comparisons for Each Group

Paired Student t-tests did not reveal changes in FA, RD, AD, and MD after exercise in our ROIs (all p-values > 0.05). A rate of change analysis for FA, RD, AD, and MD for each group found no significant differences between groups (p-value > 0.05).

2.5 Discussion

Over the various MRI measures examined, the patient group was significantly different from the healthy volunteers at baseline and follow-up in the genu, body, splenium, forceps minor, forceps major, and bilaterally in the external capsule, superior longitudinal fasciculus, sagittal stratum, and the cingulum. There were no significant changes in MWF, or DTI based measures of WM following twelve weeks of exercise. Nor were any associations between PANSS scores and the WM regions examined. This finding contrasts with other studies that have exercise interventions positively influence WM in schizophrenia (Scheewe et al., 2013; Svatkova et al., 2015). These studies demonstrated FA based changes in outpatient schizophrenia patients using aerobic exercise interventions with larger samples and also durations of at least six months (Scheewe et al., 2013; Svatkova et al., 2015). Also, of note are the differing results between MWF and DTI based MRI measures. While there are many regions in common that are significantly different between the groups, it is not a perfect overlap. This is likely due to DTI output measures being putative measures encompassing all WM components as opposed to

directly measuring of myelin with MWF imaging. This highlights the need for researchers not to rely solely on DTI based metrics for WM based disorders and include MWF imaging to determine which results are due to myelin and which are not and may be attributable to the neurite or another factor impacting WM tissue.

At baseline, healthy volunteers had lower rest heart rates than patients, lower BMI, lower triglycerides, and higher VO_2max scores than patients. At follow up resting heart rate, BMI, and VO_2max remained significantly different between groups. Surprisingly at follow-up, despite no significant changes over time or in the rates of change over time, triglycerides were no longer significantly different between groups. This finding was driven by a decrease in triglycerides for patients and an increase in healthy volunteers with smaller standard deviations. As all participants were fasting for a minimum of 12 hours prior to bloodwork it may be that diet will need to be controlled in the future to ascertain the effects of exercise on this health measure. Additionally, healthy volunteers had lower levels of cholesterol and LDL than the patient group at follow up. In clinical measures, patients saw a significant decrease in their overall PANSS score and increased their SOFAS scores. This decrease in symptoms and increase in social functioning suggest that exercise in addition to treatment as usual may help alleviate symptoms in a treatment-resistant schizophrenia population and is in line with previous research (Brokmeier et al., 2019).

2.5.1 Limitations

The study is limited by the number of participants that we were able to enroll in and the length of the study. With 15 patients and 10 healthy volunteers, only extremely large effects are detectable. It is also possible that the patients and healthy volunteers who enrolled in the exercise intervention resulted in a sampling bias for people who are pre-disposed or self-motivated to

exercise and not representative of their respective populations in general. Studies that have demonstrated FA based changes in schizophrenia that occur in exercise interventions had much larger samples and durations of at least six months (Scheewe et al., 2013; Svatkova et al., 2015). It may be that 12 weeks of exercise may not be sufficient to result in measurable changes in MWF or DTI based measures at 3T in a small sample size. A T3 field strength is also not able to measure cell proliferation or expression of myelin related markers as prior animal models have shown that exercise can restore myelin and also protect myelinated fibers (Ahn et al., 2016; Xiao et al., 2018). Thus, if changes did occur in myelin related markers or myelin cell proliferation, we may have unable to measure them.

2.5.2 Conclusion

The data in this study suggests that 12 weeks of moderate-intensity exercise did not induce measurable changes in MWF or DTI based measures in a treatment-resistant schizophrenia population. Despite this, the patients enrolled in our study benefited as shown by the significantly reduced symptoms scores (PANSS) and increased social functioning (SOFAS). Future studies should examine moderate exercise in this population with a larger sample size and different types of exercise intensity. Given the small sample and the brevity of the exercise intervention, subtle changes in our outcome measures may have been missed. A larger sample would enable the ability to detect small and medium-sized associations between WM regions and clinical symptoms. Utilizing high-intensity exercise over a duration of six months or more would also increase the ability to detect changes over time in WM that may result from sustained exercise.

Chapter 3: Emotional processing & Cognitive functioning in Schizophrenia Before and After a 12-week Exercise Intervention

3.1 Brief Introduction

A pre-/post exercise trial was conducted to examine the effects of exercise on emotional processing and cognitive functioning in a cohort of treatment resistant schizophrenia patients. As previously stated, an increase in physical activity and fitness may help induce changes that result in increased myelination of the compromised fronto-temporal WM networks in treatment resistant schizophrenia. Corollary data from healthy volunteers matched on age, sex and education were also obtained.

Prior research has suggested a number of WM tracts that may be associated with executive functions, speed of processing, and verbal working memory. Executive function has been thought of being primarily a function of the frontal lobes however they have been demonstrated to be associated with a wide range of WM regions including the cingulum, inferior fronto-occipital fasciculus, callosal WM, forceps minor, and forceps major (Alloza et al., 2016; Johnson et al., 2017; Martínez et al., 2017; Metzler-Baddeley et al., 2014; Peters, Voineskos, et al., 2014; Stoica et al., 2019). Similarly, studies examining speed of processing have found a white number of WM tracts that are associated with this cognitive domain include the forceps major, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, external capsule, and superior longitudinal fasciculus, and corpus callosum (Salami et al., 2018; Samara et al., 2019; Wang et al., 2020; Watson et al., 2018). Working memory has previously been associated with the corpus callosum, inferior fronto-occipital fasciculus, inferior longitudinal fasciculus, superior longitudinal fasciculus, cingulum, and uncinate fasciculus in regions that overlap with the

external capsule (Bettcher et al., 2016; Charlton et al., 2010; Chung et al., 2018; Karlsgodt et al., 2008; Leonard et al., 2013; C. R. McDonald et al., 2014; Ohoshi et al., 2019; Østby et al., 2011; Strangman et al., 2012).

We hypothesized that 1) schizophrenia patients would have deficits in accuracy and reaction time for facial emotion recognition compared to healthy volunteers at baseline and 2) this exercise intervention will result in improved accuracy and decreased reaction time in emotional processing tasks for schizophrenia patients. Exploratory data analyses were examined to investigate if 1) relationships between improvements in facial recognition and WM, as measured by MWF and FA exist, 2) improvements in facial recognition would be positively associated with working memory and processing speed, 3) improvements in executive functions, speed of processing, and working memory would be related to increased WM integrity as measured by MWF and FA, and 4) potential relationships between MWF, FA, RF, MD, and AD with domain level cognitive measures would exist.

3.2 Methods

Two computerized tasks collected accuracy and reaction time in emotion processing for every participant in each trial. The specifics of how accuracy and reaction were computed and analyzed are different for each test. Each emotional processing test sub-section contains the specific details of the analysis for that test. Trained neuropsychology graduate students obtained the neurocognitive measures. Analysis of neurocognitive tests with respect to WM ROIs were based on z-score transformations of neurocognitive variables (based on the mean and standard deviation of the healthy volunteer group for all participants).

3.2.1 Emotion Recognition Task

Completed at baseline and week 12, this task tests the ability of people to accurately recognize emotions expressed by people. It also differentiates how emotional processing of faces is different from non-emotion-based processing of faces with an age recognition condition. Participants must decide if each face was expressing the emotion/age for that block of trials. Each emotion, along with the age recognition condition, is evaluated separately in a block of trials. For each block of trials there is only one emotion/age given as the reference for that block (e.g., is this expression happy? yes or no) and once a block of trials is completed that emotion is not evaluated again. The age recognition trial is completed in the same manner. These methods are based on prior research using the same type of emotional recognition task (Spilka & Goghari, 2017).

3.2.2 Emotional Expression Task

The Emotional Expression task accurately measures participant's ability identify the various emotions being expressed by the faces in the trial (Diaz et al., 2016) and was completed at baseline and week 12. Participants briefly saw a face and then had unlimited time to choose from five options: anger, fear, happy, sad, or disgust and decide what emotion the face expressed. This is in contrast to the Emotional Recognition task, as it does not provide a reference emotion to compare the face against, requiring participants to decide from a number of possible emotions instead of just one.

3.2.3 Cognitive Testing Measures

Participants underwent cognitive testing at baseline and week 12. General order of tests was the same for all participants. All patients completed the study protocol prior to healthy volunteer recruitment. For tests with multiple versions, the order in which each version was

administered was tracked, and balanced, for the patient group. Healthy volunteers completed tests with multiple versions in the same order as the patient they were matched to completed them. Each participant had their baseline IQ established with the KBIT (Kaufman, 1990). The full-scale WTAR measured pre-morbid IQ. The WTAR is a validated measure of crystalized IQ, knowledge from past learning and experience, for people with schizophrenia (Dykiert & Drery, 2013). The HVLT-R assessed verbal memory performance (Belkonen, 2011). The MTCF assessed long-term visual memory. This test was used to prevent practice effects that can occur with the Rey-Osterrieth complex figure task (Casarotti et al., 2014). Participant's sustained attention was tested with the SDMT (Smith, 1995) and speed of processing, oculomotor scanning/psychomotor speed, was evaluated with Trails A and Trails B tasks (Reitan, 1958). Verbal fluency was assessed with the COWA (Spreen & Strauss, 1998) and verbal working memory evaluated with the Digit Span subtest from the Weschler memory scale (Wilde et al., 2004). A computerized MnM task was also conducted to assess the difference between the ability to hold information and to hold & manipulate it (Cassetta & Goghari, 2016). It provides further insight and depth of information regarding the working memory performance of people with treatment resistant schizophrenia in addition to the in-person neurocognitive testing conducted.

Analysis of three cognitive domains was done for baseline and follow-up measures, particularly, speed of processing, executive functions, and verbal working memory. Speed of processing combined the Trails A and SDMT test. Executive functions utilized the immediate trial of the MTCF, COWA, and Trails B. Verbal working memory combined the 1st trial of the HVLT, digit span, and the COWA. Creation of these domain variables required transforming

each test into z-scores using the mean and standard deviation of the healthy volunteer group at baseline and then averaging by the number of tests included in each specific domain.

3.2.4 Participants

The Clinical Research Ethics Board at the University of British Columbia provided ethical approval for the study in compliance with Canada Tri-council policies. A total of 27 (age range 19-50) treatment resistant schizophrenia patients from the British Columbia Psychosis Program at the University of British Columbia Hospital. Twelve had a diagnosis of schizophrenia while fifteen had a diagnosis of schizoaffective disorder. Of the twenty-seven total patients recruited only fifteen were both able to complete the exercise program and had MRI data of sufficient quality for analysis. Participants in the patient group, were lost for the following reasons: discharged from the British Columbia Psychosis Program (n=6), unable to leave the ward due to increases in symptom severity (n=3), excessive movement during either the baseline or post intervention MRI WM related sequences resulting in unusable scan data (n=2), participants unable to exercise due to contraindications (recent surgery, or metal implant) uncovered during prescreening (n=1). All patients had been in treatment for psychosis for at least thirty-six months before the baseline assessment and beginning of the exercise intervention. Prescribed antipsychotic medications included: Clozapine (n=7), Olanzapine (n=2), Aripiprazole (n=1), Quetiapine (n=1), Olanzapine + Haloperidol (n=1), Olanzapine + Paliperidone (n=1), Flupentixol + Quetiapine (n=1), Clozapine, Paliperidone, and Quetiapine (n=1). Neurocognitive tests had missing results in Trails B baseline (n=2), Trails B follow up (n=2), Trails A week 1 (n=1), HVLT Delay follow up (n=2), HVLT retention follow-up (n=2), HVLT recognition (n=2), SDMT baseline (n=1), and MTCF delay (n=1). From the fifteen patient participants (n=2) had no Emotional Recognition, Emotional Expression, or MnM data, (n=1) had no week 12 data, and

(n=5) did not have MnM data. Total participants in the patient group vary from task to task depending on the available data. As a result, each task will state the number of patient participants. Healthy volunteer recruitments came from the community at large using online advertisements and aged from 16 to 50 years of age. Matching of healthy volunteers to patients occurred using the variables of usable WM data, age, sex, and level of education. All healthy participants (n=10) were able to complete the exercise intervention, complete the Emotion Expression, Emotion Recognition, MnM task, and had good quality MRI data scans, with only one participant requiring a re-scan of a single MRI sequence due to motion during the GRASE sequence. The number of healthy volunteer participants is 10 for all tasks and measures except for missing data in the following neurocognitive tests: Trails A baseline (n=2), Trails B baseline (n=1), and SDMT oral follow-up (n=1). The criteria for exclusion from the study were similar for both groups. Exclusionary criteria included any history of angina, cardiac arrest, transient ischemia, non-independent mobility or limb prostheses, neurological disorder, head injury leading to a loss of consciousness of five minutes or greater, developmental disorders, any history of DSM diagnoses of mood, anxiety, or substance disorder in the past twelve months (tobacco excluded), IQ < 85, or if a person was currently engaging in any type of regular or semi-regular exercise regime.

3.2.5 Statistical Analyses

Baseline comparisons between groups included welch t-tests, bi-variate correlations, and multivariate general linear models. Longitudinal analyses of variables were conducted with paired t-tests and repeated-measures general linear models. Linear analyses of rate of change over time (timepoint*Group) for each variable of interest for both groups were performed. Analyses of the Emotion Recognition and Emotional Expression tasks was conducted on

multiple levels. Flowchart diagrams stating the multiple levels of analysis are found in figures 3.1 & 3.2. Missing neurocognitive data was imputed using the multiple imputation function in the Statistical Package for the Social Sciences (SPSS) software, version 24 for Macintosh (IBM, 2017). The multivariate imputation by chained equations (MICE) method was used to impute data. MICE is a Bayesian model that imputes data one variable at a time with a chain of regression equations to determine the most likely values for each missing value (van Buuren, 2018). These regression models can utilize data from all other variables in the model with the residual error to create the imputed values. After regression modeling creates the imputed values predictive mean matching (PMM) determines the final imputed data values accurately even with skewed distributions or non-linear relationships between variables (Eekhout et al., 2014, 2017; Rubin, 1987). PMM uses imputed missing data provided by MICE and then uses the closest actual observed value from the dataset for the missing values (Rubin, 1987). This ensures that the imputed missing data comes from the existing data set and does not return an unreasonable value. To ensure accuracy of the imputed data 20 iterations with 1000 imputations for each iteration was chosen in accordance with recent prior research on the topic (van Buuren, 2018). Additionally none of the imputed variables used had ≥20% of the data missing ensuring that the methods chosen would produce accurate results (van Buuren, 2018). All neurocognitive variables were used to impute missing data separately for the patient and healthy volunteer groups. Verbal working memory did not require imputed data resulting in speed of processing and executive functions using the imputed adjusted degrees of freedom (van Buuren, 2018). Welch t-tests to examined baseline differences and paired t-tests examined the data longitudinally. Effect sizes reported include Hedges' g (Ellis, 2010) for baseline between group comparison, to control for unequal group size differences, Cohen's d for within-group baseline

to week 12 comparisons, and Pearson r for the relationship between two continuous variables (Cohen, 1988). Use of Hedges' g for between group comparisons and Cohen's d for repeated measures effect sizes was done in accordance with recommended guidelines from statistical literature (Ellis, 2010; Fritz et al., 2012; Morris, 2008; Sexton et al., 2016; Vacha-Haase & Thompson, 2004). Effect sizes for Hedges' g and Cohen's d are interpreted as follows: small effect (0.2 – 0.49), intermediate effect (0.5 – 0.79), large effect (0.8 - >1.0) (Cohen, 1988). Effect sizes for Pearson 'r' are interpreted as follows: small (0.1 – 0.29), medium (0.3 – 0.49), large (0.5 – 1.0) (Cohen, 1988). Partial eta^2 is the effect size reported for rate of change results as it is appropriate for examining interaction effects. Interpretation of partial eta^2 values are as follows: of 0.01 (small), 0.09 (medium), and 0.25 (large) (Vacha-Haase & Thompson, 2004).

Figure 3-1 Flow chart describing the levels of analysis in the emotion recognition task

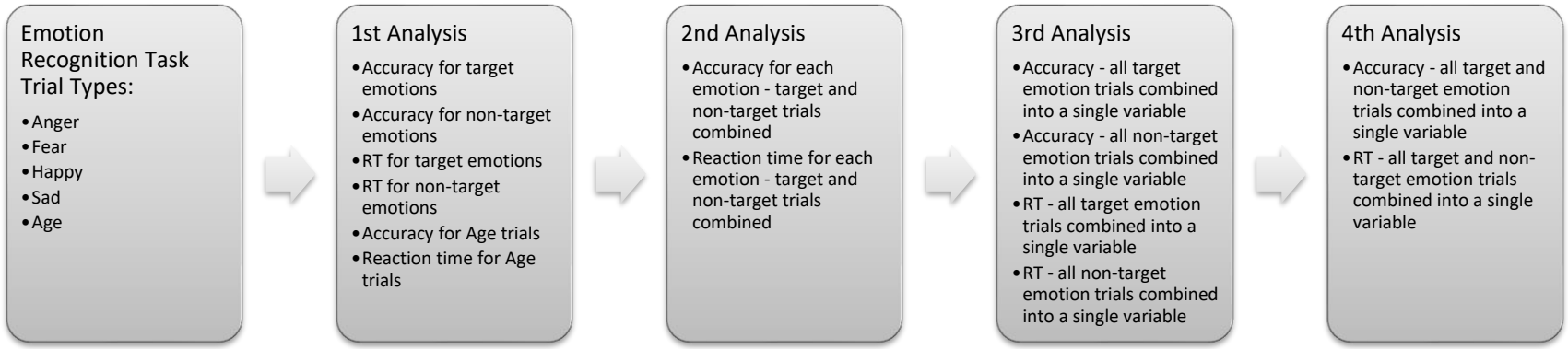
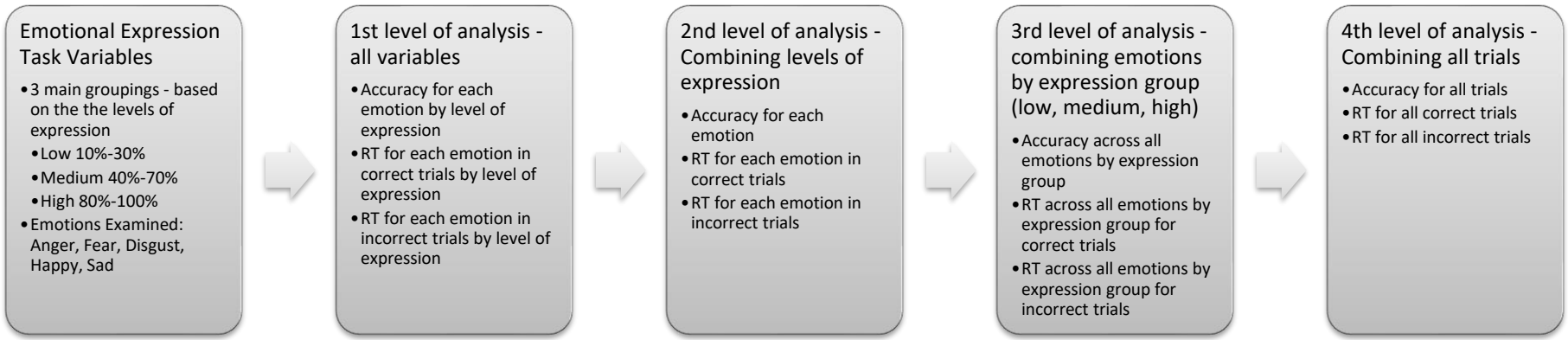


Figure 3-2 Flow chart describing the levels of analysis in the emotional expression task



3.3 Baseline Results

3.3.1 Emotional Recognition Task - Differences between groups

3.3.1.1 Accuracy and Reaction Time for Target and Non-Target Faces per Emotion

There were no differences in accuracy or reaction time between groups at baseline in the age recognition trial (all p-values> 0.05). Further, there were no differences between groups at baseline in: 1) anger trials, accuracy for target and non-target anger trials or reaction time for target anger trials, 2) sad trials, non-target accuracy along with target and non-target reaction time trials, 3) fear trials, accuracy for both target and non-target trials as well as reaction time in target trials, and 4) accuracy in target happy trials (all p-values > 0.05).

Only accuracy in target sad emotion trials remained significantly different between groups after FDR correction. In this trial patients had significantly lower accuracy in recognizing target sad faces ($t(17.85) = -3.85$, $p < 0.01$; $g = -1.48$). See table 3.1 for all trials that were significantly different between groups at baseline.

Table 3-1 Emotion recognition accuracy and reaction time results for each emotion

Emotional Recognition Trial Type	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p-value	FDR p-value	Hedges' g
Accuracy – target sad faces	78.6%	95.7%	-17.08%	17.85	-3.85	< 0.01	**0.02**	-1.48
Reaction time – non-target anger faces	2.82 s	1.3s	-37.25%	12.81	2.91	0.01	0.07	1.08
Reaction time – non-target fear faces	2.7s	1.5	-29%	13.89	2.3	0.04	0.11	0.85
Accuracy – non-target happy faces	82.7%	93.5%	-10.8%	21	-2.15	0.04	0.11	-0.91
Reaction time – non-target happy faces	3.27s	1.1s	-49.64%	12.84	3.05	0.02	0.11	0.94
Reaction time – target happy faces	2.08s	0.97s	-36.21%	22.07	-2.19	< 0.01	0.07	1.13
Result in blue remained significant after FDR correction for multiple comparisons								

3.3.1.2 Accuracy and Reaction Time for each Emotion (target and non-target trials combined within a test block)

No second level results survived FDR correction for multiple comparisons. See table 3.2 for results.

3.3.1.3 Accuracy and Reaction Time of all Target Trials and all Non-Target Trials (not separated by emotion)

No 3rd level differences between groups across all target or non-target trials survived FDR correction for both accuracy and reaction time. See table 3.2 for results.

3.3.1.4 Accuracy and Reaction Time for all Trials

No fourth level differences between groups in overall reaction time or accuracy survived FDR correction. See table 3.2 for results.

Table 3-2 Emotion recognition task accuracy and reaction time results across all trials

Emotional Recognition Trial Type	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p-value	FDR p-value	Hedges' g
Accuracy – all happy trials	87%	95.3%	-8.29%	17.62	2.26	0.04	0.12	-0.87
Reaction time – all happy trials	1.04s	0.49s	-36.18%	12.84	3.05	< 0.01	0.07	1.13
Accuracy – all sad trials	81.4%	88.8%	-7.4%	19.65	-2.15	0.04	0.12	-0.90
Reaction time – all non-target trials	2.89s	1.36s	-36.1%	12.48	2.58	0.02	0.10	0.95
Reaction time – all target trials	2.66s	1.34s	-33.13%	12.74	2.1	0.06	0.11	0.77
Reaction time – all trials	2.78	1.36s	-34.42%	12.34	2.33	0.04	0.07	0.86

3.3.2 Emotion Expression Task

In this task, the amount of a specific emotion expressed by faces shown ranged from 10%-100% with three groups for analysis: low (10-30%), medium (40-70%), and high (80%-100%) (Diaz et al., 2016). Comparisons between patients and healthy volunteers at baseline utilized two-sided welch t-tests.

3.3.2.1 Accuracy and Reaction Time results by Expression Group on a per Emotion basis (separated by correct and incorrect trials)

Results presented in this section are those that survived FDR correction. For a list of significant differences between groups at baseline, and FDR corrected p-values, see table 3.3.

There were no differences in accuracy for anger at any level of expression between groups at baseline. Of the significant differences at baseline for the anger emotion between groups only patients' slower reactions times than healthy volunteers in correct medium expression anger trials ($t(13.12) = 3.12$, $p < 0.01$; $g = 1.16$) survived FDR correction.

No significant baseline between group differences were observed in the accuracy of identifying expressions of disgust at the low, medium, or high level. For the disgust emotion, the only finding to survive FDR correction was the patient group's significantly slower reaction times for incorrect low expression trials ($t(12.51) = 3.49$, $p < 0.01$; $g = 1.29$).

In fear emotion trials five different findings survived FDR correction. Patients had significantly slower reaction time in the fear expression trials than healthy volunteers for incorrect low ($t(12.36) = 3.08$, $p < 0.01$; $g = 1.13$), incorrect medium ($t(13.27) = 3.486$, $p < 0.01$; $g = 1.29$), incorrect high ($t(16.72) = 2.79$, $p = 0.01$; $g = 1.06$) and in correct high ($t(13.63) = 2.755$, $p = 0.02$; $g = 1.02$) expression trials. Patients were also significantly less accurate at baseline in the high expression fear trial than healthy volunteers ($t(18.99) = -2.88$, $p < 0.01$; $g = -1.12$), but not in accuracy at the low and medium expression level (p-values > 0.05).

Four findings for happy emotion expression trials survived FDR correction. Patients were significantly slower than healthy volunteers in the high expression incorrect trials ($t(12.12) = 2.87$, $p = 0.01$; $g = 1.06$). Additionally, patients were also significantly slower in correct happy expression trials at the low ($t(19.29) = 3.29$, $p < 0.01$; $g = 1.29$) and high levels ($t(19.53) = 2.85$,

p = 0.01; g = 1.12) expression levels but not at the medium level. Patients were significantly less accurate than healthy volunteers in high expression trials (t (13.77) = -3.19, p < 0.01; g = -1.19).

In sad emotion trials four findings survived FDR correction. Patients were significantly slower than healthy volunteers in incorrect sad expression trials at the low (t (13.19) = 3.94, p < 0.01; g = 1.17), medium (t (12.62) = 4.75, p < 0.01; g = 0.86), and high (t (12.4) = 3.17, p < 0.01; g = 1.17) expression levels. Patients were also slower in correct sad medium expression trials (t (13.33) = 2.99, p = 0.01; g = 1.11). There were no differences in accuracy between groups at baseline in the sad trials at all three levels of expression.

Table 3-3 Accuracy and reaction time results by expression group on a per emotion basis

Emotion and Expression level	Trial Type	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p - value	FDR p-value	Hedges' g
Anger, low	RT – incorrect trials	3.69s	0.83s	-63.1%	12.1	2.5	0.03	0.07	0.92
Anger, medium	RT – incorrect trials	4.06s	1.44s	-47.58%	14.01	2.62	0.02	0.06	0.98
Anger, medium	RT – correct trials	1.76s	0.72s	-42.09%	13.12	3.12	< 0.01	**0.04**	1.16
Disgust, low	RT – incorrect trials	3.04s	0.96s	-52.17%	12.51	3.49	< 0.01	**0.04**	1.29
Disgust, low	RT – correct trials	1.2s	0.43s	-47.73%	16.68	2.18	0.04	0.08	0.83
Disgust, medium	RT – correct trials	1.92s	0.86s	-37.36%	12.8	2.4	0.03	0.07	0.89
Disgust, high	RT – correct trials	1.88s	0.94s	-33.68%	14.9	2.51	0.02	0.06	0.95
Fear, low	RT – incorrect trials	3.38s	0.86s	-59.22%	12.36	3.08	< 0.01	**0.04**	1.13
Fear, medium	RT – incorrect trials	4.36s	1.24s	-55.61%	13.27	3.49	< 0.01	**0.04**	1.29
Fear, high	RT – incorrect trials	4.02s	1.25s	-52.68%	13.63	2.76	0.01	< **0.05**	1.06
Fear, low	RT – correct trials	0.70s	0.1s	-75.32%	13.11	2.25	0.04	0.08	0.83
Fear, medium	RT – correct trials	2.63s	1.4s	-30.34%	14.31	2.5	0.03	0.07	0.94
Fear, high	RT – correct trials	3.25s	1.32s	-42.14%	13.63	2.76	0.02	< **0.05**	1.02
Fear, high	Accuracy	61.5%	86.7%	-25.12%	18.99	-2.88	< 0.01	**0.04**	-1.12
Happy, low	RT – incorrect trials	3.51s	0.91s	-58.85%	13.08	2.18	< 0.05	0.08	0.81
Happy, medium	RT – incorrect trials	2.27s	0.3s	-76.34%	13.02	2.19	< 0.05	0.08	0.81
Happy, high	RT – incorrect trials	1.19s	0.03s	-95.33%	12.12	2.87	0.01	< **0.05**	1.06
Happy, low	RT – correct trials	1.44s	0.75s	-31.57%	19.29	3.29	< 0.01	**0.04**	1.29
Happy, high	RT – correct trials	1.44s	0.86s	-25.22%	19.53	2.85	0.01	**0.04**	1.12
Happy, medium	Accuracy	82.2%	94.4%	12.2%	20	-2.8	0.03	0.07	-0.9
Happy, high	Accuracy	89.1%	99.2%	10.01%	13.77	-3.2	< 0.01	**0.04**	-1.19
Sad, low	RT – incorrect trials	2.93s	0.94s	-51.55%	13.19	3.94	< 0.01	**0.04**	1.46
Sad, medium	RT – incorrect trials	3.76s	1.03s	-56.88%	12.62	4.75	< 0.01	< **0.01**	1.75
Sad, high	RT – incorrect trials	4.67s	0.99s	-64.90%	12.4	3.17	< 0.01	**0.04**	1.17
Sad, low	RT – correct trials	0.93s	0.16s	-70.24%	15.41	2.28	0.03	0.08	0.86
Sad, medium	RT – correct trials	2.11s	0.55s	-58.65%	13.33	2.99	0.01	**0.04**	1.11
Results in blue remained significant after FDR correction for multiple comparisons									

3.3.2.2 Accuracy and Reaction Time for Correct and Incorrect Trials per Emotion (not separated by expression level)

Results presented in this section are those that survived FDR correction. For a list of significant differences between groups at baseline, and FDR corrected p-values, see table 3.4.

In anger trials there was no difference in accuracy across all expression levels. But the patient group was significantly slower overall across all incorrect anger ($t(12.88) = 3.02$, $p = 0.01$; $g = 1.11$) and correct anger expression trials ($t(12.45) = 2.66$, $p = 0.02$; $g = 0.98$) compared to healthy volunteers. There were no significant differences between groups at baseline in the disgust emotion recognition trial for overall accuracy, but the patient group was slower than healthy volunteers across all correct disgust trials ($t(13.4) = 3.57$, $p < 0.01$; $g = 1.32$). In the fear emotion trials, the groups were significantly different with patients had slower reaction times across all incorrect ($t(13.08) = 3.27$, $p < 0.01$; $g = 1.21$) and correct fear expression trials ($t(13.58) = 3.35$, $p < 0.01$; $g = 1.25$). Happy emotion expression trials were not significantly different in accuracy across expression levels (p-values > 0.05). But groups did differ significantly in reaction time across expression levels in both incorrect ($t(12.52) = 2.68$, $p = 0.02$; $g = 0.99$) and correct trials ($t(14.19) = 2.87$, $p = 0.01$; $g = 1.07$), with patients being slower than healthy volunteers in both instances. For sad emotion trials no differences in accuracy across expression levels occurred (p-values > 0.05). However, like the anger, disgust, fear, and happy emotions reaction time for sad emotion expression trials were significantly different between groups for incorrect ($t(12.46) = 4.19$, $p < 0.01$; $g = 1.54$) and correct trials ($t(14.09) = 3.2$, $p < 0.01$; $g = 1.20$).

Table 3-4 Accuracy and reaction time for correct and incorrect trials per emotion

Emotion	Trial Type	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p-value	FDR p-value	Hedges' g
Anger	RT – incorrect trials	3.49s	1.13s	-50.98%	12.88	3.02	0.01	**0.02**	1.11
Anger	RT – correct trials	1.6s	0.62s	-44.21%	12.45	2.66	0.02	**0.03**	0.98
Disgust	RT – incorrect trials	3.29s	1.14s	-48.48%	12.84	2.28	0.04	0.06	0.84
Disgust	RT – correct trials	1.67s	0.75s	-38.26%	13.4	3.57	< 0.01	**0.02**	1.32
Fear	RT – incorrect trials	3.92s	1.12s	-55.6%	13.08	3.27	< 0.01	**0.02**	1.21
Fear	RT – correct trials	2.2s	0.94s	-40.07%	13.58	3.35	< 0.01	**0.02**	1.25
Fear	Accuracy	36.8%	48.3%	-11.5%	20.43	-2.11	< 0.05	0.07	-0.84
Happy	RT – incorrect trials	2.32s	0.41s	-69.75%	12.52	2.68	0.02	**0.03**	0.99
Happy	RT – correct trials	1.84s	0.85s	-36.84%	14.19	2.87	0.01	**0.03**	1.07
Sad	RT – incorrect trials	3.79s	0.99s	-58.61%	12.46	4.19	< 0.01	**0.01**	1.54
Sad	RT – correct trials	1.59s	0.73s	-37.11%	14.09	3.2	< 0.01	**0.02**	1.20
Results in blue remained significant after FDR correction for multiple comparisons									

3.3.2.3 Accuracy and Reaction Time for Correct and Incorrect Trials by Expression level (no separation of results by emotion type)

Results presented in this section are those that survived FDR correction. For a list of significant differences between groups at baseline, and FDR corrected p-values, see table 3.5.

There were no significant differences at baseline between groups in the accuracy of responses in the low expression group but there was a trend for worse performance on accuracy for the medium expression for the patients ($t(20.04) = -2.01$, $p = 0.057$; $g = -0.84$). However, on high expression trials patient were less accurate than healthy volunteers ($t(20.23) = -2.90$, $p = 0.01$; $g = -1.11$). Reaction times were slower in patients compared to healthy volunteers for incorrect trials at all three levels; low ($t(12.38) = 3.66$, $p < 0.01$; $g = 1.35$), medium ($t(12.48) = 2.82$, $p = 0.01$; $g = 1.04$), and high ($t(13.05) = 2.7$, $p = 0.02$; $g = 1.0$). Patients also had slower reaction times in correct trials compared to healthy volunteers at all three levels; low ($t(15.11) = 3.8$, $p < 0.01$; $g = 1.43$), medium ($t(13.09) = 3.6$, $p < 0.01$; $g = 1.33$), and high ($t(13.65) = 2.84$, $p = 0.01$; $g = 1.06$).

Table 3-5 Accuracy and reaction time for correct and incorrect trials by expression level

Expression Level	Trial Type	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p-value	FDR p-value	Hedges' g
Low	RT – incorrect trials	3.31s	0.9s	-57.23s	12.38	3.66	< 0.01	< **0.01**	1.35
Low	RT – correct trials	1.01s	0.36s	-47.65%	15.11	3.8	< 0.01	< **0.01**	1.43
Medium	RT – incorrect trials	3.94s	1.14s	-55.02%	12.48	2.82	0.01	**0.02**	1.04
Medium	RT – correct trials	1.97s	0.86s	-39.29%	13.09	3.6	< 0.01	< **0.01**	1.33
Medium	Accuracy	47.3%	57.1%	-9.82%	20.04	-2.01	0.06	0.07	-0.84
High	RT – incorrect trials	3.55s	1.13s	51.67%	13.05	2.7	0.02	**0.03**	1.00
High	RT – correct trials	2.12s	1.05s	-33.59%	13.65	2.84	0.01	**0.02**	1.06
High	Accuracy	60.6%	75.5%	-14.86%	20.23	-2.90	0.01	**0.02**	-1.11
Results in blue remained significant after FDR correction for multiple comparisons									

3.3.2.4 Overall Accuracy and Reaction Time for all Trials (separated by correct and incorrect trial types)

Overall accuracy ($t(20.88) = -2.03$, $p = 0.056$; $g = -0.83$) had a strong trend towards significance with the patient group not performing as well as the healthy volunteers. Patients' reaction times were worse than healthy volunteers over all incorrect trials ($t(12.43) = 3.29$, $p < 0.01$; $g = 1.21$) and all correct trials ($t(13.67) = 4.07$, $p < 0.01$; $g = 1.51$). Additionally, patients were slower in overall reaction time across all trials ($t(12.52) = 3.54$, $p < 0.01$; $g = 1.30$). Differences in reaction time for patients versus healthy volunteers all remained significant after FDR correction for this trial.

3.3.3 Neurocognitive Tests: Baseline Results

3.3.3.1 Individual Test Results at Baseline

Welch t-tests were used to examine potential neurocognitive differences between groups at baseline. Results listed all survived FDR correction. For a full list of significant results that did and did not survive correction see table 3.6. Analyses did not reveal any significant differences between patients and healthy volunteers at baseline in HVLT recognition and MTCF copy scores (all p-values > 0.05). At baseline, patients performed worse than healthy volunteers on HVLT retention ($t(22.31) = -3.24$, $p < 0.01$; $g = -1.26$), HVLT immediate recall ($t(22) = -3.5$, $p < 0.01$; $g = -1.37$), and HVLT delayed recall s ($t(22.86) = -3.24$, $p < 0.01$; $g = -1.78$), MTCF immediate recall ($t(19.73) = -7.29$, $p < 0.01$; $g = -2.56$), MTCF delayed recall ($t(16.39) = -7.91$, $p < 0.01$; -2.84), SDMT oral score ($t(15.61) = -6.44$, $p < 0.01$; $g = -2.81$), SDMT written ($t(17.22) = -6.21$, $p < 0.01$; $g = -2.62$), Trails A ($t(18.51) = 3.62$, $p < 0.01$; $g = 1.3$), Trails B ($t(14.33) = 2.88$, $p = 0.01$; $g = 1.06$), COWA total ($t(17.74) = -2.22$, $p = 0.04$; $g = -0.93$), and Digit Span raw ($t(13.1) = -2.72$, $p = 0.02$). In 'MnM hold' trials, patients had significantly lower accuracy scores at

baseline (t (9.82) = -3.26, $p < 0.01$; g = -1.46) and trended towards a significant difference between groups in flip trial accuracy (t (10.4) = -2.14, $p = 0.06$; g = -0.96). Patients also had increased reaction times compared to healthy volunteer group in correct hold trials (t (11.8) = 4.28, $p < 0.01$; g = 1.92) and in correct flip trials (t (14.78) = 2.35, $p = 0.03$; g = 1.05). There were no significant differences in reaction times on incorrect hold or incorrect flip trials (p-values > 0.05).

Table 3-6 Neurocognitive between group differences at baseline

Neurocognitive test	Subtest	Mean - patients	Mean – Healthy volunteers	% different	DF	t	p-value	FDR p-value	Hedges' g
HVLT	Retention	71.87	97	-14.88%	22.31	-3.24	< 0.01	**< 0.01**	-1.26
HVLT	Immediate recall	20	27.3	-15.42%	22	-3.5	< 0.01	**< 0.01**	-1.37
HVLT	Delayed recall	6	10	-25%	22.86	-3.24	< 0.01	**< 0.01**	-1.78
MTCF	Immediate recall	15.5	31.6	-34.18%	19.73	-7.29	< 0.01	**< 0.01**	-2.56
MTCF	Delayed recall	15.5	31.95	-34.67%	16.39	-7.91	< 0.01	**< 0.01**	-2.84
SDMT	Written	39.57	74.9	-30.86%	17.22	-6.21	< 0.01	**< 0.01**	-2.62
SDMT	Oral	35.07	59.9	-26.15%	15.61	-6.44	< 0.01	**< 0.01**	-2.81
COWA	n/a	28.07	38.5	15.67%	17.74	-2.14	0.04	**< 0.05**	-0.93
Trails	A	40.19s	20.58s	-32.26%	18.51	3.62	< 0.01	**< 0.01**	1.30
Trails	B	126s	58.55s	-36.55%	14.33	-2.72	0.01	**0.02**	1.06
Digit Span	n/a	22.93	30.1	-13.51%	13.1	-2.72	0.02	**0.02**	-1.23
MnM	Accuracy - Hold trials	66%	92.5%	-26.5%	9.82	-3.26	< 0.01	**0.02**	-1.46
MnM	Accuracy - Flip trials	65.5%	82.5%	-17%	10.4	-2.14	0.06	0.09	-0.96
MnM	RT - correct hold trials	1.63s	1.06s	-21.2%	11.8	4.28	< 0.01	**< 0.01**	1.92
MnM	RT – correct flip trials	1.56s	1.3s	-9.42%	14.78	2.35	0.03	0.06	1.05
Results in blue remained significant after FDR correction for multiple comparisons									

3.3.3.2 Domain level Between-Group findings at Baseline

Using the pooled imputed data results independent t-tests found the patient group had significantly lower mean levels of executive function ($t(19.99) = -2.966$, $p < 0.01$; $g = -1.07$) and lower mean speed of processing ($t(19.82) = -5.259$, $p < 0.01$; $g = -1.91$) that the healthy volunteers. An Independent t-test, which did not require the use of imputed data, also revealed lower mean levels of verbal working memory in the patient group than healthy volunteers at baseline ($t(23) = -3.714$, $p < 0.01$; $g = -1.52$). These were still significant after FDR correction.

3.4 Follow Up Results

3.4.1 Emotional Recognition Task at Follow-up

3.4.1.1 Accuracy and Reaction Time for Target and Non-Target faces per Emotion

Results listed in text all survived FDR correction. For a full list of significant results that did and did not survive correction see table 3.7. Patients saw improvements in accuracy of recognizing non-target faces in the happy emotion trial from baseline to week 12 ($t(11) = -3.9$, $p < 0.01$; $d = -1.14$). However, patients did not significantly change in accuracy for any other trials in this task (all p-values > 0.05). Patients also had several significant changes in reaction time that did not survive FDR correction. For a full list see table 3.7. Healthy volunteers had no significant changes in accuracy that survived FDR correction and only one change in reaction time that did. This improvement in reaction time came in non-target sad trials ($t(9) = 4.3$, $p < 0.01$; $d = 1.36$).

Table 3-7 Emotion recognition follow-up results: accuracy and reaction time for target and non-target faces per emotion

Group	Emotion	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Fear	Accuracy - Target faces	-12.1%	-9.18%	11	2.5	0.03	0.07	0.74
Patients	Happy	Accuracy - Non-target faces	0.07	4.28%	11	-.39	< 0.01	**0.04**	-1.14
Patients	Angry	RT – Non-target faces	-0.87s	-18.15%	11	-3.4	< 0.01	0.054	0.97
Patients	Fear	RT – Non-target faces	-0.97s	-21.68%	11	3.0	0.01	0.07	0.88
Patients	Happy	RT – Non-target faces	-1.7s	-34.97%	11	2.4	0.03	0.08	0.7
Patients	Happy	RT – Target	-0.92s	-29.19%	11	2.6	0.02	0.07	0.76
Patients	Sad	RT – Non-target faces	-0.88s	-19.27s	11	2.6	0.03	0.07	0.74
Healthy Volunteers	Sad	Accuracy – Non-target faces	6.9%	4.04%	9	-2.65	0.03	0.19	-0.84
Healthy Volunteers	Fear	RT – Non-target faces	-0.47s	-18.78%	9	2.5	0.04	0.19	0.78
Healthy Volunteers	Happy	RT – Target faces	-0.14s	-7.74%	9	2.4	0.04	0.19	0.75
Healthy Volunteers	Sad	RT – Non-target faces	-0.48s	-18.65%	9	4.3	< 0.01	**0.04**	1.36
Results in blue remained significant after FDR correction for multiple comparisons									

3.4.1.2 Accuracy and Reaction Time per Emotion Trial Block (target and non-target trials combined)

At second level of analysis patients there were no significant differences for either the patient group or healthy volunteers that survived FDR correction. For a full list of significant results that did not survive FDR correction see table 3.8.

3.4.1.3 Accuracy and Reaction Time of all Target Trials and all Non-Target Trials (not separated by emotion type)

Results listed in text all survived FDR correction. For a full list of significant results that did and did not survive correction see table 3.9. At the third level of analysis, patients significantly improved their reaction times in non-target emotion trials ($t(11) = 3.16$, $p < 0.01$; $d = 0.91$) Patients did not significantly change in accuracy for target and non-target trials from baseline to week 12 for any other trials. Healthy volunteers also significantly improved in non-target trial reaction time ($t(9) = 3.74$, $p < 0.01$; $d = 1.18$).

Table 3-8 Emotion recognition: reaction time follow-up results on a per emotion basis (target and non-target trials combined)

Group	Emotion	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Anger	RT	-0.94s	-20.55%	11	2.61	0.02	0.07	0.75
Patients	Fear	RT	-1.14s	-24.37%	11	2.79	0.02	0.07	0.81
Patients	Happy	RT	-1.31s	-32.25%	11	2.53	0.03	0.07	0.73
Healthy Volunteers	Fear	RT	-0.46s	-16.87%	9	2.85	0.02	0.12	0.9
Healthy Volunteers	Sad	RT	-0.34s	-14.07%	9	2.57	0.03	0.12	0.81
Healthy Volunteers	Happy	RT	-0.18s	-9.48%	9	2.19	0.06	0.15	0.69

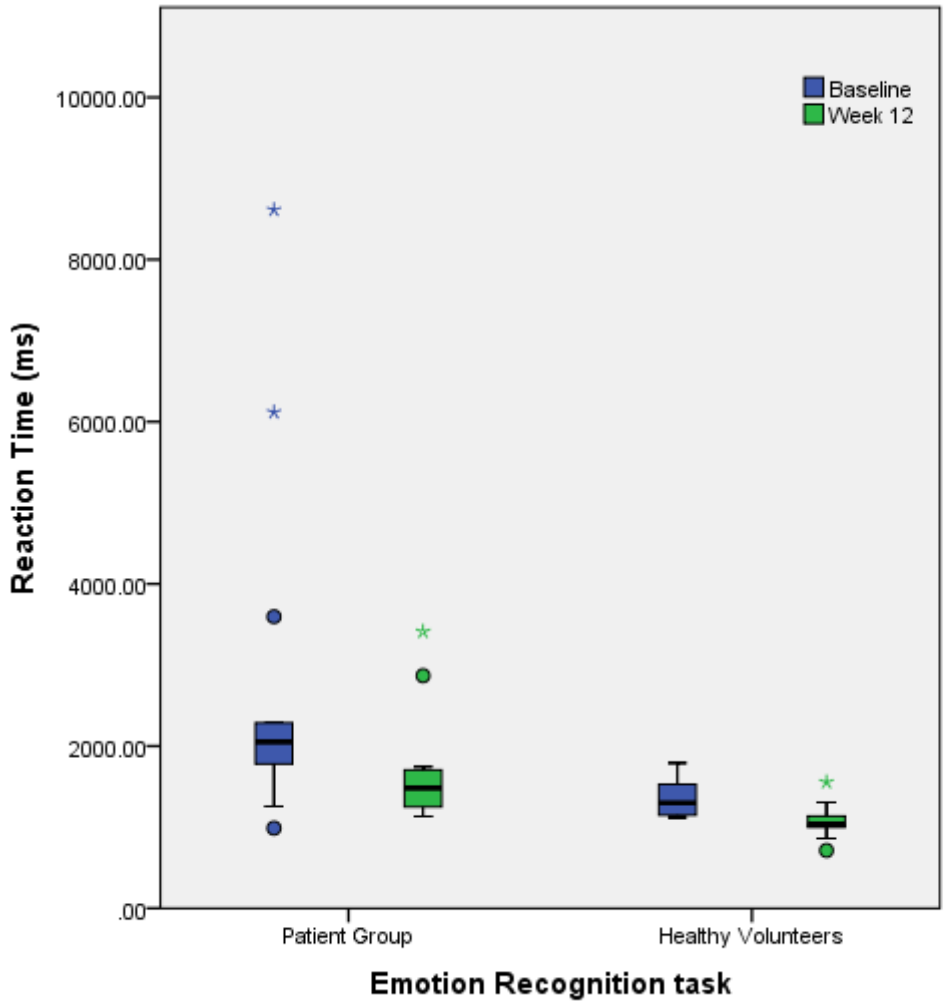
Table 3-9 Emotion recognition follow up results: changes in overall reaction time

Group	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	RT – all non-target trials	-1.11s	-23.63%	11	3.16	< 0.01	**0.02**	0.91
Healthy Volunteers	RT – all non-target trials	-0.36s	-15.24%	9	3.74	< 0.01	**0.04**	1.18
Healthy Volunteers	RT – all target trials	-0.24s	-9.89%	9	2.19	0.06	0.15	0.69
Results in blue remained significant after FDR correction for multiple comparisons								

3.4.1.4 Accuracy and Reaction Time across all Trials – Emotion Recognition Task

Examining overall reaction time across all emotions and both trial types revealed that both groups decreased their reaction time, from baseline to week 12, with patients having an average decrease of 1.09 seconds (-24.25%), (t (11) = 2.5, p = 0.030; d = 0.72), and healthy volunteers having a decrease of 0.74 seconds (-11.69%), (t (9) = 3.2, p = 0.01; d = 0.64) [see figure 3.3]. These survived FDR correction for multiple comparisons. There were no significant differences in accuracy or reaction time in the age condition for either group (all p-values> 0.05).

Figure 3-3 Changes over time – emotion recognition reaction time (Circles are values 1.5 times above the 3rd interquartile range or below the 1st. Stars are values 3 times above the 3rd interquartile range.)



3.4.1.5 Rate of Change results – Emotion Recognition Task

No significant results survived FDR correction for multiple comparisons. Further levels of analyses in this task did not reveal any significant differences in the rate of change between groups in accuracy or reaction time for all target trials, all foil trials, or the combination of target and foil trials (all p-values > 0.05). See table 3.10 for a table of results that did not survive FDR correction.

Table 3-10 Emotion recognition: rate of change differences

Rate of Change trial	DF	F	p-value	FDR p-value	Partial eta^2
Accuracy – target anger	1,20	5.0	0.04	0.23	0.20
Accuracy – target fear	1,20	5.7	0.03	0.23	0.22
Reaction time – target happy	1,20	4.0	0.06	0.23	0.17
Reaction time – non-target anger	1,20	4.2	> 0.05	0.23	0.17

3.4.2 Emotion Expression Task: Follow-up Results

3.4.2.1 Accuracy and Reaction Time results by Expression Group (per emotion and separated by correct and incorrect trials)

At follow-up, patients did not have any statistically significant changes in accuracy for each of the emotions examined in any of the expression groups (all p-values >0.05). Of the significant changes in reaction time from baseline to week 12 only the reduction in reaction time for the incorrect medium expression sad emotion trials remained significant after FDR correction ($t(12) = 4.49$, $p < 0.01$; $d = 1.24$). Health volunteers did not have any significant changes from baseline to week 12 that survived FDR correction. See table 3.11 for a full list of significant results that did and did not survive FDR correction.

Table 3-11 Emotion expression task follow-up results: accuracy and reaction time per emotion by correct or incorrect trial

Group	Emotion	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Anger	RT - Low expression incorrect trials	-1.15s	-18.39%	12	2.29	0.04	0.22	0.64
Patients	Anger	RT - Medium expression incorrect trials	-2.2s	-37.15%	12	3.19	< 0.01	0.18	0.88
Patients	Anger	RT - Medium expression correct trials	-0.55s	-18.49%	12	2.08	0.06	0.27	0.58
Patients	Happy	RT - Low expression correct trials	-0.41s	-16.58%	12	2.33	0.04	0.22	0.65
Patients	Happy	RT – High expression correct trials	-0.35s	-14.04%	12	2.06	0.06	0.27	0.57
Patients	Fear	RT – Low expression incorrect trials	-1.79s	-36.12%	12	2.34	0.04	0.22	0.65
Patients	Fear	RT – Medium expression incorrect trials	-1.77s	-25.44%	12	2.86	0.01	0.18	0.79
Patients	Fear	RT – High expression correct trials	-1.16s	-21.72%	12	2.22	0.04	0.22	0.61
Patients	Sad	RT – Low expression incorrect trials	-1.21s	-25.92%	12	2.79	0.02	0.18	0.77
Patients	Sad	RT – Medium expression incorrect trials	-1.98s	-35.62%	12	4.49	< 0.01	**0.04**	1.24
Patients	Sad	RT – Low expression correct trials	-0.48s	-34.9%	12	2.28	0.04	0.22	0.63
Patients	Sad	RT – Medium expression correct trials	-0.86s	-25.68%	12	2.21	0.05	0.26	0.61
Healthy Volunteers	Anger	Accuracy – Medium expression trials	11.88%	+9.84%	9	-2.58	0.03	0.19	-0.82
Healthy Volunteers	Fear	Accuracy – Low expression trials	4.17%	38.46%	9	-3.0	0.02	0.19	-0.95

Healthy Volunteers	Disgust	RT – Medium expression correct trials	-0.31s	-21.65%	9	3.31	< 0.01	0.19	1.05
Healthy Volunteers	Fear	RT – High expression incorrect trials	-0.88s	-54.91%	9	2.26	0.05	0.24	0.71
Healthy Volunteers	Fear	RT – Medium expression correct trials	-0.48s	-20.87%	9	2.65	0.03	0.19	0.84
Healthy Volunteers	Happy	RT – Medium expression correct trials	-0.26s	-16.46%	9	2.35	0.04	0.24	0.74
Healthy Volunteers	Happy	RT – High expression correct trials	-0.25s	-16.98%	9	2.57	0.03	0.19	0.81
Healthy Volunteers	Sad	RT – Low expression incorrect trials	0.16s	15.12%	9	2.66	0.03	0.19	0.84
Healthy Volunteers	Sad	RT – High expression correct trials	-0.51s	-21.12%	9	3.16	0.01	0.19	1.0
Result in blue remained significant after FDR correction for multiple comparisons									

3.4.2.2 Accuracy and Reaction Time for Correct and Incorrect Trials per Emotion (no separation of results by expression level)

Patients had no significant changes in their ability to accurately recognize difference emotional expressions at follow-up. After FDR correction, only the improvement in reaction time for correct disgust trials remained significant ($t(12) = 3.74$, $p < 0.01$). Healthy volunteers did not have any significant results survive FDR correction. See table 3.12 for a full list of results.

3.4.2.3 Accuracy and Reaction Time for Correct and Incorrect Trials by Level of Expression (no separation of results by emotion)

Patients did not improve their accuracy in any of the three groups (low, medium, high levels of emotional expression) (all p-values > 0.05) and no significant changes in reaction time that survived FDR correction. Healthy volunteers also had no changes in accuracy or reaction time that survived FDR correction. All significant changes from baseline to week 12 are found in table 3.13.

Table 3-12 Emotion Expression follow-up results: Accuracy and reaction time for correct and incorrect trials per emotion

Group	Emotion	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Disgust	RT - Correct trials	-0.43s	-14.71%	12	3.74	< 0.01	**0.04**	1.04
Patients	Fear	RT – Correct trials	-0.65s	-17.39%	12	2.59	0.02	0.1	0.72
Patients	Happy	RT – Correct trials	-0.72s	-24.17%	12	2.33	0.03	0.1	0.68
Patients	Sad	RT – Correct trials	-0.29s	-10.07%	12	2.16	0.052	0.11	0.6
Patients	Anger	RT – Incorrect trials	-1.24s	-21.58%	12	2.26	0.04	0.11	0.62
Patients	Fear	RT – Incorrect trials	-1.44s	-22.56%	12	2.4	0.03	0.1	0.67
Patients	Sad	RT – Incorrect trials	-1.64s	-27.71%	12	2.95	0.01	0.09	0.82
Healthy Volunteers	Anger	Accuracy	7.01%	6.87%	9	-2.36	0.04	0.22	-0.75
Healthy Volunteers	Disgust	RT – Correct trials	-0.2s	-15.1%	9	2.73	0.02	0.17	0.86
Health Volunteers	Fear	RT – Incorrect trials	-0.52s	-29.97%	9	3.06	0.01	0.17	0.97
Result in blue remained significant after FDR correction for multiple comparisons									

Table 3-13 Emotion expression follow-up results: accuracy and reaction time for correct and incorrect trials by level of expression

Group	Expression level	Subtest	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Low	RT – correct trials	-0.37s	-22.09%	12	-2.9	0.01	0.06	0.08
Patients	Medium	RT – correct trials	-0.52s	-15.25%	12	2.2	0.05	0.11	0.61
Patients	High	RT – correct trials	-0.49s	-12.97%	12	3.16	< 0.01	0.06	0.88
Patients	Medium	RT – incorrect trials	-1.94s	-32.7%	12	2.56	0.02	0.07	0.71
Healthy Volunteers	Low	Accuracy	-1.5%	-4.96%	9	-2.18	0.06	0.21	-0.69
Healthy Volunteers	High	RT – incorrect trials	-1.02	-16.71%	9	2.77	0.02	0.20	0.87

3.4.2.4 Overall Accuracy and Reaction Time across all Correct and Incorrect trials and all Trials Combined

The only finding that survived FDR correct was patient's improvement in reaction time from baseline to week 12 for all correct trials ($t(12) = 3.615$, $p < 0.01$; $d = 1.0$). Patients had no significant changes in accuracy. While healthy volunteers did see significant changes in accuracy and reaction time in this task, they did not survive FDR correction. Results of all measures at this level of analysis can be found in table 3.14.

Table 3-14 Emotion expression follow-up results: accuracy and reaction time for all correct, incorrect, and all trials combined

Group	Measure	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Patients	Accuracy – all trials	1.13%	1.35%	12	-0.61	0.56	0.56	-0.17
Patients	RT – all trials	-0.9s	-21.12%	12	2.59	0.02	< 0.05	0.71
Patients	RT – all correct trials	-0.52s	-17.11%	12	3.62	< 0.01	**0.02**	1.0
Patients	RT – all incorrect trials	-1.27s	-23.36%	12	2.23	0.05	0.06	0.62
Healthy Volunteers	Accuracy – all trials	3.65%	3.59%	9	-2.4	0.04	0.14	-0.76
Healthy Volunteers	RT – all trials	-0.19s	-12.4%	9	1.82	0.1	0.14	0.58
Healthy Volunteers	RT – all correct trials	-0.12s	-8.1%	9	1.43	0.19	0.19	0.45
Healthy Volunteers	RT – all incorrect trials	-0.27s	-16.15%	9	1.93	0.09	0.14	0.61
Result in blue remained significant after FDR correction for multiple comparisons								

3.4.2.5 Rate of Change Differences

3.4.2.5.1 Rate of Change Differences (accuracy and reaction time by expression group on a per emotion basis separated by correct and incorrect trials)

None of the significant changes over time in this analysis survived FDR correct in either the patient or healthy volunteer group. These results can be found in table 3.15.

Table 3-15 Emotion expression: rate of change differences by expression group, per emotion

Rate of Change trial	DF	F	p-value	FDR p-value	Partial eta^2
Accuracy – medium expression anger	1,21	7.8	0.01	0.2	0.27
Accuracy – low expression fear	1,21	5.8	0.03	0.2	0.22
Accuracy – low expression sad	1,21	5.1	0.03	0.2	0.2
RT – correct low expression fear	1,21	3.9	0.06	0.28	0.13
RT – correct low expression sad	1,21	5.9	0.02	0.2	0.22
RT– correct medium expression sad	1,20	5.3	0.03	0.2	0.2
RT– incorrect medium expression anger	1,21	4.7	0.04	0.24	0.18
RT – incorrect medium expression sad	1,21	10.7	< 0.01	0.18	0.34

3.4.2.5.2 Rate of Change Differences in Accuracy and Reaction Time for Correct and Incorrect Trials per Emotion (no separation of results by expression level)

No results remained significant after FDR correction for both the patient group and the health volunteers. Findings that were significant prior to FDR correct are all characterized by increased perform by patients and slightly decreased performance by health volunteers. See table 3.16 for results.

3.4.2.5.3 Rate of Change Differences in Accuracy and Reaction Time for Correct and Incorrect Trials by level of Expression

No results remained significant after FDR correction for either the patients or health volunteers. Findings that were significant prior to FDR correct are all characterized by increased

perform by patients and slightly decreased performance by health volunteers. See table 3.16 for results.

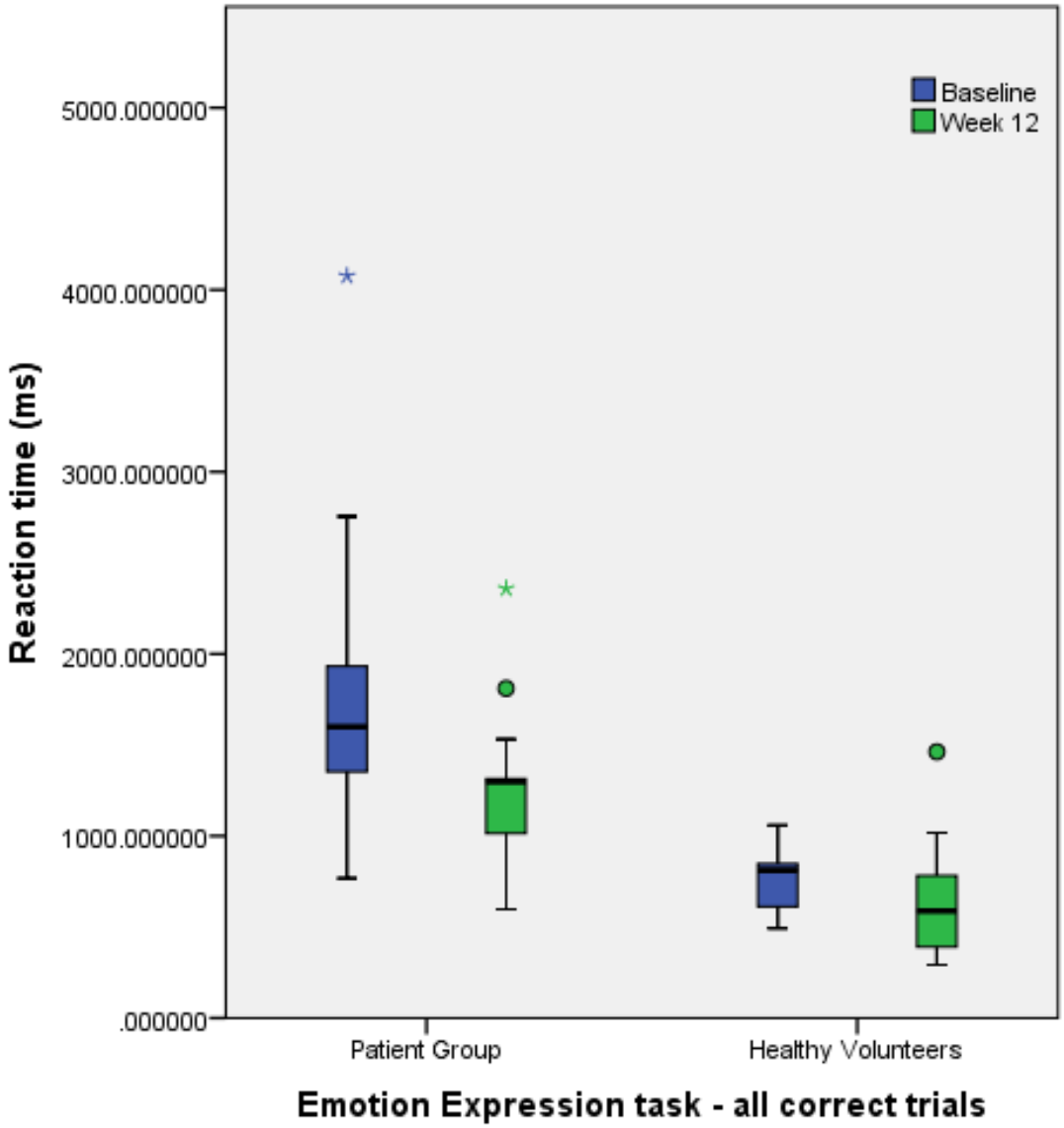
Table 3-16 Emotion expression: rate of change differences all emotion trials and across and across all emotions at specific expression levels

Rate of Change trial	DF	F	p-value	FDR p-value	Partial eta^2
Accuracy – all anger trial	1,21	4.25	0.052	0.26	0.17
RT – incorrect anger trials	1,21	8.98	< 0.01	0.10	0.30
RT – incorrect sad trials	1,21	5.05	0.04	0.26	0.19
Accuracy – low expression trials	1,21	4.44	0.05	0.21	0.17
RT – Low expression correct trials	1,21	8.11	0.01	0.09	0.28

3.4.2.5.4 Rate of Change Differences in Overall Accuracy for all Trials and Overall Reaction Time for Correct and Incorrect Trials

With all trial types and emotions grouped together, there was no significant difference in the rate of accuracy scores between groups ($p > 0.05$). There was a significant difference in the rate of change for reaction time for all correct trials ($F(1,21) = 5.0$, $p = 0.035$; $eta^2_{partial} = 0.19$), but it did not survive FDR correction. (see Figure 3.4). There was no significant difference at this analysis level in reaction times for incorrect trials ($p > 0.05$).

Figure 3-4 Change in correct trial reaction times for the Emotion Expression task across all emotions and expression levels. Circles are values 1.5 times above the 3rd interquartile range. Stars are values 3 times above the 3rd interquartile range.



3.4.3 Cognitive Testing Follow-up Results

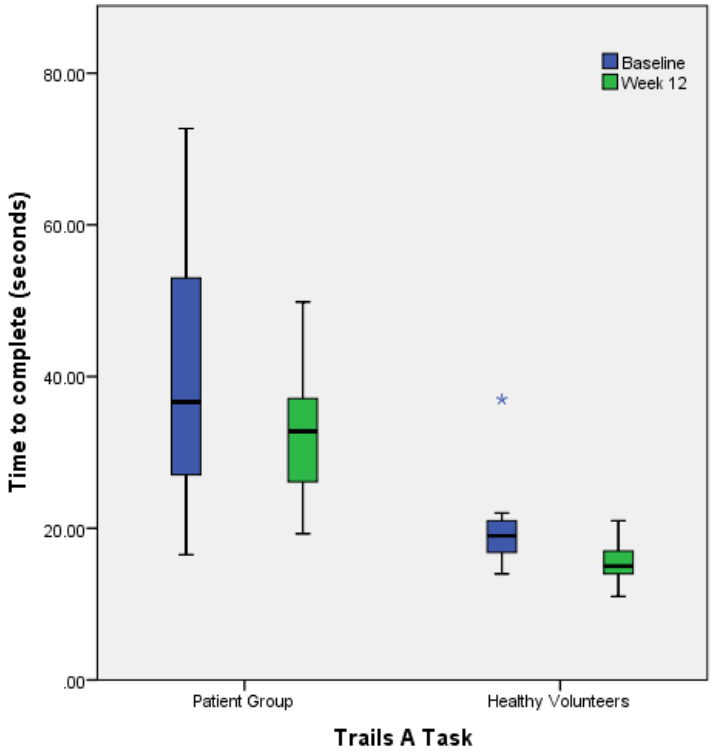
3.4.3.1 Individual Test Results Follow-up Results

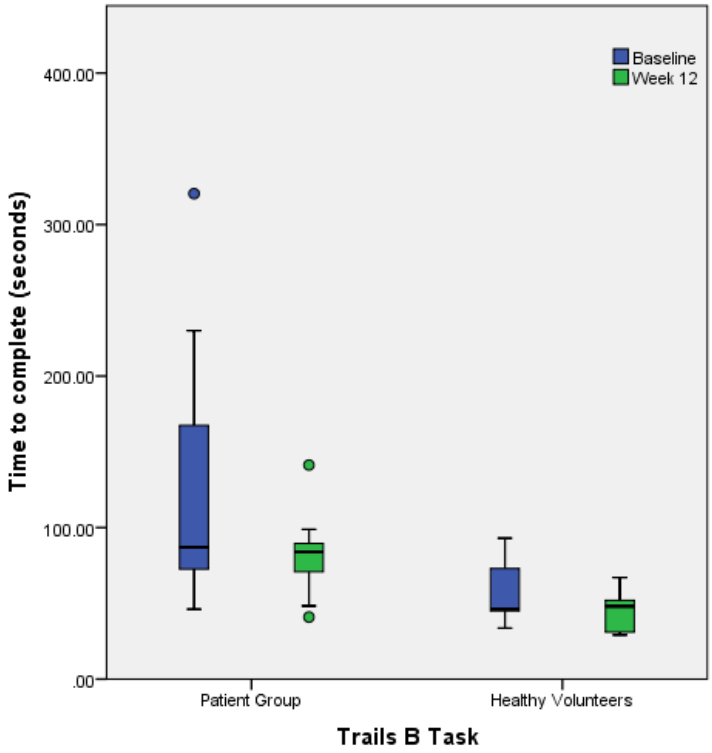
No changes from baseline to week 12 survived FDR correction for either patient and healthy volunteer groups. The results that did not survive FDR correction are found in table 3.17 with Trails A and Trails B performance at baseline and week 12 found in figure 3.5.

Table 3-17 Neurocognitive test results at follow-up

Neurocognitive Test	Group	Mean difference	% different	DF	t	p-value	FDR p-value	Cohen's d
Trails A	Patients	-7.54s	-10.35%	13	2.27	0.04	0.42	0.61
Trails B	Patients	-45.5s	-22.04%	11	2.24	0.05	0.42	0.65
SDMT (written)	Healthy Volunteers	8.8	6.84%	9	-3.2	0.01	0.07	-1.01
COWA	Healthy Volunteers	6.7	8%	9	-3.2	0.01	0.07	-1.0
MnM – Flip trial accuracy	Healthy Volunteers	7%	4.07%	9	-3.5	< 0.01	0.07	-1.11
MnM – RT, correct flip trials	Healthy Volunteers	-0.14s	-5.51%	9	2.88	0.02	0.09	0.91
MnM – Hold trial accuracy	Healthy Volunteers	3%	1.6%	9	-2.25	0.051	0.17	-0.71

Figure 3-5 Trails A & B task performance by timepoint and group. Circles are values 1.5 times above the 3rd interquartile range or 1.5 times below the 1st. Stars are values 3 times above the 3rd interquartile range.





3.4.3.2 Domain Level Between-group Findings at Follow-Up

At the domain level, neither group had significant changes from baseline to follow up in executive functions or in verbal working memory. In contrast, patients improved their speed of processing ($t(20.04) = -2.14$, $p = 0.03$; $d = -0.57$) and as did the healthy volunteers ($t(16.26) = -2.27$, $p = 0.02$; $d = -0.84$).

3.5 Exploratory Neurocognitive domain Correlations with White Matter ROIs

There were no significant correlations found between WM ROIs and domain level neurocognitive measures of executive functioning, processing speed, or verbal working memory for either patients or healthy volunteers.

3.6 Discussion

There were no significant changes at 12-week follow-up in accuracy in the emotion expression or the emotion recognition tasks for either group that survived correction for multiple comparisons. The patients did significantly improve their overall reaction time at follow-up in the emotion recognition and the emotion expression tasks. Healthy volunteers also significantly improved their reaction time in the emotion expression task at follow-up. No differences in any cognitive task performance survived FDR correction for multiple comparisons. Exploratory domain level analysis revealed significant improvements in uncorrected speed of processing for both patients and healthy volunteers at follow-up.

Few studies have examined the effects of exercise on emotion processing deficits in schizophrenia. For those that have, yoga has been the exercise paradigm, and have reported inconclusive results (Behere et al., 2011; Jayaram et al., 2013). While we demonstrated that exercise could induce reaction time improvements in schizophrenia patients, we did not see any increases in accuracy. It may be that more intense exercise for a longer duration, or an alternate

form of cognitive remediation is needed to induce improvements in emotion recognition accuracy. Potentially, exercise could also be combined with emotion recognition training to see if there is any benefit to adding exercise to existing emotion recognition training protocols that have shown positive results (Lado-Codesido et al., 2019; Silver et al., 2004).

Our lack of findings regarding exercise-based improvements in cognitive measures for patients contrasts with recent meta-analytic results that exercise improved working memory and social cognition (Firth et al., 2017). However, this meta-analysis also concluded that the most significant benefits came at higher dosages of exercise. It is likely that 12-weeks may not be a long enough time to induce exercise-driven cognition changes in schizophrenia. Additionally, our exploratory finding of significant improvements in speed of processing in both the patient and healthy volunteer group is both at odds with recent findings that stated that speed of processing was not a domain improved by exercise in schizophrenia (Firth et al., 2017).

The lack of association between cognitive domains and WM areas may be related to sample size and focus on mid-level cognitive domains instead of individual tests. With our small sample, we chose to reduce the number of comparisons and focus on more global factors instead of individual tests. Z-score transformations and averaging across tests to examine cognitive domains also followed the recommended course of action to not generalize a single test result to the function of an entire cognitive domain by the clinical neuropsychologist on our research team (AT).

3.6.1 Limitations

The main limitations of this study are the short 12-week length and the small number of participants that we were able to enroll. With 15 patients and 10 healthy volunteers, only large effects are readily detectable. It is also possible that the patients and healthy volunteers who

enrolled in the exercise intervention resulted in a sampling bias for people who are pre-disposed or self-motivated to exercise and not representative of their respective populations in general. Increased exercise intensity or longer intervention periods of 6 to 12 months may be required to trigger improvements in patient's accuracy of recognizing facial emotions or in cognitive domains. It may also be that exercise is best served as an adjunct therapy to cognitive training, as was recently demonstrated in first-episode schizophrenia patients (Nuechterlein et al., 2016).

3.6.2 Conclusion

The data here suggests that exercise is a viable intervention to increase efficiency in determination, but not accuracy, of facial emotional expression. It also suggests that exercise may be an avenue to improve the overall processing speed for treatment-resistant schizophrenia patients. However, replication of these results will need to be done with larger cohort given the small sample size in our study. The use of higher intensity exercise over a longer duration may be required to induce improvements in correctly identifying facial emotions, executive functioning, and verbal working memory domains in a treatment resistant schizophrenia population.

Chapter 4: Discussion

4.1 Overview of Findings

This thesis examined the effects of exercise on WM and facial emotion recognition in treatment resistant schizophrenia patients. Exercise has many well-established physical benefits but the potential effects of it on WM in the brain and improving accuracy of facial emotion judgement in treatment resistant schizophrenia patients is unknown. We were able to show that from baseline to week 12 that patients in our sample had decreased symptom severity, PANSS scores, and increased social functioning, SOFAS. Exercise also appears to be beneficial to speed of processing and decreasing the amount of time taken to decide what emotion a face is showing.

4.1.1 The Effects of Exercise in Treatment-resistant Schizophrenia

We were unable to demonstrate the potential benefits of exercise to the integrity WM regions in the brain as measured with MWF and FA. However, if subtle changes myelin did occur over the 12-weeks of moderate-intensity exercise they may not have been detectable due to the small sample size or current technological constraints of WM imaging. Future research should focus on more intense forms of exercise, larger sample sizes, and/or exercise of a longer duration to uncover the benefits of exercise to WM in treatment resistant schizophrenia. It remains unclear if different forms of exercise lead to differential changes in either WM indices or cognition. At the end of our trial patients had decreased symptom severity, increased social function, and decreased the amount of time it took to identify emotions but did not have any changes in their accuracy identifying emotions. Our findings contrast others that found that exercise did improve WM in schizophrenia patients in a 6 month exercise intervention study (Svatkova et al., 2015). While it is possible for oligodendrocytes to change on the order of minutes or hours, *de novo* myelination of axons, re-myelination, or other changes to myelin take

place on a longer time scale that is dependent on neuronal activity, growth factors, oligodendrocyte precursor cells, and associated cytoplasmic channels such as those opened by the Akt signaling pathway (Zheng et al., 2012). The 12-week intervention may not have had sufficient length or intensity to induce large enough changes in Akt to increase myelin as levels of Akt in schizophrenia are much lower than normal to begin with (Zheng et al., 2012). Despite this, in previously published work, it was demonstrated detectable increases in hippocampal volumes with 12-weeks of exercise was observed in chronic schizophrenia (Woodward et al., 2018), replicating prior findings with similar length exercise interventions (Lin et al., 2015; Pajonk et al., 2010). Current analyses were drawn from the same sample studied by the 2018 Woodward et al study, but due to uncorrectable motion in the GRASE sequences for some patient participants there were two fewer participants in the current study that had usable 3DT1 data than reported on by Woodward et al 2018. In the current analyses, exercise was again associated with improved PANSS and SOFAS scores for patients in our study. This is consistent with meta-analytic findings that moderate intensity exercise improves positive and negative symptoms in schizophrenia (Mittal et al., 2017). In contrast, we did not see statistically significant decreases in BMI, anti-psychotic medication, or significant increases in cardiovascular fitness that have been shown in other studies (Mittal et al., 2017). Despite our lack of specific MRI-based findings regarding WM plasticity after exercise, it is still warranted as an adjunct clinical treatment as it remains an avenue of therapy in treatment resistant schizophrenia for the negative side of medications, and addressing poor health behaviors in this population (Mittal et al., 2017).

4.2 Effects of Exercise on Emotion and Cognitive Deficits in Treatment-resistant Schizophrenia

While we found no improvements in accuracy in recognition of facial emotions in patients, we did see decreased reaction times in our patient group that were greater than those seen in the healthy volunteer group in these tasks after an exercise intervention. As decreased speed of processing is a hallmark of schizophrenia, it is possible that changes in WM microstructure that we were unable to detect changed enough to support this improvement. Alternatively, these improvements could be due to practice effects. However, the greater improvement seen in the patient group, versus the healthy volunteers, suggests that even if practice effects are present in these tests, improvements in reaction time as a result of 12-weeks of exercise are beyond the practice effect that may have occurred.

At baseline, we established large differences between treatment resistant schizophrenia patients and in verbal memory, speed of processing, and tests related to executive functions as measured by the COWA and Trails B. At follow up we noted preliminary improvements in speed of processing which may be attributable to the 12-weeks of exercise. It is known that poor myelination reduces the speed at which neuronal signals travel and hypothesized that re-myelination would result in increased or restored speed of processing affected individuals. However, these results may have also occurred due to practice effects on our testing measures. We did not see any improvements in cognition in our sample in contrast with recent meta-analytic findings suggesting moderate intensity exercise can have a positive effect on cognition for schizophrenia patients (Mittal et al., 2017).

4.3 Strengths and Limitations

This study investigated the effects of 12-weeks of exercise in treatment resistant psychosis patients with a healthy volunteer group that were matched on sex (60/40% male to female), age, level of education, and included participants from Caucasian, Asian, Latino, and Indigenous backgrounds. It represents a diverse portion of Canadian society and addresses a lack of female participation that occurred in prior exercise schizophrenia research studies (Pajonk et al., 2010; Scheewe et al., 2013).

The main limitation of the study was the small sample size in both groups. Every effort was made to recruit a larger sample, but difficulties were encountered in recruiting patients and in finding healthy volunteers that matched the patients on age, sex, and level of education. Another limitation is the shorter duration of our exercise intervention. Interventions showing detectable positive correlations between exercise and physical activity and WM in schizophrenia are typically 6 months in length (Brokmeier et al., 2019; Firth et al., 2017; Svatkova et al., 2015). However, these studies typically are not able to include treatment resistant schizophrenia limiting their applicability to our chosen population. We chose 12-weeks of exercise to replicate the study by Pajonk (Pajonk et al., 2010) that found increases in hippocampal volumes in this population. Further, a 12-weeks of exercise was an appropriate length of time as many people with treatment resistant schizophrenia are difficult to engage and motivate due to their emotional and cognitive deficits and may not be able to complete a 6-month trial without extensive support. This support would be difficult to provide as most treatment resistant schizophrenia patients and do not remain on the BC psychosis ward long enough for a 6-month study.

4.4 Clinical Implications

Exercise programs are a low-risk intervention that can safely compliment antipsychotic medications in treatment resistance schizophrenia. We found that treatment resistant psychosis patients benefit from a 12-week exercise program to address symptom severity, speed of processing, social functioning, and potentially metabolic concerns. The majority of patients attended most exercise sessions indicating that the lack of energy and motivation usually associated with this patient group did not prevent participation. They are able to incorporate exercise into their everyday routine with customized programs and with clinical staff that are able to motivate them. With the high metabolic and cardiovascular risks that come with treatment of the disorder it is laudable, if not urgent, to increase in physical activity as part of treatment for schizophrenia.

4.5 Conclusion

This work brought to light the improvements in facial emotion recognition reaction time, symptom reduction, improvements in social functioning, and exploratory overall improvements in processing speed that can result from 12-weeks of moderate intensity exercise in a treatment resistant group of schizophrenia patients. It provides further support for the utility of exercise in clinical in-patient psychosis wards as safe, beneficial treatment for patients. Exercise has the potential to address the metabolic and cardiovascular problems that occur as part of treating the disorder. While the effects of exercise on WM in the brain remain unclear, we established that MWF is a more sensitive marker of differences between schizophrenia patients and age, sex, and education level matched healthy volunteers than DTI based measures such as FA are. There are compelling physical and psychological reasons to ensure that patients can reap the benefits of exercise (Ashdown-Franks et al., 2020; Behere et al., 2011; Bredin et al., 2013; Falkai et al.,

2017; Firth et al., 2017; Hayes et al., 2015; Mittal et al., 2017; Phillips et al., 2014; Romain et al., 2018; Svatkova et al., 2015; Torres et al., 2015; van der Stouwe et al., 2018). These data also highlight the need for future exercise-based research with this population. Deeper exploration of the potential for other types of exercise, or larger sample sizes may to induce marked improvement in neurological functioning and optimize physiological measures of health.

Bibliography

Addington, D., Addington, J., & Maticka-tyndale, E. (1993). Assessing Depression in Schizophrenia: The Calgary Depression Scale. *British Journal of Psychiatry*, *163*(S22), 39–44. https://doi.org/10.1192/S0007125000292581

Ahn, J. H., Choi, J. H., Park, J. H., Kim, I. H., Cho, J.-H., Lee, J.-C., Koo, H.-M., Hwangbo, G., Yoo, K.-Y., Lee, C. H., Hwang, I. K., Cho, J. H., Choi, S. Y., Kwon, Y.-G., Kim, Y.-M., Kang, I.-J., & Won, M.-H. (2016). Long-Term Exercise Improves Memory Deficits via Restoration of Myelin and Microvessel Damage, and Enhancement of Neurogenesis in the Aged Gerbil Hippocampus After Ischemic Stroke. *Neurorehabilitation and Neural Repair*, *30*(9), 894–905. https://doi.org/10.1177/1545968316638444

Alloza, C., Cox, S. R., Duff, B., Semple, S. I., Bastin, M. E., Whalley, H. C., & Lawrie, S. M. (2016). Information processing speed mediates the relationship between white matter and general intelligence in schizophrenia. *Psychiatry Research - Neuroimaging*, *254*, 26–33. https://doi.org/10.1016/j.pscychresns.2016.05.008

Alves, D., Pires, M. M., Guimarães, A., & Miranda, M. C. (1986). Four cases of late onset metachromatic leucodystrophy in a family: Clinical, biochemical and neuropathological studies. *Journal of Neurology, Neurosurgery and Psychiatry*, *49*(12), 1417–1422. https://doi.org/10.1136/jnnp.49.12.1417

American Psychiatric Association, T. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890423349.

Anderson, V., Jacobs, R. K., & Anderson, P. J. (2008). Executive functions and the frontal lobes: A lifespan perspective. In Vicki Anderson, R. Jacobs, & P. J. Anderson (Eds.), *Executive functions and the frontal lobes: A lifespan perspective.* Taylor & Francis.

Arnedo, J., Mamah, D., Baranger, D. A., Harms, M. P., Barch, D. M., Svrakic, D. M., de Erausquin, G. A., Cloninger, C. R., & Zwir, I. (2015). Decomposition of brain diffusion imaging data uncovers latent schizophrenias with distinct patterns of white matter anisotropy. *NeuroImage, 120*, 43–54. https://doi.org/10.1016/j.neuroimage.2015.06.083

Arshad, M., Stanley, J. A., & Raz, N. (2016). Adult age differences in subcortical myelin content are consistent with protracted myelination and unrelated to diffusion tensor imaging indices. *NeuroImage*, *143*, 26–39. https://doi.org/10.1016/j.neuroimage.2016.08.047

Ashdown-Franks, G., Firth, J., Carney, R., Carvalho, A. F., Hallgren, M., Koyanagi, A., Rosenbaum, S., Schuch, F. B., Smith, L., Solmi, M., Vancampfort, D., & Stubbs, B. (2020). *Exercise as Medicine for Mental and Substance Use Disorders: A Meta-review of the Benefits for Neuropsychiatric and Cognitive Outcomes*. *50*, 151–170. https://doi.org/10.1007/s40279-019-01187-6

Assaf, Y., & Pasternak, O. (2008). Diffusion tensor imaging (DTI)-based white matter mapping in brain research: A review. In *Journal of Molecular Neuroscience* (Vol. 34, Issue 1, pp. 51–61). Springer. https://doi.org/10.1007/s12031-007-0029-0

Aston, C., Jiang, L., & Sokolov, B. P. (2004). Microarray analysis of postmortem temporal cortex from patients with schizophrenia. *Journal of Neuroscience Research, 77*(6), 858–866. https://doi.org/10.1002/jnr.20208

Bammer, R., Acar, B., & Moseley, M. E. (2003). In vivo MR tractography using diffusion imaging. *European Journal of Radiology*, *45*(3), 223–234. https://doi.org/10.1016/S0720-048X(02)00311-X

Barnes, T. R. E. (2018). Pharmacological management of treatment-resistant schizophrenia: alternatives to clozapine. In *Treatment Response and Resistance in Schizophrenia*. Oxford

University Press.

Bartzokis, G., Beckson, M., Lu, P. H., Nuechterlein, K. H., Edwards, N., & Mintz, J. (2001). Age-related changes in frontal and temporal lobe volumes in men: A magnetic resonance imaging study. *Archives of General Psychiatry*, *58*(5), 461–465. https://doi.org/10.1001/archpsyc.58.5.461

Bartzokis, George, Lu, P. H., Heydari, P., Couvrette, A., Lee, G. J., Kalashyan, G., Freeman, F., Grinstead, J. W., Villablanca, P., Finn, J. P., Mintz, J., Alger, J. R., & Altshuler, L. L. (2012). Multimodal magnetic resonance imaging assessment of white matter aging trajectories over the lifespan of healthy individuals. *Biological Psychiatry*, *72*(12), 1026–1034. https://doi.org/10.1016/j.biopsych.2012.07.010

Basser, P. J., Mattiello, J., & LeBihan, D. (1994). MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, *66*(1), 259–267. https://doi.org/10.1016/S0006-3495(94)80775-1

Beaulieu, C. (2002). The basis of anisotropic water diffusion in the nervous system - A technical review. In *NMR in Biomedicine* (Vol. 15, Issues 7–8, pp. 435–455). John Wiley & Sons, Ltd. https://doi.org/10.1002/nbm.782

Beaulieu, C., & Allen, P. S. (1994). Determinants of anisotropic water diffusion in nerves. *Magnetic Resonance in Medicine*, *31*(4), 394–400. https://doi.org/10.1002/mrm.1910310408

Bediou, B., Krolak-Salmon, P., Saoud, M., Henaff, M.-A., Burt, M., Dalery, J., & D'Amato, T. (2005). Facial Expression and Sex Recognition in Schizophrenia and Depression. *The Canadian Journal of Psychiatry*, *50*(9), 525–533. https://doi.org/10.1177/070674370505000905

Behere, R. V., Arasappa, R., Jagannathan, A., Varambally, S., Venkatasubramanian, G., Thirthalli, J., Subbakrishna, D. K., Nagendra, H. R., & Gangadhar, B. N. (2011). Effect of yoga therapy on facial emotion recognition deficits, symptoms and functioning in patients with schizophrenia. *Acta Psychiatrica Scandinavica*, *123*(2), 147–153. https://doi.org/10.1111/j.1600-0447.2010.01605.x

Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society: Series B (Methodological)*, *57*(1), 289–300. https://doi.org/10.1111/j.2517-6161.1995.tb02031.x

Bettcher, B. M., Mungas, D., Patel, N., Elofson, J., Dutt, S., Wynn, M., Watson, C. L., Stephens, M., Walsh, C. M., & Kramer, J. H. (2016). Neuroanatomical substrates of executive functions: Beyond prefrontal structures. *Neuropsychologia*, *85*, 100–109. https://doi.org/10.1016/j.neuropsychologia.2016.03.001

Birkl, C., Birkl-Toeglhofer, A. M., Endmayr, V., Höftberger, R., Kasprian, G., Krebs, C., Haybaeck, J., & Rauscher, A. (2019). The influence of brain iron on myelin water imaging. *NeuroImage*, *199*, 545–552. https://doi.org/10.1016/j.neuroimage.2019.05.042

Bleuler, E. (1911). *Dementia Praecox, or the Group of Schizophrenias*. International University Press.

Bowers, M. B. (1974). Retreat from sanity: The structure of emerging psychosis. In *Retreat from sanity: The structure of emerging psychosis.* Human Sciences Press.

Bracht, T., Jones, D. K., Bells, S., Walther, S., Drakesmith, M., & Linden, D. (2016). Myelination of the right parahippocampal cingulum is associated with physical activity in young healthy adults. *Brain Structure and Function*, *221*(9), 4537–4548. https://doi.org/10.1007/s00429-016-1183-3

Braga, R. J., Reynolds, G. P., & Siris, S. G. (2013). Anxiety comorbidity in schizophrenia. In *Psychiatry Research* (Vol. 210, Issue 1, pp. 1–7). Psychiatry Res. https://doi.org/10.1016/j.psychres.2013.07.030

Bredin, S. S. D., Warburton, D. E. R., & Lang, D. J. (2013). The health benefits and challenges of exercise training in persons living with schizophrenia: a pilot study. *Brain Sciences*, *3*(2), 821–848. https://doi.org/10.3390/brainsci3020821

Broder, M. S., Greene, M., Chang, E., Hartry, A., Touya, M., Munday, J., & Yan, T. (2018). Health Care Resource Use, Costs, and Diagnosis Patterns in Patients With Schizophrenia and Bipolar Disorder: Real-world Evidence From US Claims Databases. *Clinical Therapeutics*, *40*(10), 1670–1682. https://doi.org/10.1016/j.clinthera.2018.08.004

Brokmeier, L. L., Firth, J., Vancampfort, D., Smith, L., Deenik, J., Rosenbaum, S., Stubbs, B., & Schuch, F. B. (2019). *Does physical activity reduce the risk of psychosis? A systematic review and meta-analysis of prospective studies.* https://doi.org/10.1016/j.psychres.2019.112675

Buchanan, R. W., Davis, M., Goff, D. C., Green, M. F., Keefe, R. S. E., Leon, A. C., Nuechterlein, K. H., Laughren, T., Levin, R., Stover, E., Fenton, W., & Marder, S. R. (2005). A summary of the FDA-NIMH-MATRICS workshop on clinical trial design for neurocognitive drugs for schizophrenia. *Schizophrenia Bulletin*, *31*(1), 5–19. https://doi.org/10.1093/schbul/sbi020

Caprihan, A., Jones, T., Chen, H., Lemke, N., Abbott, C., Qualls, C., Canive, J., Gasparovic, C., & Bustillo, J. R. (2015). The Paradoxical Relationship between White Matter, Psychopathology and Cognition in Schizophrenia: A Diffusion Tensor and Proton Spectroscopic Imaging Study. *Neuropsychopharmacology*, *40*(9), 2248–2257.

https://doi.org/10.1038/npp.2015.72

Casarotti, A., Papagno, C., & Zarino, B. (2014). Modified Taylor Complex Figure: Normative data from 290 adults. *Journal of Neuropsychology*, *8*(2), 186–198. https://doi.org/10.1111/jnp.12019

Cassel, J. C., Duconseille, E., Jeltsch, H., & Will, B. (1997). The fimbria-fornix/cingular bundle pathways: A review of neurochemical and behavioural approaches using lesions and transplantation techniques. *Progress in Neurobiology*, *51*(6), 663–716. https://doi.org/10.1016/S0301-0082(97)00009-9

Cassetta, B. D., & Goghari, V. M. (2016). Working memory and processing speed training in schizophrenia: Study protocol for a randomized controlled trial. *Trials*, *17*(1). https://doi.org/10.1186/s13063-016-1188-5

Chan, R. C. K., Li, H., Cheung, E. F. C., & Gong, Q. yong. (2010). Impaired facial emotion perception in schizophrenia: A meta-analysis. In *Psychiatry Research* (Vol. 178, Issue 2, pp. 381–390). Psychiatry Res. https://doi.org/10.1016/j.psychres.2009.03.035

Charlson, F. J., Ferrari, A. J., Santomauro, D. F., Diminic, S., Stockings, E., Scott, J. G., McGrath, J. J., & Whiteford, H. A. (2018). Global Epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. *Schizophrenia Bulletin*, *44*(6), 1195–1203. https://doi.org/10.1093/schbul/sby058

Charlton, R. A., Barrick, T. R., Lawes, I. N. C., Markus, H. S., & Morris, R. G. (2010). White matter pathways associated with working memory in normal aging. *Cortex*, *46*(4), 474–489. https://doi.org/10.1016/j.cortex.2009.07.005

Chechlacz, M., Rotshtein, P., Hansen, P. C., Deb, S., Riddoch, M. J., & Humphreys, G. W. (2013). The central role of the temporo-parietal junction and the superior longitudinal

fasciculus in supporting multi-item competition: Evidence from lesion-symptom mapping of extinction. *Cortex*, *49*(2), 487–506. https://doi.org/10.1016/j.cortex.2011.11.008

Chen, L.-J., Hao, J. C., Ku, P.-W., & Stubbs, B. (2018). Prospective associations of physical fitness and cognitive performance among inpatients with Schizophrenia. *Psychiatry Research*, *270*, 738–743. https://doi.org/10.1016/J.PSYCHRES.2018.10.044

Chouinard, G., & Margolese, H. C. (2005). Manual for the Extrapyramidal Symptom Rating Scale (ESRS). *Schizophrenia Research*, *76*(2–3), 247–265. https://doi.org/10.1016/j.schres.2005.02.013

Chung, S., Fieremans, E., Kucukboyaci, N. E., Wang, X., Morton, C. J., Novikov, D. S., Rath, J. F., & Lui, Y. W. (2018). Working Memory And Brain Tissue Microstructure: White Matter Tract Integrity Based On Multi-Shell Diffusion MRI. *Scientific Reports*, *8*(1). https://doi.org/10.1038/s41598-018-21428-4

Clark, K. A., Nuechterlein, K. H., Asarnow, R. F., Hamilton, L. S., Phillips, O. R., Hageman, N. S., Woods, R. P., Alger, J. R., Toga, A. W., & Narr, K. L. (2011). Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia. *Journal of Psychiatric Research*, *45*(7), 980–988. https://doi.org/10.1016/j.jpsychires.2011.01.006

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences*. L. Erlbaum Associates.

Crocker, C. E., & Tibbo, P. G. (2018). Confused Connections? Targeting White Matter to Address Treatment Resistant Schizophrenia. *Frontiers in Pharmacology*, *9*, 1172. https://doi.org/10.3389/fphar.2018.01172

Curcic, D., Stojmenovic, T., Djukic-Dejanovic, S., Dikic, N., Vesic-Vukasinovic, M., Radivojevic, N., Andjelkovic, M., Borovcanin, M., & Djokic, G. (2017). Positive impact of prescribed physical activity on symptoms of schizophrenia: Randomized clinical trial.

Psychiatria Danubina, *29*(4), 459–465. https://doi.org/10.24869/psyd.2017.459

Davis, K. L., Stewart, D. G., Friedman, J. I., Buchsbaum, M., Harvey, P. D., Hof, P. R., Buxbaum, J., & Haroutunian, V. (2003). White matter changes in schizophrenia evidence for myelin-related dysfunction. In *Archives of General Psychiatry* (Vol. 60, Issue 5, pp. 443–456). https://doi.org/10.1001/archpsyc.60.5.443

Debenedetti, P. G., & Klein, M. L. (2017). Chemical physics of water. *PNAS*, *114*(51), 13325–13326. https://doi.org/10.1073/pnas.1719350115

Deicken, R. F., Calabrese, G., Merrin, E. L., Meyerhoff, D. J., Dillon, W. P., Weiner, M. W., & Fein, G. (1994). 31Phosphorus magnetic resonance spectroscopy of the frontal and parietal lobes in chronic schizophrenia. *Biological Psychiatry*, *36*(8), 503–510. https://doi.org/10.1016/0006-3223(94)90613-0

del Re, E. C., Bouix, S., Fitzsimmons, J., Blokland, G. A. M., Mesholam-Gately, R., Wojcik, J., Kikinis, Z., Kubicki, M., Petryshen, T., Pasternak, O., Shenton, M. E., & Niznikiewicz, M. (2019). Diffusion abnormalities in the corpus callosum in first episode schizophrenia: Associated with enlarged lateral ventricles and symptomatology. *Psychiatry Research*, *277*, 45–51. https://doi.org/10.1016/j.psychres.2019.02.038

Diaz, R. L., Wong, U., Hodgins, D. C., Chiu, C. G., & Goghari, V. M. (2016). Violent video game players and non-players differ on facial emotion recognition. *Aggressive Behavior*, *42*(1), 16–28. https://doi.org/10.1002/ab.21602

Domènech-Estévez, E., Baloui, H., Meng, X., Zhang, Y., Deinhardt, K., Dupree, J. L., Einheber, S., Chrast, R., & Salzer, J. L. (2016). Akt regulates axon wrapping and myelin sheath thickness in the PNS. *Journal of Neuroscience*, *36*(16), 4506–4521. https://doi.org/10.1523/JNEUROSCI.3521-15.2016

Drakesmith, M., Parker, G. D., Smith, J., Linden, S. C., Rees, E., Williams, N., Owen, M. J., van den Bree, M., Hall, J., Jones, D. K., & Linden, D. E. J. (2019). Genetic risk for schizophrenia and developmental delay is associated with shape and microstructure of midline white-matter structures. *Translational Psychiatry*, *9*(1). https://doi.org/10.1038/s41398-019-0440-7

Drew, L. J., Crabtree, G. W., Markx, S., Stark, K. L., Chaverneff, F., Xu, B., Mukai, J., Fenelon, K., Hsu, P. K., Gogos, J. A., & Karayiorgou, M. (2011). The 22q11.2 microdeletion: Fifteen years of insights into the genetic and neural complexity of psychiatric disorders. *International Journal of Developmental Neuroscience*, *29*(3), 259–281. https://doi.org/10.1016/j.ijdevneu.2010.09.007

Eastwood, S. L., & Harrison, P. J. (2005). Interstitial white matter neuron density in the dorsolateral prefrontal cortex and parahippocampal gyrus in schizophrenia. *Schizophrenia Research*, *79*(2–3), 181–188. https://doi.org/10.1016/j.schres.2005.07.001

Eekhout, I., De Vet, H. C. W., Twisk, J. W. R., Brand, J. P. L., De Boer, M. R., & Heymans, M. W. (2014). Missing data in a multi-item instrument were best handled by multiple imputation at the item score level. *Journal of Clinical Epidemiology*, *67*(3), 335–342. https://doi.org/10.1016/j.jclinepi.2013.09.009

Eekhout, I., Van De Wiel, M. A., & Heymans, M. W. (2017). Methods for significance testing of categorical covariates in logistic regression models after multiple imputation: Power and applicability analysis. *BMC Medical Research Methodology*, *17*(1). https://doi.org/10.1186/s12874-017-0404-7

Elkis, H., & Buckley, P. F. (2016). Treatment-Resistant Schizophrenia. In *Psychiatric Clinics of North America* (Vol. 39, Issue 2, pp. 239–265). W.B. Saunders.

https://doi.org/10.1016/j.psc.2016.01.006

Ellis, P. D. (2010). The Essential Guide to Effect Sizes. In *The Essential Guide to Effect Sizes*. Cambridge University Press. https://doi.org/10.1017/cbo9780511761676

Falkai, P., Malchow, B., & Schmitt, A. (2017). Aerobic exercise and its effects on cognition in schizophrenia. *Current Opinion in Psychiatry*, *30*(3), 171–175. https://doi.org/10.1097/YCO.0000000000000326

Feter, N., Freitas, M. P., Gonzales, N. G., Umpierre, D., Cardoso, R. K., & Rombaldi, A. J. (2018). Effects of physical exercise on myelin sheath regeneration: A systematic review and meta-analysis. *Science & Sports*, *33*(1), 8–21. https://doi.org/10.1016/J.SCISPO.2017.06.009

Firth, J., Stubbs, B., Rosenbaum, S., Vancampfort, D., Malchow, B., Schuch, F., Elliott, R., Nuechterlein, K. H., & Yung, A. R. (2017). Aerobic Exercise Improves Cognitive Functioning in People With Schizophrenia: A Systematic Review and Meta-Analysis. *Greater Manchester West NHS Mental Health Foundation Trust*, *43*(3), 546–556. https://doi.org/10.1093/schbul/sbw115

Fitzsimmons, J., Kubicki, M., Smith, K., Bushell, G., Estepar, R. S. J., Westin, C.-F., Nestor, P. G., Niznikiewicz, M. A., Kikinis, R., McCarley, R. W., & Shenton, M. E. (2009). Diffusion tractography of the fornix in schizophrenia. *Schizophrenia Research*, *107*(1), 39–46. https://doi.org/10.1016/J.SCHRES.2008.10.022

Flores, A. I., Narayanan, S. P., Morse, E. N., Shick, H. E., Yin, X., Kidd, G., Avila, R. L., Kirschner, D. A., & Macklin, W. B. (2008). Constitutively active Akt induces enhanced myelination in the CNS. *Journal of Neuroscience*, *28*(28), 7174–7183. https://doi.org/10.1523/JNEUROSCI.0150-08.2008

Flynn, S. W., Lang, D. J., Mackay, A. L., Goghari, V. M., Vavasour, I. M., Whittall, K. P., Smith, G. N., Arango, V., Mann, J. J., Dwork, A. J., Falkai, P., & Honer, W. G. (2003). Abnormalities of myelination in schizophrenia detected in vivo with MRI, and post-mortem with analysis of oligodendrocyte proteins. *Molecular Psychiatry*, *8*(9), 811–820. https://doi.org/10.1038/sj.mp.4001337

Friedman, J. I., Tang, C., Carpenter, D., Buchsbaum, M., Schmeidler, J., Flanagan, L., Golembo, S., Kanellopoulou, I., Ng, J., Hof, P. R., Harvey, P. D., Tsopelas, N. D., Stewart, D., & Davis, K. L. (2008). Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. *American Journal of Psychiatry*, *165*(8), 1024–1032. https://doi.org/10.1176/appi.ajp.2008.07101640

Fritz, C. O., Morris, P. E., & Richler, J. J. (2012). Effect size estimates: Current use, calculations, and interpretation. *Journal of Experimental Psychology: General*, *141*(1), 2–18. https://doi.org/10.1037/a0024338

Fukutani, Y., Noriki, Y., Sasaki, K., Isaki, K., Kuriyama, M., Kurosawa, K., & Ida, H. (1999). Adult-type metachromatic leukodystrophy with a compound heterozygote mutation showing character change and dementia. *Psychiatry and Clinical Neurosciences*, *53*(3), 425–428. https://doi.org/10.1046/j.1440-1819.1999.00569.x

German, D. C., Liang, C. L., Song, T., Yazdani, U., Xie, C., & Dietschy, J. M. (2002). Neurodegeneration in the Niemann-Pick C mouse: Glial involvement. *Neuroscience*, *109*(3), 437–450. https://doi.org/10.1016/S0306-4522(01)00517-6

Glickman, M. E., Rao, S. R., & Schultz, M. R. (2014). False discovery rate control is a recommended alternative to Bonferroni-type adjustments in health studies. In *Journal of Clinical Epidemiology* (Vol. 67, Issue 8, pp. 850–857). Elsevier USA.

https://doi.org/10.1016/j.jclinepi.2014.03.012

Goghari, V. M., MacDonald, A. W., & Sponheim, S. R. (2011). Temporal Lobe Structures and Facial Emotion Recognition in Schizophrenia Patients and Nonpsychotic Relatives. *Schizophrenia Bulletin*, *37*(6), 1281–1294. https://doi.org/10.1093/schbul/sbq046

Goghari, V. M., Sanford, N., Spilka, M. J., & Woodward, T. S. (2017). Task-Related Functional Connectivity Analysis of Emotion Discrimination in a Family Study of Schizophrenia. *Schizophrenia Bulletin*, *43*(6), 1348–1362. https://doi.org/10.1093/schbul/sbx004

Gons, R. A. R., Tuladhar, A. M., de Laat, K. F., van Norden, A. G. W., van Dijk, E. J., Norris, D. G., Zwiers, M. P., & de Leeuw, F.-E. (2013). Physical activity is related to the structural integrity of cerebral white matter. *Neurology*, *81*(11), 971–976. https://doi.org/10.1212/WNL.0b013e3182a43e33

Gur, R. C., Sara, R., Hagendoorn, M., Marom, O., Hughett, P., Macy, L., Turner, T., Bajcsy, R., Posner, A., & Gur, R. E. (2002). A method for obtaining 3-dimensional facial expressions and its standardization for use in neurocognitive studies. *Journal of Neuroscience Methods*, *115*(2), 137–143. https://doi.org/10.1016/S0165-0270(02)00006-7

H. Karlsgodt, K., C. Jacobson, S., Seal, M., & Fusar-Poli, P. (2012). The Relationship of Developmental Changes in White Matter to the Onset of Psychosis. *Current Pharmaceutical Design*, *18*(4), 422–433. https://doi.org/10.2174/138161212799316073

Haigh, S. M., Eack, S. M., Keller, T., Minshew, N. J., & Behrmann, M. (2019). White matter structure in schizophrenia and autism: Abnormal diffusion across the brain in schizophrenia. *Neuropsychologia*, *135*. https://doi.org/10.1016/j.neuropsychologia.2019.107233

Hakak, Y., Walker, J. R., Li, C., Wong, W. H., Davis, K. L., Buxbaum, J. D., Haroutunian, V., & Fienberg, A. A. (2001). Genome-wide expression analysis reveals dysregulation of

myelination-related genes in chronic schizophrenia. *Proceedings of the National Academy of Sciences of the United States of America*, *98*(8), 4746–4751. https://doi.org/10.1073/pnas.081071198

Hamilton, M. (1959). THE ASSESSMENT OF ANXIETY STATES BY RATING. *British Journal of Medical Psychology*, *32*(1), 50–55. https://doi.org/10.1111/j.2044-8341.1959.tb00467.x

Hanlon, F. M., Houck, J. M., Klimaj, S. D., Caprihan, A., Mayer, A. R., Weisend, M. P., Bustillo, J. R., Hamilton, D. A., & Tesche, C. D. (2012). Frontotemporal anatomical connectivity and working-relational memory performance predict everyday functioning in schizophrenia. *Psychophysiology*, *49*(10), 1340–1352. https://doi.org/10.1111/j.1469-8986.2012.01448.x

Hasan, K. M., Iftikhar, A., Kamali, A., Kramer, L. A., Ashtari, M., Cirino, P. T., Papanicolaou, A. C., Fletcher, J. M., & Ewing-Cobbs, L. (2009). Development and aging of the healthy human brain uncinate fasciculus across the lifespan using diffusion tensor tractography. *Brain Research*, *1276*, 67–76. https://doi.org/10.1016/J.BRAINRES.2009.04.025

Hayes, S. M., Salat, D. H., Forman, D. E., Sperling, R. A., & Verfaellie, M. (2015). Cardiorespiratory fitness is associated with white matter integrity in aging. *Annals of Clinical and Translational Neurology*, *2*(6), 688–698. https://doi.org/10.1002/acn3.204

Heinrichs, R. W. (2003). Historical origins of schizophrenia: Two early madmen and their illness. *Journal of the History of the Behavioral Sciences*, *39*(4), 349–363. https://doi.org/10.1002/jhbs.10152

Highley, J. R., Esiri, M. M., McDonald, B., Roberts, H. C., Walker, M. A., & Crow, T. J. (1999). The size and fiber composition of the anterior commissure with respect to gender and

schizophrenia. *Biological Psychiatry*, *45*(9), 1120–1127. https://doi.org/10.1016/S0006-3223(98)00323-0

Holleran, L., Kelly, S., Alloza, C., Agartz, I., Andreassen, O. A., Arango, C., Banaj, N., Calhoun, V., Cannon, D., Carr, V., Corvin, A., Glahn, D. C., Gur, R., Hong, E., Hoschl, C., Howells, F. M., James, A., Janssen, J., Kochunov, P., … Donohoe, G. (2020). The relationship between white matter microstructure and general cognitive ability in patients with schizophrenia and healthy participants in the ENIGMA consortium. *American Journal of Psychiatry*, *177*(6), 537–547. https://doi.org/10.1176/appi.ajp.2019.19030225

Howes, O. D., Kambeitz, J., Kim, E., Stahl, D., Slifstein, M., Abi-Dargham, A., & Kapur, S. (2012). The nature of dopamine dysfunction in schizophrenia and what this means for treatment: Meta-analysisof imaging studies. *Archives of General Psychiatry*, *69*(8), 776–786. https://doi.org/10.1001/archgenpsychiatry.2012.169

Howes, O. D., McCutcheon, R., Agid, O., De Bartolomeis, A., Van Beveren, N. J. M., Birnbaum, M. L., Bloomfield, M. A. P., Bressan, R. A., Buchanan, R. W., Carpenter, W. T., Castle, D. J., Citrome, L., Daskalakis, Z. J., Davidson, M., Drake, R. J., Dursun, S., Ebdrup, B. H., Elkis, H., Falkai, P., … Correll, C. U. (2017). Treatment-ResistantSchizophrenia: TreatmentResponse and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *American Journal of Psychiatry*, *174*(3), 216–229. https://doi.org/10.1176/appi.ajp.2016.16050503

Hummer, T. A., Francis, M. M., Vohs, J. L., Liffick, E., Mehdiyoun, N. F., & Breier, A. (2018). Characterization of white matter abnormalities in early-stage schizophrenia. *Early Intervention in Psychiatry*, *12*(4), 660–668. https://doi.org/10.1111/eip.12359

Hyde, T. M., Ziegler, J. C., & Weinberger, D. R. (1992). Psychiatric Disturbances in

Metachromatic Leukodystrophy: Insights into the Neurobiology of Psychosis. *Archives of Neurology*, *49*(4), 401–406. https://doi.org/10.1001/archneur.1992.00530280095028

IBM. (2017). *IBM SPSS Statistics for Macintosh* (25.0). IBM CORP. https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss

Jahshan, C., Heaton, R. K., Golshan, S., & Cadenhead, K. S. (2010). Course of neurocognitive deficits in the prodrome and first episode of schizophrenia. *Neuropsychology*, *24*(1), 109–120. https://doi.org/10.1037/a0016791

Jayaram, N., Varambally, S., Behere, R. V., Venkatasubramanian, G., Arasappa, R., Christopher, R., & Gangadhar, B. N. (2013). Effect of yoga therapy on plasma oxytocin and facial emotion recognition deficits in patients of schizophrenia. *Indian Journal of Psychiatry*, *55*(7), S409. https://doi.org/10.4103/0019-5545.116318

Jenkinson, M., Beckmann, C. F., Behrens, T. E. J., Woolrich, M. W., & Smith, S. M. (2012). FSL. *NeuroImage*, *62*(2), 782–790. https://doi.org/10.1016/j.neuroimage.2011.09.015

Johnson, N. F., Gold, B. T., Brown, C. A., Anggelis, E. F., Bailey, A. L., Clasey, J. L., & Powell, D. K. (2017). Endothelial function is associated with white matter microstructure and executive function in older adults. *Frontiers in Aging Neuroscience*, *9*(AUG). https://doi.org/10.3389/fnagi.2017.00255

Johnstone, E. C., Frith, C. D., Crow, T. J., Husband, J., & Kreel, L. (1976). CEREBRAL VENTRICULAR SIZE AND COGNITIVE IMPAIRMENT IN CHRONIC SCHIZOPHRENIA. *The Lancet*, *308*(7992), 924–926. https://doi.org/10.1016/S0140-6736(76)90890-4

Joo, S. W., Yoon, W., Shon, S.-H., Kim, H., Cha, S., Park, K. J., & Lee, J. (2018). Altered white matter connectivity in patients with schizophrenia: An investigation using public

neuroimaging data from SchizConnect. *PLOS ONE*, *13*(10), e0205369. https://doi.org/10.1371/journal.pone.0205369

Karbasforoushan, H., Duffy, B., Blackford, J. U., & Woodward, N. D. (2015). Processing speed impairment in schizophrenia is mediated by white matter integrity. *Psychological Medicine*, *45*, 109–120. https://doi.org/10.1017/S0033291714001111

Karlsgodt, K. H., Niendam, T. A., Bearden, C. E., & Cannon, T. D. (2009). White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis. *Biological Psychiatry*, *66*(6), 562–569. https://doi.org/10.1016/j.biopsych.2009.03.013

Karlsgodt, K. H., van Erp, T. G. M., Poldrack, R. A., Bearden, C. E., Nuechterlein, K. H., & Cannon, T. D. (2008). Diffusion Tensor Imaging of the Superior Longitudinal Fasciculus and Working Memory in Recent-Onset Schizophrenia. *Biological Psychiatry*, *63*(5), 512–518. https://doi.org/10.1016/j.biopsych.2007.06.017

Karvonen, J., & Vuorimaa, T. (1988). Heart Rate and Exercise Intensity During Sports Activities: Practical Application. In *Sports Medicine: An International Journal of Applied Medicine and Science in Sport and Exercise* (Vol. 5, Issue 5, pp. 303–311). Springer. https://doi.org/10.2165/00007256-198805050-00002

Kavanagh, D. J. (1992). Recent developments in expressed emotion and schizophrenia. In *British Journal of Psychiatry* (Vol. 160, Issue MAY., pp. 601–620). https://doi.org/10.1192/bjp.160.5.601

Kay, S. R., Opler, L. A., & Lindenmayer, J. P. (1988). Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Research*, *23*(1), 99–110. https://doi.org/10.1016/0165-1781(88)90038-8

Kelly, S., Jahanshad, N., Zalesky, A., Kochunov, P., Agartz, I., Alloza, C., Andreassen, O. A., Arango, C., Banaj, N., Bouix, S., Bousman, C. A., Brouwer, R. M., Bruggemann, J., Bustillo, J., Cahn, W., Calhoun, V., Cannon, D., Carr, V., Catts, S., … Donohoe, G. (2018). Widespread white matter microstructural differences in schizophrenia across 4322 individuals: results from the ENIGMA Schizophrenia DTI Working Group. *Molecular Psychiatry*, *23*(5), 1261–1269. https://doi.org/10.1038/mp.2017.170

Keymer-Gausset, A., Alonso-Solís, A., Corripio, I., Sauras-Quetcuti, R. B., Pomarol-Clotet, E., Canales-Rodriguez, E. J., Grasa-Bello, E., Álvarez, E., & Portella, M. J. (2018). Gray and white matter changes and their relation to illness trajectory in first episode psychosis. *European Neuropsychopharmacology*, *28*(3), 392–400. https://doi.org/10.1016/j.euroneuro.2017.12.117

Kim, G. W., & Jeong, G. W. (2015). White matter volume change and its correlation with symptom severity in patients with schizophrenia: A VBM-DARTEL study. *NeuroReport*, *26*(18), 1095–1100. https://doi.org/10.1097/WNR.0000000000000471

Kohler, C. G., Walker, J. B., Martin, E. A., Healey, K. M., & Moberg, P. J. (2010). Facial emotion perception in schizophrenia: A meta-analytic review. *Schizophrenia Bulletin*, *36*(5), 1009–1019. https://doi.org/10.1093/schbul/sbn192

Kraepelin, E. (1904). *Lectures on Clinical Psychiatry*. William Wood & Co.

Kraepelin, E. (1908). Die Prognose der Dementia praecox (Schizophreniegruppe). *Allgemeine Zeitschrift Für Psychiatrie Und Psychisch-Gerichtliche Medizin*, *31*, 436–480.

Krebs, Claudia, P., Weinberg, Joanne, P., & Akesson, Elizabeth, Ms. (2012). *Lippincott's Illustrated Review of Neurocience*. http://webcat1.library.ubc.ca.ezproxy.library.ubc.ca/vwebv/holdingsInfo?bibId=5201447

Kubicki, M., Niznikiewicz, M., Connor, E., Ungar, L., Nestor, P. G., Bouix, S., Dreusicke, M., Kikinis, R., McCarley, R. W., & Shenton, M. E. (2009). Relationship between white matter integrity, attention, and memory in schizophrenia: A diffusion tensor imaging study. *Brain Imaging and Behavior*, *3*(2), 191–201. https://doi.org/10.1007/s11682-009-9061-8

Kubicki, M., Styner, M., Bouix, S., Gerig, G., Markant, D., Smith, K., Kikinis, R., McCarley, R. W., & Shenton, M. E. (2008). Reduced interhemispheric connectivity in schizophrenia-tractography based segmentation of the corpus callosum. *Schizophrenia Research*, *106*(2–3), 125–131. https://doi.org/10.1016/j.schres.2008.08.027

Kuhn R. (2004). Eugen Bleuler's Concepts of Psychopathology. History of Psychiatry. In *History of Psychiatry* (Vol. 15, Issue 3, pp. 361–366). Sage PublicationsSage CA: Thousand Oaks, CA. https://doi.org/10.1177/0957154X04044603

Kuswanto, C. N., Teh, I., Lee, T. S., & Sim, K. (2012). Diffusion tensor imaging findings of white matter changes in first episode schizophrenia: A systematic review. In *Clinical Psychopharmacology and Neuroscience* (Vol. 10, Issue 1, pp. 13–24). Korean College of Neuropsychopharmacology. https://doi.org/10.9758/cpn.2012.10.1.13

Lado-Codesido, M., Pérez, C. M., Mateos, R., Olivares, J. M., & Caballero, A. G. (2019). Improving emotion recognition in schizophrenia with "VOICES": An on-line prosodic self-training. *PLoS ONE*, *14*(1). https://doi.org/10.1371/journal.pone.0210816

Lamberti, J. S., Olson, D., Crilly, J. F., Olivares, T., Williams, G. C., Tu, X., Tang, W., Wiener, K., Dvorin, S., & Dietz, M. B. (2006). Prevalence of the metabolic syndrome among patients receiving clozapine. *American Journal of Psychiatry*, *163*(7), 1273–1276. https://doi.org/10.1176/ajp.2006.163.7.1273

Lang, D. J., Yip, E., MacKay, A. L., Thornton, A. E., Vila-Rodriguez, F., MacEwan, G. W.,

Kopala, L. C., Smith, G. N., Laule, C., MacRae, C. B., & Honer, W. G. (2014). 48 echo T2 myelin imaging of white matter in first-episode schizophrenia: Evidence for aberrant myelination. *NeuroImage: Clinical*, *6*, 408–414. https://doi.org/10.1016/J.NICL.2014.10.006

Laule, C., Leung, E., Li, D. K. B., Traboulsee, A. L., Paty, D. W., MacKay, A. L., & Moore, G. R. W. (2006). Myelin water imaging in multiple sclerosis: Quantitative correlations with histopathology. *Multiple Sclerosis*. https://doi.org/10.1177/1352458506070928

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess Early Mortality in Schizophrenia. *Annual Review of Clinical Psychology*, *10*(1), 425–448. https://doi.org/10.1146/annurev-clinpsy-032813-153657

Lee, D.-K., Lee, H., Park, K., Joh, E., Kim, C.-E., & Ryu, S. (2020). Common gray and white matter abnormalities in schizophrenia and bipolar disorder. *PLOS ONE, 15*(5), e0232826. https://doi.org/10.1371/journal.pone.0232826

Lee, P., Li, P. C., Liu, C. H., & Hsieh, C. L. (2011). Test-retest reliability of two attention tests in schizophrenia. *Archives of Clinical Neuropsychology*, *26*(5), 405–411. https://doi.org/10.1093/arclin/acr038

Lener, M. S., Wong, E., Tang, C. Y., Byne, W., Goldstein, K. E., Blair, N. J., Haznedar, M. M., New, A. S., Chemerinski, E., Chu, K. W., Rimsky, L. S., Siever, L. J., Koenigsberg, H. W., & Hazlett, E. A. (2015). White matter abnormalities in schizophrenia and schizotypal personality disorder. *Schizophrenia Bulletin*, *41*(1), 300–310. https://doi.org/10.1093/schbul/sbu093

Leonard, C. J., Kaiser, S. T., Robinson, B. M., Kappenman, E. S., Hahn, B., Gold, J. M., & Luck, S. J. (2013). Toward the neural mechanisms of reduced working memory capacity in

schizophrenia. *Cerebral Cortex*, *23*(7), 1582–1592. https://doi.org/10.1093/cercor/bhs148

Lin, J., Chan, S. K., Lee, E. H., Chang, W. C., Tse, M., Su, W. W., Sham, P., Hui, C. L., Joe, G., Chan, C. L., Khong, P. L., So, K. F., Honer, W. G., & Chen, E. Y. (2015). Aerobic exercise and yoga improve neurocognitive function in women with early psychosis. *Npj Schizophrenia*, *1*(1), 15047. https://doi.org/10.1038/npjschz.2015.47

Lynall, M. E., Bassett, D. S., Kerwin, R., McKenna, P. J., Kitzbichler, M., Muller, U., & Bullmore, E. (2010). Functional connectivity and brain networks in schizophrenia. *Journal of Neuroscience*, *30*(28), 9477–9487. https://doi.org/10.1523/JNEUROSCI.0333-10.2010

MacKay, A. L., & Laule, C. (2016). Magnetic Resonance of Myelin Water: An in vivo Marker for Myelin. *Brain Plasticity*, *2*(1), 71–91. https://doi.org/10.3233/BPL-160033

Mackay, A., Whittall, K., Adler, J., Li, D., Paty, D., & Graeb, D. (1994). In vivo visualization of myelin water in brain by magnetic resonance. *Magnetic Resonance in Medicine*, *31*(6), 673–677. https://doi.org/10.1002/mrm.1910310614

Maillard, A. M., Ruef, A., Pizzagalli, F., Migliavacca, E., Hippolyte, L., Adaszewski, S., Dukart, J., Ferrari, C., Conus, P., Männik, K., Zazhytska, M., Siffredi, V., Maeder, P., Kutalik, Z., Kherif, F., Hadjikhani, N., Beckmann, J. S., Reymond, A., Draganski, B., & Jacquemont, S. (2015). The 16p11.2 locus modulates brain structures common to autism, schizophrenia and obesity. *Molecular Psychiatry*, *20*(1), 140–147. https://doi.org/10.1038/mp.2014.145

Mamah, D., Conturo, T. E., Harms, M. P., Akbudak, E., Wang, L., McMichael, A. R., Gado, M. H., Barch, D. M., & Csernansky, J. G. (2010). Anterior Thalamic Radiation Integrity in Schizophrenia: A Diffusion-Tensor Imaging Study. *Psychiatry Research*, *183*(2), 144–150. https://doi.org/10.1016/J.PSCYCHRESNS.2010.04.013

Marder, S. R., & Cannon, T. D. (2019). Schizophrenia. *New England Journal of Medicine*,

381(18), 1753–1761. https://doi.org/10.1056/NEJMra1808803

Martínez, K., Merchán-Naranjo, J., Pina-Camacho, L., Alemán-Gómez, Y., Boada, L., Fraguas, D., Moreno, C., Arango, C., Janssen, J., & Parellada, M. (2017). Atypical age-dependency of executive function and white matter microstructure in children and adolescents with autism spectrum disorders. *European Child and Adolescent Psychiatry*, *26*(11), 1361–1376. https://doi.org/10.1007/s00787-017-0990-2

McCreadie, R. G., Srinivasan, T. N., Padmavati, R., & Thara, R. (2005). Extrapyramidal symptoms in unmedicated schizophrenia. *Journal of Psychiatric Research*, *39*(3), 261–266. https://doi.org/10.1016/j.jpsychires.2004.08.002

McCutcheon, R., Correll, C. U., Howes, O., & Kane, J. (2018). Treatment response and resistance in schizophrenia: principles and definitions. In *Treatment Response and Resistance in Schizophrenia*. Oxford University Press. https://doi.org/10.1093/med/9780198828761.003.0002

McDonald, C. R., Leyden, K. M., Hagler, D. J., Kucukboyaci, N. E., Kemmotsu, N., Tecoma, E. S., & Iragui, V. J. (2014). White matter microstructure complements morphometry for predicting verbal memory in epilepsy. *Cortex*, *58*, 139–150. https://doi.org/10.1016/j.cortex.2014.05.014

McDonald, S., Rushby, J. A., Dalton, K. I., Allen, S. K., & Parks, N. (2018). The role of abnormalities in the corpus callosum in social cognition deficits after Traumatic Brain Injury. *Social Neuroscience*, *13*(4), 471–479. https://doi.org/10.1080/17470919.2017.1356370

McRobbie, D. W., Moore, E. A., Graves, M. J., & Prince, M. R. (2006). *MRI From Picture to Proton* (2nd ed.). Cambridge University Press.

Metzler-Baddeley, C., Cantera, J., Coulthard, E., Rosser, A., Jones, D. K., & Baddeley, R. J. (2014). Improved executive function and callosal white matter microstructure after rhythm exercise in Huntington'S Disease. *Journal of Huntington's Disease*, *3*(3), 273–283. https://doi.org/10.3233/JHD-140113

Mier, D., & Kirsch, P. (2016). Social-cognitive deficits in schizophrenia. In *Current Topics in Behavioral Neurosciences* (Vol. 30, pp. 397–409). Springer Verlag. https://doi.org/10.1007/7854_2015_427

Mighdoll, M. I., Tao, R., Kleinman, J. E., & Hyde, T. M. (2015). Myelin, myelin-related disorders, and psychosis. In *Schizophrenia Research* (Vol. 161, Issue 1, pp. 85–93). Elsevier. https://doi.org/10.1016/j.schres.2014.09.040

Miller, J. N., & D.W., B. (2019). Schizoaffective disorder: A review. *Annals of Clinical Psychiatry: Official Journal of the American Academy of Clinical Psychiatrists*, *31*(1), 47–53.

Mishara, A. (2010). Klaus Conrad (1905–1961): Delusional Mood, Psychosis, and Beginning Schizophrenia. *Schizophrenia Bulletin*, *36*(1), 9–13. https://doi.org/10.1093/schbul/sbp144

Mittal, V. A., Vargas, T., Juston Osborne, K., Dean, D., Gupta, T., Ristanovic, I., Hooker, C. I., & Shankman, S. A. (2017). Exercise Treatments for Psychosis: a Review. In *Current Treatment Options in Psychiatry* (Vol. 4, Issue 2, pp. 152–166). Springer. https://doi.org/10.1007/s40501-017-0112-2

Miyamoto, S., Fredrik Jarskog, L., & Wolfgang Fleischhacker, W. (2014). New therapeutic approaches for treatment-resistant schizophrenia: A look to the future. In *Journal of Psychiatric Research* (Vol. 58, pp. 1–6). Elsevier Ltd. https://doi.org/10.1016/j.jpsychires.2014.07.001

Moreno-Küstner, B., Martín, C., & Pastor, L. (2018). Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses. In *PLoS ONE* (Vol. 13, Issue 4). Public Library of Science. https://doi.org/10.1371/journal.pone.0195687

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A. V., Mahmood, A., Woods, R., Toga, A. W., Pike, G. B., Neto, P. R., Evans, A., Zhang, J., Huang, H., Miller, M. I., van Zijl, P., & Mazziotta, J. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. *NeuroImage*, *40*(2), 570–582. https://doi.org/10.1016/j.neuroimage.2007.12.035

Mori, S., & Zhang, J. (2006). Principles of Diffusion Tensor Imaging and Its Applications to Basic Neuroscience Research. *Neuron*, *51*, 527–539. https://doi.org/10.1016/j.neuron.2006.08.012

Morris, S. B. (2008). Estimating Effect Sizes From Pretest-Posttest-Control Group Designs. *Organizational Research Methods*, *11*(2), 364–386. https://doi.org/10.1177/1094428106291059

Multani, N., Galantucci, S., Wilson, S. M., Shany-Ur, T., Poorzand, P., Growdon, M. E., Jang, J. Y., Kramer, J. H., Miller, B. L., Rankin, K. P., Gorno-Tempini, M. L., & Tartaglia, M. C. (2017). Emotion detection deficits and changes in personality traits linked to loss of white matter integrity in primary progressive aphasia. *NeuroImage: Clinical*, *16*, 447–454. https://doi.org/10.1016/j.nicl.2017.08.020

Mwansisya, T. E., Hu, A., Li, Y., Chen, X., Wu, G., Huang, X., Lv, D., Li, Z., Liu, C., Xue, Z., Feng, J., & Liu, Z. (2017). *Task and resting-state fMRI studies in first-episode schizophrenia: A systematic review*. https://doi.org/10.1016/j.schres.2017.02.026

Myin-Germeys, I., Delespaul, P. A. E. G., & DeVries, M. W. (2000). Schizophrenia patients are more emotionally active than is assumed based on their behavior. *Schizophrenia Bulletin*, *26*(4), 847–854. https://doi.org/10.1093/oxfordjournals.schbul.a033499

Nakamura, M., McCarley, R. W., Kubicki, M., Dickey, C. C., Niznikiewicz, M. A., Voglmaier, M. M., Seidman, L. J., Maier, S. E., Westin, C.-F., Kikinis, R., & Shenton, M. E. (2005). Fronto–Temporal Disconnectivity in Schizotypal Personality Disorder: A Diffusion Tensor Imaging Study. *Biological Psychiatry*, *58*(6), 468–478. https://doi.org/10.1016/J.BIOPSYCH.2005.04.016

Noordsy, D. L., Burgess, J. D., Hardy, K. V., Yudofsky, L. M., & Ballon, J. S. (2018). Therapeutic potential of physical exercise in early psychosis. *American Journal of Psychiatry*, *175*(3), 209–214. https://doi.org/10.1176/appi.ajp.2017.17060716

Nuechterlein, K. H., Ventura, J., McEwen, S. C., Gretchen-Doorly, D., Vinogradov, S., & Subotnik, K. L. (2016). Enhancing Cognitive Training Through Aerobic Exercise after a First Schizophrenia Episode: Theoretical Conception and Pilot Study. *Schizophrenia Bulletin*, *42*(1), S44–S52. https://doi.org/10.1093/schbul/sbw007

Ohoshi, Y., Takahashi, S., Yamada, S., Ishida, T., Tsuda, K., Tsuji, T., Terada, M., Shinosaki, K., & Ukai, S. (2019). Microstructural abnormalities in callosal fibers and their relationship with cognitive function in schizophrenia: A tract-specific analysis study. *Brain and Behavior*, *9*(8). https://doi.org/10.1002/brb3.1357

Olszewski, A. K., Kikinis, Z., Gonzalez, C. S., Coman, I. L., Makris, N., Gong, X., Rathi, Y., Zhu, A., Antshel, K. M., Fremont, W., Kubicki, M. R., Bouix, S., Shenton, M. E., & Kates, W. R. (2017). The social brain network in 22q11.2 deletion syndrome: a diffusion tensor imaging study. *Behavioral and Brain Functions*, *13*(1), 4. https://doi.org/10.1186/s12993-

017-0122-7

Oouchi, H., Yamada, K., Sakai, K., Kizu, O., Kubota, T., Ito, H., & Nishimura, T. (2007). Diffusion anisotropy measurement of brain white matter is affected by voxel size: Underestimation occurs in areas with crossing fibers. *American Journal of Neuroradiology*, *28*(6), 1102–1106. https://doi.org/10.3174/ajnr.A0488

Østby, Y., Tamnes, C. K., Fjell, A. M., & Walhovd, K. B. (2011). Morphometry and connectivity of the fronto-parietal verbal working memory network in development. *Neuropsychologia*, *49*(14), 3854–3862. https://doi.org/10.1016/j.neuropsychologia.2011.10.001

Pajonk, F.-G., Wobrock, T., Gruber, O., Scherk, H., Berner, D., Kaizl, I., Kierer, A., Müller, S., Oest, M., Meyer, T., Backens, M., Schneider-Axmann, T., Thornton, A. E., Honer, W. G., & Falkai, P. (2010). Hippocampal Plasticity in Response to Exercise in Schizophrenia. *Archives of General Psychiatry*, *67*(2), 133. https://doi.org/10.1001/archgenpsychiatry.2009.193

Park, J. Y., Park, H. J., Kim, D. J., & Kim, J. J. (2014). Positive symptoms and water diffusivity of the prefrontal and temporal cortices in schizophrenia patients: A pilot study. *Psychiatry Research - Neuroimaging*, *224*(1), 49–57. https://doi.org/10.1016/j.pscychresns.2014.07.003

Perea, R. D., Vidoni, E. D., Morris, J. K., Graves, R. S., Burns, J. M., & Honea, R. A. (2016). Cardiorespiratory fitness and white matter integrity in Alzheimer's disease. *Brain Imaging and Behavior*. https://doi.org/10.1007/s11682-015-9431-3

Pérez-Iglesias, R., Tordesillas-Gutiérrez, D., McGuire, P. K., Barker, G. J., Roiz-Santiañez, R., Mata, I., De Lucas, E. M., Rodríguez-Sánchez, J. M., Ayesa-Arriola, R., Vazquez-Barquero,

J. L., & Crespo-Facorro, B. (2010). White matter integrity and cognitive impairment in first-episode psychosis. *American Journal of Psychiatry*, *167*(4), 451–458. https://doi.org/10.1176/appi.ajp.2009.09050716

Perneger, T. V. (1998). What's wrong with Bonferroni adjustments. In *British Medical Journal* (Vol. 316, Issue 7139, pp. 1236–1238). British Medical Journal Publishing Group. https://doi.org/10.1136/bmj.316.7139.1236

Peters, B. D., Ikuta, T., Derosse, P., John, M., Burdick, K. E., Gruner, P., Prendergast, D. M., Szeszko, P. R., & Malhotra, A. K. (2014). Age-related differences in white matter tract microstructure are associated with cognitive performance from childhood to adulthood. *Biological Psychiatry*, *75*(3), 248–256. https://doi.org/10.1016/j.biopsych.2013.05.020

Peters, B. D., & Karlsgodt, K. H. (2015). White matter development in the early stages of psychosis. In *Schizophrenia Research* (Vol. 161, Issue 1, pp. 61–69). Elsevier. https://doi.org/10.1016/j.schres.2014.05.021

Peters, B. D., Voineskos, A. N., Szeszko, P. R., Lett, T. A., DeRosse, P., Guha, S., Karlsgodt, K. H., Ikuta, T., Felsky, D., John, M., Rotenberg, D. J., Kennedy, J. L., Lencz, T., & Malhotra, A. K. (2014). Brain white matter development is associated with a human-specific haplotype increasing the synthesis of long chain fatty acids. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *34*(18), 6367–6376. https://doi.org/10.1523/JNEUROSCI.2818-13.2014

Phillips, C., Baktir, M. A., Srivatsan, M., & Salehi, A. (2014). Neuroprotective effects of physical activity on the brain: a closer look at trophic factor signaling. *Frontiers in Cellular Neuroscience*, *8*, 170. https://doi.org/10.3389/fncel.2014.00170

Picardi, A. (2019). The Two Faces of First-Rank Symptoms. *Psychopathology*, *52*(4), 221–231.

https://doi.org/10.1159/000503152

Plewes, D. B., & Kucharczyk, W. (2012). Physics of MRI: A primer. *Journal of Magnetic Resonance Imaging*, *35*(5), 1038–1054. https://doi.org/10.1002/jmri.23642

Prasad, K. M., Upton, C. H., Schirda, C. S., Nimgaonkar, V. L., & Keshavan, M. S. (2015). White matter diffusivity and microarchitecture among schizophrenia subjects and first-degree relatives. *Schizophrenia Research*, *161*(1), 70–75. https://doi.org/10.1016/j.schres.2014.09.045

Reitan, R. M. (1958). Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Perceptual and Motor Skills*, *8*(3), 271–276. https://doi.org/10.2466/pms.1958.8.3.271

Ripke, S., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K.-H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., Albus, M., Alexander, M., Amin, F., Bacanu, S. A., Begemann, M., Jr, R. A. B., … O'Donovan, M. C. (2014). Biological insights from 108 schizophrenia-associated genetic loci. *Nature*, *511*(7510), 421–427. https://doi.org/10.1038/nature13595

Ripke, S., O'Dushlaine, C., Chambert, K., Moran, J. L., Kähler, A. K., Akterin, S., Bergen, S. E., Collins, A. L., Crowley, J. J., Fromer, M., Kim, Y., Lee, S. H., Magnusson, P. K. E., Sanchez, N., Stahl, E. A., Williams, S., Wray, N. R., Xia, K., Bettella, F., … Sullivan, P. F. (2013). Genome-wide association analysis identifies 13 new risk loci for schizophrenia. *Nature Genetics*, *45*(10), 1150–1159. https://doi.org/10.1038/ng.2742

Roalf, D. R., Eric Schmitt, J., Vandekar, S. N., Satterthwaite, T. D., Shinohara, R. T., Ruparel, K., Elliott, M. A., Prabhakaran, K., McDonald-McGinn, D. M., Zackai, E. H., Gur, R. C., Emanuel, B. S., & Gur, R. E. (2017). White matter microstructural deficits in 22q11.2

deletion syndrome. *Psychiatry Research - Neuroimaging*, *268*, 35–44. https://doi.org/10.1016/j.pscychresns.2017.08.001

Romain, A. J., Fankam, C., Karelis, A. D., Letendre, E., Mikolajczak, G., Stip, E., & Abdel-Baki, A. (2018). Effects of high intensity interval training among overweight individuals with psychotic disorders: A randomized controlled trial. *Schizophrenia Research*. https://doi.org/10.1016/J.SCHRES.2018.12.021

Rubin, D. B. (1987). *Multiple Imputation for Nonresponse in Surveys* (D. B. Rubin (ed.)). John Wiley & Sons, Inc. https://doi.org/10.1002/9780470316696

Salami, A., Rieckmann, A., Karalija, N., Avelar-Pereira, B., Andersson, M., Wåhlin, A., Papenberg, G., Garrett, D. D., Riklund, K., Lövdén, M., Lindenberger, U., Bäckman, L., & Nyberg, L. (2018). Neurocognitive Profiles of Older Adults with Working-Memory Dysfunction. *Cerebral Cortex (New York, N.Y. : 1991)*, *28*(7), 2525–2539. https://doi.org/10.1093/cercor/bhy062

Samara, A., Feng, K., Pivik, R. T., Jarratt, K. P., Badger, T. M., & Ou, X. (2019). White Matter Microstructure Correlates with Memory Performance in Healthy Children: A Diffusion Tensor Imaging Study. *Journal of Neuroimaging*, *29*(2), 233–241. https://doi.org/10.1111/jon.12580

Scheewe, T. W., van Haren, N. E. M., Sarkisyan, G., Schnack, H. G., Brouwer, R. M., de Glint, M., Hulshoff Pol, H. E., Backx, F. J. G., Kahn, R. S., & Cahn, W. (2013). Exercise therapy, cardiorespiratory fitness and their effect on brain volumes: A randomised controlled trial in patients with schizophrenia and healthy controls. *European Neuropsychopharmacology*, *23*(7), 675–685. https://doi.org/10.1016/j.euroneuro.2012.08.008

Seok, J. H., Park, H. J., Chun, J. W., Lee, S. K., Cho, H. S., Kwon, J. S., & Kim, J. J. (2007).

White matter abnormalities associated with auditory hallucinations in schizophrenia: A combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. *Psychiatry Research - Neuroimaging*, *156*(2), 93–104. https://doi.org/10.1016/j.pscychresns.2007.02.002

Sexton, C. E., Betts, J. F., Demnitz, N., Dawes, H., Ebmeier, K. P., & Johansen-Berg, H. (2016). A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. *NeuroImage*, *131*, 81–90. https://doi.org/10.1016/j.neuroimage.2015.09.071

Silver, H., Goodman, C., Knoll, G., & Isakov, V. (2004). Brief emotion training improves recognition of facial emotions in chronic schizophrenia. A pilot study. *Psychiatry Research*, *128*(2), 147–154. https://doi.org/10.1016/j.psychres.2004.06.002

Silverstein, S. M., Osborn, L. M., & Palumbo, D. R. (1998). Rey-osterrieth complex figure test performance in acute, chronic, and remitted schizophrenia patients. *Journal of Clinical Psychology*, *54*(7), 985–994. https://doi.org/10.1002/(SICI)1097-4679(199811)54:7<985::AID-JCLP12>3.0.CO;2-G

Smetanin, P., Adair, C., Ahmad, C. E., & And Khan, S. (2011). *The Life and Economic Impact of Major Mental Illnesses in Canada: 2011 to 2041*. https://www.mentalhealthcommission.ca/sites/default/files/MHCC_Report_Base_Case_FINAL_ENG_0_0.pdf

Souza, J. S., Kayo, M., Tassell, I., Martins, C. B., & Elkis, H. (2013). Efficacy of olanzapine in comparison with clozapine for treatment-resistant schizophrenia: evidence from a systematic review and meta-analyses. In *CNS spectrums* (Vol. 18, Issue 2, pp. 82–89). Cambridge University Press. https://doi.org/10.1017/S1092852912000806

Spalletta, G., De Rossi, P., Piras, F., Iorio, M., Dacquino, C., Scanu, F., Girardi, P., Caltagirone, C., Kirkpatrick, B., & Chiapponi, C. (2015). Brain white matter microstructure in deficit and non-deficit subtypes of schizophrenia. *Psychiatry Research - Neuroimaging*, *231*(3), 252–261. https://doi.org/10.1016/j.pscychresns.2014.12.006

Spalletta, G., Piras, F., Piras, F., Caltagirone, C., & Orfei, M. D. (2014). The structural neuroanatomy of metacognitive insight in schizophrenia and its psychopathological and neuropsychological correlates. *Human Brain Mapping*, *35*(9), 4729–4740. https://doi.org/10.1002/hbm.22507

Spilka, M. J., & Goghari, V. M. (2017). Similar patterns of brain activation abnormalities during emotional and non-emotional judgments of faces in a schizophrenia family study. *Neuropsychologia*, *96*, 164–174. https://doi.org/10.1016/j.neuropsychologia.2017.01.014

Stämpfli, P., Sommer, S., Manoliu, A., Burrer, A., Schmidt, A., Herdener, M., Seifritz, E., Kaiser, S., & Kirschner, M. (2019). Subtle white matter alterations in schizophrenia identified with a new measure of fiber density. *Scientific Reports*, *9*(1), 1–11. https://doi.org/10.1038/s41598-019-40070-2

Stilo, S. A., & Murray, R. M. (2019). Non-Genetic Factors in Schizophrenia. In *Current Psychiatry Reports* (Vol. 21, Issue 10, pp. 1–10). Current Medicine Group LLC 1. https://doi.org/10.1007/s11920-019-1091-3

Stoica, T., Knight, L. K., Naaz, F., Ramic, M., & Depue, B. E. (2019). Cortical morphometry and structural connectivity relate to executive function and estradiol level in healthy adolescents. *Brain and Behavior*, *9*(12). https://doi.org/10.1002/brb3.1413

Strangman, G. E., O'Neil-Pirozzi, T. M., Supelana, C., Goldstein, R., Katz, D. I., & Glenn, M. B. (2012). Fractional anisotropy helps predicts memory rehabilitation outcome after traumatic

brain injury. *NeuroRehabilitation*, *31*(3), 295–310. https://doi.org/10.3233/NRE-2012-0797

Subramaniam, K., Gill, J., Fisher, M., Mukherjee, P., Nagarajan, S., & Vinogradov, S. (2018). White matter microstructure predicts cognitive training-induced improvements in attention and executive functioning in schizophrenia. *Schizophrenia Research*, *193*, 276–283. https://doi.org/10.1016/J.SCHRES.2017.06.062

Svatkova, A., Mandl, R. C. W., Scheewe, T. W., Cahn, W., Kahn, R. S., & Hulshoff Pol, H. E. (2015). Physical Exercise Keeps the Brain Connected: Biking Increases White Matter Integrity in Patients With Schizophrenia and Healthy Controls. *Schizophrenia Bulletin*, *41*(4), 869–878. https://doi.org/10.1093/schbul/sbv033

Szamosi, A., Kelemen, O., & Kéri, S. (2012). Hippocampal volume and the AKT signaling system in first-episode schizophrenia. *Journal of Psychiatric Research*, *46*(3), 279–284. https://doi.org/10.1016/J.JPSYCHIRES.2011.12.005

Takahashi, N., Sakurai, T., Davis, K. L., & Buxbaum, J. D. (2011). Linking oligodendrocyte and myelin dysfunction to neurocircuitry abnormalities in schizophrenia. In *Progress in Neurobiology* (Vol. 93, Issue 1, pp. 13–24). Pergamon. https://doi.org/10.1016/j.pneurobio.2010.09.004

Tombaugh, T. N. (2004). Trail Making Test A and B: Normative data stratified by age and education. *Archives of Clinical Neuropsychology*, *19*(2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8

Torres, E. R., Strack, E. F., Fernandez, C. E., Tumey, T. A., & Hitchcock, M. E. (2015). Physical activity and white matter hyperintensities: A systematic review of quantitative studies. *Preventive Medicine Reports*, *2*, 319–325. https://doi.org/10.1016/j.pmedr.2015.04.013

Tripathi, A., Kar, S. K., & Shukla, R. (2018). Cognitive Deficits in Schizophrenia:

Understanding the Biological Correlates and Remediation Strategies. *Clinical Psychopharmacology and Neuroscience : The Official Scientific Journal of the Korean College of Neuropsychopharmacology*, *16*(1), 7–17. https://doi.org/10.9758/cpn.2018.16.1.7

Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: Improved N3 Bias Correction. *IEEE Transactions on Medical Imaging*, *29*(6), 1310. https://doi.org/10.1109/TMI.2010.2046908

Tustison, N. J., Cook, P. A., Klein, A., Song, G., Das, S. R., Duda, J. T., Kandel, B. M., van Strien, N., Stone, J. R., Gee, J. C., & Avants, B. B. (2014). Large-scale evaluation of ANTs and FreeSurfer cortical thickness measurements. *NeuroImage*, *99*, 166–179. https://doi.org/10.1016/J.NEUROIMAGE.2014.05.044

Urbanski, M., Thiebaut de Schotten, M., Rodrigo, S., Catani, M., Oppenheim, C., Touzé, E., Chokron, S., Méder, J.-F., Lévy, R., Dubois, B., & Bartolomeo, P. (2008). Brain networks of spatial awareness: evidence from diffusion tensor imaging tractography. *Journal of Neurology, Neurosurgery, and Psychiatry*, *79*(5), 598–601. https://doi.org/10.1136/jnnp.2007.126276

Vacha-Haase, T., & Thompson, B. (2004). How to Estimate and Interpret Various Effect Sizes. *Journal of Counseling Psychology*, *51*, 473–481. https://doi.org/10.1037/0022-0167.51.4.473

van Buuren, S. (2018). Flexible Imputation of Missing Data, Second Edition. In *Flexible Imputation of Missing Data, Second Edition*. Chapman and Hall/CRC. https://doi.org/10.1201/9780429492259

van der Stouwe, E. C. D., van Busschbach, J. T., de Vries, B., Cahn, W., Aleman, A., & Pijnenborg, G. H. M. (2018). Neural correlates of exercise training in individuals with

schizophrenia and in healthy individuals: A systematic review. *NeuroImage: Clinical*, *19*, 287–301. https://doi.org/10.1016/J.NICL.2018.04.018

Vancampfort, D., Knapen, J., Probst, M., Scheewe, T., Remans, S., & De Hert, M. (2012). A systematic review of correlates of physical activity in patients with schizophrenia. *Acta Psychiatrica Scandinavica*, *125*(5), 352–362. https://doi.org/10.1111/j.1600-0447.2011.01814.x

Vancampfort, Davy, Probst, M., De Hert, M., Soundy, A., Stubbs, B., Stroobants, M., & De Herdt, A. (2014). Neurobiological effects of physical exercise in schizophrenia: A systematic review. In *Disability and Rehabilitation* (Vol. 36, Issue 21, pp. 1749–1754). Informa Healthcare. https://doi.org/10.3109/09638288.2013.874505

Vancampfort, Davy, Stubbs, B., Mitchell, A. J., De Hert, M., Wampers, M., Ward, P. B., Rosenbaum, S., & Correll, C. U. (2015). Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: A systematic review and meta-analysis. In *World Psychiatry* (Vol. 14, Issue 3, pp. 339–347). Blackwell Publishing Ltd. https://doi.org/10.1002/wps.20252

Vanes, L. D., Mouchlianitis, E., Wood, T. C., & Shergill, S. S. (2018). White matter changes in treatment refractory schizophrenia: Does cognitive control and myelination matter? *NeuroImage: Clinical*, *18*, 186–191. https://doi.org/10.1016/J.NICL.2018.01.010

Viher, P. V, Stegmayer, K., Giezendanner, S., Federspiel, A., Bohlhalter, S., Vanbellingen, T., Wiest, R., Strik, W., & Walther, S. (2016). Cerebral white matter structure is associated with DSM-5 schizophrenia symptom dimensions. *NeuroImage. Clinical*, *12*, 93–99. https://doi.org/10.1016/j.nicl.2016.06.013

Vos, T., Allen, C., Arora, M., Barber, R. M., Brown, A., Carter, A., Casey, D. C., Charlson, F. J.,

Chen, A. Z., Coggeshall, M., Cornaby, L., Dandona, L., Dicker, D. J., Dilegge, T., Erskine, H. E., Ferrari, A. J., Fitzmaurice, C., Fleming, T., Forouzanfar, M. H., … Zuhlke, L. J. (2016). Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. *The Lancet*, *388*(10053), 1545–1602. https://doi.org/10.1016/S0140-6736(16)31678-6

Voss, M. W., Heo, S., Prakash, R. S., Erickson, K. I., Alves, H., Chaddock, L., Szabo, A. N., Mailey, E. L., Wójcicki, T. R., White, S. M., Gothe, N., Mcauley, E., Sutton, B. P., & Kramer, A. F. (2013). The influence of aerobic fitness on cerebral white matter integrity and cognitive function in older adults: Results of a one-year exercise intervention. *Human Brain Mapping*, *34*(11), 2972–2985. https://doi.org/10.1002/hbm.22119

Walterfang, M., Wood, S. J., Velakoulis, D., Copolov, D., & Pantelis, C. (2005). Diseases of white matter and schizophrenia-like psychosis. *The Australian and New Zealand Journal of Psychiatry*, *39*(9), 746–756. https://doi.org/10.1080/j.1440-1614.2005.01678.x

Wang, S., Jiaerken, Y., Yu, X., Shen, Z., Luo, X., Hong, H., Sun, J., Xu, X., Zhang, R., Zhou, Y., Lou, M., Huang, P., & Zhang, M. (2020). Understanding the association between psychomotor processing speed and white matter hyperintensity: A comprehensive multi-modality MR imaging study. *Human Brain Mapping*, *41*(3), 605–616. https://doi.org/10.1002/hbm.24826

Watson, C. G., Stopp, C., Wypij, D., Bellinger, D. C., Newburger, J. W., & Rivkin, M. J. (2018). Altered White Matter Microstructure Correlates with IQ and Processing Speed in Children and Adolescents Post-Fontan. *Journal of Pediatrics*, *200*, 140-149.e4. https://doi.org/10.1016/j.jpeds.2018.04.022

Whitford, T. J., Kubicki, M., Pelavin, P. E., Lucia, D., Schneiderman, J. S., Pantelis, C., McCarley, R. W., & Shenton, M. E. (2015). Cingulum bundle integrity associated with delusions of control in schizophrenia: Preliminary evidence from diffusion-tensor tractography. *Schizophrenia Research*, *161*(1), 36–41. https://doi.org/10.1016/j.schres.2014.08.033

Whittall, K. P., & MacKay, A. L. (1989). Quantitative interpretation of NMR relaxation data. *Journal of Magnetic Resonance (1969)*, *84*(1), 134–152. https://doi.org/10.1016/0022-2364(89)90011-5

Wilde, N. J., Strauss, E., & Tulsky, D. S. (2004). Memory span on the wechsler scales. *Journal of Clinical and Experimental Neuropsychology*, *26*(4), 539–549. https://doi.org/10.1080/13803390490496605

Won, S., Lee, W. K., Kim, S.-W., Kim, J. J., Lee, B. J., Yu, J.-C., Lee, K. Y., Lee, S.-H., Kim, S.-H., Kang, S. H., Kim, E., & Chung, Y.-C. (2019). Distinct Differences in Emotional Recognition According to Severity of Psychotic Symptoms in Early-Stage Schizophrenia. *Frontiers in Psychiatry*, *10*. https://doi.org/10.3389/fpsyt.2019.00564

Woodward, M. L., Gicas, K. M., Warburton, D. E., White, R. F., Rauscher, A., Leonova, O., Su, W., Smith, G. N., Thornton, A. E., Vertinsky, A. T., Phillips, A. A., Goghari, V. M., Honer, W. G., & Lang, D. J. (2018). Hippocampal volume and vasculature before and after exercise in treatment-resistant schizophrenia. *Schizophrenia Research*, *202*, 158–165. https://doi.org/10.1016/J.SCHRES.2018.06.054

Xiao, Q., Wang, F., Luo, Y., Chen, L., Chao, F., Tan, C., Gao, Y., Huang, C., Zhang, L., Liang, X., Tang, J., Qi, Y., Jiang, L., Zhang, Y., Zhou, C., & Tang, Y. (2018). Exercise protects myelinated fibers of white matter in a rat model of depression. *Journal of Comparative*

Neurology, *526*(3), 537–549. https://doi.org/10.1002/cne.24350

Yakovlev, P, Lecours, A. (1967). *Regional Development of Brain in Early Life*. Blackwell Scientific Publications.

Yakovlev, P., Lecours, A., & Lecours, K. (1967). The myelogenetic cycles of regional maturation of the brain. In A. Minkowski (Ed.), *Regional Development of the Brain in Early Life* (pp. 3–70). Blackwell Scientific.

Yang, A. C., & Tsai, S. J. (2017). New targets for schizophrenia treatment beyond the dopamine hypothesis. In *International Journal of Molecular Sciences* (Vol. 18, Issue 8). MDPI AG. https://doi.org/10.3390/ijms18081689

Zang, J., Liu, Y., Li, W., Xiao, D., Zhang, Y., Luo, Y., Liang, W., Liu, F., & Wei, W. (2017). Voluntary exercise increases adult hippocampal neurogenesis by increasing GSK-3β activity in mice. *Neuroscience*, *354*, 122–135. https://doi.org/10.1016/J.NEUROSCIENCE.2017.04.024

Zeng, B., Ardekani, B. A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D. C., & Wang, J. (2016a). Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. *Schizophrenia Research*, *172*, 1–8. https://doi.org/10.1016/j.schres.2016.01.051

Zeng, B., Ardekani, B. A., Tang, Y., Zhang, T., Zhao, S., Cui, H., Fan, X., Zhuo, K., Li, C., Xu, Y., Goff, D. C., & Wang, J. (2016b). Abnormal white matter microstructure in drug-naive first episode schizophrenia patients before and after eight weeks of antipsychotic treatment. *Schizophrenia Research*, *172*(1–3), 1–8. https://doi.org/10.1016/J.SCHRES.2016.01.051

Zhao, X., Sui, Y., Yao, J., Lv, Y., Zhang, X., Jin, Z., Chen, L., & Zhang, X. (2017). Reduced white matter integrity and facial emotion perception in never-medicated patients with first-

episode schizophrenia: A diffusion tensor imaging study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *77*, 57–64. https://doi.org/10.1016/j.pnpbp.2017.03.025

Zheng, W., Wang, H., Zeng, Z., Lin, J., Little, P. J., Srivastava, L. K., & Quirion, R. (2012). The possible role of the Akt signaling pathway in schizophrenia. *Brain Research*, *1470*, 145–158. https://doi.org/10.1016/J.BRAINRES.2012.06.032

Zhou, F. C., Xiang, Y. T., Wang, C. Y., Dickerson, F., Au, R. W. C., Zhou, J. J., Zhou, Y., Shum, D. H. K., Chiu, H. F. K., Man, D., Lee, E. H. M., Yu, X., Chan, R. C. K., & Ungvari, G. S. (2012). Characteristics and clinical correlates of prospective memory performance in first-episode schizophrenia. *Schizophrenia Research*, *135*(1–3), 34–39. https://doi.org/10.1016/j.schres.2011.12.001

Zimmerman, D. W. (2004). A note on preliminary tests of equality of variances. *British Journal of Mathematical and Statistical Psychology*, *57*(1), 173–181. https://doi.org/10.1348/000711004849222