Aerobic Exercise and Hippocampal Plasticity in Young Adults with Depression

by

Allegra Katasha Courtright

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Abstract

Major depressive disorder (MDD) is a significant public health problem. Exercise has shown promise in reducing symptoms and promoting brain plasticity in MDD. A relationship between symptom severity, hippocampus volume and N-acetyl-aspartate (NAA) concentration, a marker of neuron density/viability, has been shown. The relationship of these variables to fitness (as assessed by volume of oxygen uptake - VO$_2$ max) is underexplored. In this study, unmedicated, inactive young adults with MDD and healthy controls underwent neuroimaging, fitness and clinical assessments at baseline and after 12-weeks. After 12-weeks of aerobic exercise, VO$_2$max increased and depression scores decreased relative to baseline in participants with MDD. No changes in hippocampal volume or NAA levels were observed, compared to controls. This finding may have resulted from small samples and high variability on the measures of interest. Depression symptom decreases were not related with VO$_2$max changes or exercise compliance.
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Dedication

This thesis is dedicated to many people in my life:

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Table of Contents

Abstract .......................................................................................................................... ii
Acknowledgements ........................................................................................................ iii
Dedication ........................................................................................................................ iv
Table of Contents .......................................................................................................... v
List of Tables .................................................................................................................. viii
List of Figures and Illustrations .................................................................................... ix
List of Symbols, Abbreviations and Nomenclature ....................................................... x
Epigraph .......................................................................................................................... xi

CHAPTER ONE: INTRODUCTION .............................................................................. 13
1.1 Thesis Overview ........................................................................................................ 13
1.2 Study Purpose ........................................................................................................... 14

CHAPTER TWO: BACKGROUND AND LITERATURE REVIEW .......................... 15
2.1 Major Depressive Disorder ...................................................................................... 15
  2.1.1 Prevalence, Clinical Presentation, Course and Outcomes .............................. 15
  2.1.2 Basic Neurobiology of Major Depressive Disorder ........................................ 17
  2.1.3 Neurobiology of the Hippocampus .................................................................. 18
    2.1.3.1 Hippocampal Anatomy .............................................................................. 18
    2.1.3.2 Hippocampal Neuroplasticity ................................................................. 20
    2.1.3.3 Hippocampal Function ............................................................................ 21
    2.1.3.4 Hippocampus Volume in Major Depressive Disorder .............................. 21
    2.1.3.5 NAA in Major Depressive Disorder ......................................................... 23
  2.1.4 Antidepressant Treatment .................................................................................. 25
    2.1.4.1 Overview .................................................................................................. 25
    2.1.4.2 Standard Treatment for Major Depressive Disorder ............................... 26
    2.1.4.3 Limitations and Need for Novel Interventions ........................................ 27
  2.2 Exercise ................................................................................................................... 29
    2.2.1 Exercise and Major Depressive Disorder ...................................................... 29
    2.2.2 Exercise and Hippocampal Plasticity ............................................................ 31
      2.2.2.1 Animal Models ....................................................................................... 31
      2.2.2.2 Studies in Humans ................................................................................ 32
    2.2.3 Research Questions & Hypotheses ............................................................... 35

CHAPTER THREE: METHODS .................................................................................. 37
3.1 General Methods ..................................................................................................... 37
  3.1.1 Participant Recruitment and Screening Overview .......................................... 37
  3.1.2 Telephone Pre-Screen ...................................................................................... 38
  3.1.3 Intake Session: In-Person Assessments and Screening ................................... 38
    3.1.3.1 Baseline Clinical Assessments and Screening ........................................ 38
    3.1.3.2 Non-Depressed Control Group ............................................................... 39
    3.1.3.3 Inclusion and Exclusion Criteria ............................................................. 40
  3.2 Specific Methods ................................................................................................. 42
    3.2.1 Magnetic Resonance Imaging ....................................................................... 42
      3.2.1.1 Fundamentals of Magnetic Resonance Imaging .................................... 42
APPENDIX G: PRIMARY EMAIL CORRESPONDENCE ........................................... 131
APPENDIX H: FITNESS ASSESSMENT CORRESPONDENCE .......................... 132
APPENDIX I: MDD FITNESS ASSESSMENT RECORD SHEETS ......................... 134
APPENDIX J: AEROBIC EXERCISE INTERVENTION RECORD SHEETS .......... 135
APPENDIX K: POLAR HEART RATE MONITOR, KINETIX EXERCISE FACILITY,
MRI & MRS SCANNING .................................................................................. 141
List of Tables

Table 1: Participant Inclusion and Exclusion Criteria ............................................................. 40

Table 2: Mean demographic characteristics of healthy controls and MDD participants at baseline ................................................................. 62

Table 3: MDD participants’ exercise intervention adherence and effort in designated HR zone (expressed as percent), percent VO2max change pre- to post-exercise intervention, exercise responders, and depression score response .......................................................... 66

Table 4: Mean Hamilton depression rating scale (HAMD17) scores for control and major depressive disorder (MDD) groups pre- and post- 12-weeks ......................................................... 69

Table 5: Mean Hamilton depression rating scale (HAMD17) scores in MDD responders and non-responders pre- and post- 12-weeks of exercise intervention, as well as change scores. .................................................................................................................. 70

Table 6: Hippocampal volume (adjusted for whole brain volume) measures pre- and post-12-weeks in control and MDD groups .................................................................................. 72

Table 8: Mean hippocampal N-acetyl aspartate concentrations (NAA) in control and MDD groups at pre- and post- 12-weeks .......................................................................................... 73

Table 9: Percent change in hippocampal N-acetyl aspartate concentrations from pre- to post-12-weeks in control and MDD groups .................................................................................. 74

Table 10: Spearman’s correlations between VO2max, time in target HR zone, and HAMD17 score changes (expressed as a percent from baseline to week 12) and changes in hippocampal volume and N-acetyl aspartate (NAA) levels. ........................................................................................ 75
List of Figures and Illustrations

Figure 1: Coronal View: Hippocampal Anatomy .................................................................19
Figure 2. Outline of participant recruitment, screening and enrolment.................................41
Figure 3. A typical $^1$H-MRS spectrum from a voxel in the human brain..........................44
Figure 4. Sagittal slice selection of human hippocampus. ....................................................48
Figure 5. Hippocampal demarcations: transverse (A), coronal (B), sagittal (C).......................48
Figure 6. Anatomical boundaries used hippocampal tracing ..............................................49
Figure 7. Transverse intracranial volume (ICV) ................................................................51
Figure 8. $^1$H-MRS spectrum voxel placement in the human hippocampus .........................52
Figure 9. Aerobic exercise intervention outline and associated measures following MDD participant enrollment........................................................................................................57
Figure 10: Mean VO$_2$max scores of the healthy control group at baseline and major depressive disorder (MDD) group pre- and post- 12-week exercise intervention. ............63
Figure 11: Individual VO$_2$max (ml/kg/min) measures in MDD patients throughout 12-weeks of aerobic exercise intervention....................................................................................64
Figure 12: Mean percent of exercise adherence (sessions attended), exercise effort (time below and in heart rate [HR] zone), expressed as a percent (%) of total sessions. .............67
Figure 13: Breakdown of mean percent session adherence exercising in appropriate heart rate (HR) zone when less than prescribed amount.................................................................68
Figure 14: Individual Hamilton depression rating scores (HAMD$_{17}$) in MDD patients throughout 12-weeks of an aerobic exercise intervention.............................................................71
List of Symbols, Abbreviations and Nomenclature

ACSM: American college of sports medicine
BDI: Beck depression inventory
BDNF: Brain-derived neurotrophic factor
BP: Blood pressure
BMI: Body mass index
CEP: Certified exercise physiologist
CI: Confidence interval
CPAFLA: Canadian Physical Activity, Fitness & Lifestyle Approach
HAMD17: 17-item Hamilton rating scale for depression
HC: Hippocampus
HIIT: High-intensity interval training
HRmax: Maximum heart rate
HRR: Heart rate reserve
ICC: Interclass correlation coefficient
ICV: Intracranial volume
IPAQ: International Physical Activity Questionnaire
MDD: Major Depressive Disorder
MINI: Mini International Neuropsychiatric Interview
MRI: Magnetic resonance imaging
MRS: Magnetic resonance spectroscopy
NAA: N-acetyl aspartate
PAR-Q+: Physical activity readiness questionnaire for everyone
PARmed-X: Physical activity readiness medical examination

SD: Standard deviation

SGZ: sub-granular zone

VO₂ max: Maximal oxygen consumption (aerobic fitness)

WC: Waist circumference
**Epigraph**

“You have brains in your head. You have feet in your shoes. You can steer yourself any direction you choose. You're on your own. And you know what you know. And YOU are the one who’ll decide where you go…”

Dr. Seuss
Chapter One: Introduction

1.1 Thesis Overview

Major depressive disorder (MDD) is a common mental illness, with a high burden of disease. Antidepressant treatments, often consisting of pharmacotherapy and/or psychotherapy, vary in their effectiveness and do not always lead to positive response or remission from depression. Numerous studies have evaluated aerobic exercise for its mood-enhancing effects, including in individuals with sub-threshold depression symptoms. Despite this, there is a paucity of research evaluating the neurobiological mechanisms through which these mood-enhancing effects of aerobic exercise occur in the context of MDD. Structural and biochemical studies evaluating differences between MDD populations and healthy controls are feasible and have been conducted using neuroimaging techniques such as magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). A key brain structure of research interest in MDD is the hippocampus, a region implicated in spatial navigation, episodic memory, emotional control, and stress feedback - all areas in which deficiencies have been observed in individuals with MDD. The hippocampus is highly sensitive to environmental factors (e.g., stress and exercise), which may lead to synaptic restructuring and effect neuroplasticity (e.g., neurogenesis - new cell growth), among other changes. Broadly, such changes in brain function and structure due to cellular-level changes are referred to as neuroplasticity. Additionally, changes in the neuronal level of N-acetyl-aspartate (NAA), a marker of neuronal health, may be present. We are interested in determining whether the magnitude of aerobic fitness capacity improvement - measured by maximal oxygen uptake (VO₂max) - correlates with or drives the magnitude of hippocampal neuroplastic and neurochemical changes that may be associated with mood changes in the context of MDD.
1.2 Study Purpose

This project focused on examining hippocampal volume and NAA concentrations changes in relatively sedentary young adults 18-24 years of age with MDD before and after a structured 12-week aerobic exercise-training program. Changes in depression scores (HAMD17), and fitness levels (VO₂ max) were also measured; correlations between these outcome measures were assessed. The aerobic exercise intervention was individually tailored and based on 60-85% of individual’s Heart Rate Reserve (HHR). MDD participants were also compared to matched healthy controls on these measures.
Chapter Two: **Background and Literature Review**

2.1 Major Depressive Disorder

2.1.1 Prevalence, Clinical Presentation, Course and Outcomes

Major depressive disorder (MDD) is a prevalent and serious public health problem (Ferrari et al., 2013). According to the World Health Organization (2012) globally, more than 350 million people of all ages suffer from MDD, with a 1:2 sex ratio biased towards females (Emslie, Weinberg, Rush, Adams, & Rintelmann, 1990). This is roughly equivalent to the entire Canadian and US populations combined. Projections for the year 2020 indicate that MDD will be second only to coronary heart disease as a cause of illness burden worldwide (Murray & Lopez, 1997). By 2030, the leading cause of disability in high-income countries is projected to be unipolar depression (Mathers & Loncar, 2006). First MDD episodes typically present during adolescence/early childhood (Mezuk & Kendler, 2012) and worldwide the disorder is estimated to affect approximately 15 percent of adolescents (Cullen, Klimes-Dougan, Kumra, & Schulz, 2009). Mental health conditions typically continue into adulthood and half of all lifetime cases of mental disorders start by age 14, and about 75% by age 24 (Kutcher, Hampton, & Wilson, 2010). Adolescents with MDD will often experience a large burden of illness as they struggle with social, academic and family settings, causing widespread functional impairment (Kondo et al., 2011). Although MDD is highly prevalent, child and adolescent mental health services are poorly developed across Canada (Kutcher et al., 2010). Furthermore, the duration of an MDD episode is important as epidemiological data has indicated that patients tend to become progressively more treatment-resistant over the course of illness (Patten, 2006).

MDD is characterized by an array of physiological, psychological and cognitive symptoms. The diagnosis criteria for depression are not based on objective diagnostic tests, but
rather on a set of symptoms. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, (DSM-IV) defines a depressive episode as a continuous period lasting longer than two weeks that is characterized by five or more symptoms ranging from depressed mood, sadness (dysphoria), inability to experience pleasure from activities usually found enjoyable (anhedonia), feelings of worthlessness or guilt, and decreased ability to think or concentrate, among other symptoms (American Psychiatric Association, 2000). Individuals with MDD are at a significantly higher risk for suicide because of these symptoms (Cullen et al., 2009).

Unfortunately, suicide is the third leading cause of death in 10-24 year olds and 50 percent of the time MDD is the diagnosis associated with suicide (Cullen et al., 2009). Furthermore, there is strong evidence linking depression to later development of other medical illnesses, such as dementia (Byers & Yaffe, 2011), hypertension, stroke, asthma, osteoarthritis and diabetes (Katon, 2011).

Although MDD is characterized as an episodic illness, recurrence is common. According to a longitudinal prospective study evaluating characteristics and recovery of MDD in childhood, within 5 years, 70–75% of children and adolescents with previous history of depression will again become depressed (Kovacs, Feinberg, Crouse-Novak, Paulauskas, & Finkelstein, 1984). As the number of depressive episodes increase, future episodes are more easily predicted by the number of prior episodes rather than by life stress (Maletic et al., 2007). Furthermore, as the duration of depressive episodes increases, the probability of remission substantially decreases over time (Maletic et al., 2007). As such, intervention and prevention in earlier stages of the illness are paramount.
2.1.2 Basic Neurobiology of Major Depressive Disorder

MDD has profound effects on neural structure and function but the exact cause and neuropathology of depression is still not well understood (Wainwright & Galea, 2013). Several brain regions and functional brain circuits implicated in the regulation of emotion, reward, and executive functions are affected in MDD. Most notable are irregularities in the limbic/paralimbic system; some of these will be discussed below.

Several theories of depression exist, including: 1) modulation of monoaminergic neurotransmission (Palazidou, 2012), 2) alterations in neurotrophic factors (Wainwright & Galea, 2013), 3) down-regulation of adult hippocampal neurogenesis (Wainwright & Galea, 2013) and 4) hormonal fluctuations (McEwen, 1999). Though other theories exist they are beyond the scope of this thesis. Further, it is generally accepted that disturbances in one system affect another (e.g., alterations in monoamines affect neurotrophins). Briefly, the monoamine theory of depression proposes that the pathophysiological basis of depression is due to deficient activity of monoamines in the central nervous system. This theory is largely based on the fact that most antidepressant interventions up-regulate monomanergic activity (particularly serotonin activity) in the long term (Krishnan & Nestler, 2008). The neurogenesis hypothesis suggests that reduced adult hippocampal neurogenesis may be critical in MDD based on evidence that antidepressant efficacy is dependent on upregulation of hippocampal neurogenesis (Wainwright & Galea, 2013). The role of neurotrophic factors, such as brain derived neurotrophic factor (BDNF), is also important to consider due to their involvement in maintaining synaptic integrity. Gonadal hormones are also likely a factor in the treatment and etiology of depression (Wainwright & Galea, 2013) and likely play a role in the over-representation of females with depression. None of these theories, however, sufficiently explain the pathology of depression, or
how antidepressant treatments work. This is perhaps not surprising given that depression and vulnerability to its development have been associated with numerous other influences, including environmental and genetic factors (Krishnan & Nestler, 2008).

Current neurobiological models of MDD indicate that neuronal dysfunction, loss, or damage in the hippocampus is a hallmark of the disease (Sapolsky, 2000). Several reviews have indicated that patients with MDD have smaller hippocampal volumes compared to individuals with no history of psychiatric illness (MacMaster & Kusumakar, 2004; MacMaster, Mirza, et al., 2008; G. M. MacQueen et al., 2003; Steffens et al., 2000). Thus, there is evidence that hippocampal volumes can be a useful index of MDD presence and/or vulnerability and an index for treatment response.

2.1.3 Neurobiology of the Hippocampus

2.1.3.1 Hippocampal Anatomy

The hippocampus is located in the medial temporal lobe of the brain and consists of two interlocking U shaped grey matter structures; the dentate gyrus and the Cornu Ammonis. The dentate gyrus consists of a tightly packed layer of small granule cells wrapped around the end of the hippocampus proper. Subfields in the dentate gyrus include the facia dentate and the hilus (region CA4). The Cornu Ammonis, also known as the hippocampus proper, consists of other subfields including the CA4, CA3, CA2, CA1 areas. The dentate gyrus is separated from CA1-CA3 by the hippocampal sulcus. CA contains densely packed pyramidal cells. After the CA1 region comes the subiculum, which is the main output for the hippocampus. The hippocampal formation refers to the hippocampus proper plus the dentate gyrus and subiculum. Below the
subiculum is an area called the entorhinal cortex and below that, the parahippocampal gyrus (Duvernoy, Cattin, & Risold, 2013).

**Figure 1: Coronal View: Hippocampal Anatomy**
Adapted from Frank Gaillard Designs 2006 from Wikimedia Commons
2.1.3.2 Hippocampal Neuroplasticity

Neuroplasticity is complex and encompasses an array of varied processes, from the birth, survival, migration, and integration of new neurons, to outgrowth, synaptogenesis, and the modulation of mature synapses (Wainwright & Galea, 2013). Neuroplasticity is often used as an umbrella term referring to the brain’s ability to change/adapt, whether via new cell growth (neurogenesis), programmed cell death (apoptosis), or connectivity modulations (synaptic plasticity or dendritic arborisation). Neuroplasticity underlies structural changes in the brain, especially in the hippocampus, where detrimental changes (e.g., neuronal dysfunction, loss, damage) are now considered hallmarks in MDD (Sapolsky, 2000; MacQueen et al., 2003; MacMaster et al, 2004, 2008; Erickson, K. I. 2010).

Contrary to early dogma, the adult nervous system can generate new neurons. Neurogenesis is typically limited to two regions: the subventricular zone in the olfactory bulb and the subgranular zone (SGZ) of the hippocampus (Palazidou, 2012), which is located between the granule cell layer and the hilus. Furthermore, adult neurogenesis can be up- or down-regulated by a number of stimuli, such as exercise, learning, hormones, and antidepressant drugs (Duman, Nakagawa, & Malberg, 2001). It has also been implicated in the acquisition of new memories as well as in the retention of long-term memories (Snyder, Hong, McDonald, & Wojtowicz, 2005). Because neurogenesis occurs in the hippocampus, it is a structure that exhibits one of the greatest degrees of plasticity in the brain. Therefore, if structural brain changes were to be observed with exercise intervention in MDD participants, they would likely be seen in the hippocampus. Other brain regions may also demonstrate structural changes, however, for the purposes of this thesis, the hippocampus exclusively will be examined.
2.1.3.3 Hippocampal Function

The hippocampus has been the subject of extensive MDD research as it is a stress-sensitive brain region and MDD is recognized as a stress-sensitive illness (MacQueen & Frodl, 2011). The hippocampus exhibits rapid plasticity at the molecular, cellular, structural and functional levels in response to specific stimuli. It is an important structure involved in learning and memory. Most notably, it has been cited as a crucial brain structure in the formation of episodic memories (Scoville & Milner, 1957) (a category of long-term memory that involves contextual memory for specific events, situations and experiences). MDD is associated with perceived and measurable problems in cognition and memory, even in adolescents (Brooks, Iverson, Sherman, & Roberge, 2010).

Depression is associated with hyperactivity of the hypothalamic-pituitary adrenal (HPA) axis function, which is a stress regulator. Adrenal steroids are secreted during stress, and it is thought that the secretion of these steroids may contribute to hippocampal atrophy (Sapolsky, 2000). The hippocampus is a key brain structure involved in shutting off the HPA response to stress and in maintaining normal diurnal rhythms in stress hormones (McEwen & Magarinos, 2001). Furthermore, the hippocampus is important in the processing of emotional information (McKinnon, Yucel, Nazarov, & MacQueen, 2009). Impairment of each of these functions is not limited to MDD, but can be seen in several other psychiatric illnesses such as schizophrenia, bipolar disorder, post-traumatic stress disorder, borderline personality disorder, and obsessive-compulsive disorder (Gueuze, Vermetten & Bremner, 2004).

2.1.3.4 Hippocampus Volume in Major Depressive Disorder

Studies have shown that smaller hippocampal volume is often noted in individuals with depression compared to controls, and this may be one of the underlying reasons for depressive
symptoms (MacMaster, Mirza, et al., 2008; Pittenger & Duman, 2008; Sapolsky, 2000). Small hippocampal volumes have also been shown to predict poor antidepressant treatment responses in young adults being treated for a first episode of depression (MacQueen, Yucel, Taylor, Macdonald, & Joffe, 2008).

A study by Sheline et al (2003) found that decreased hippocampus volume was associated with burden of disease and duration of untreated MDD. Individuals on maintenance antidepressant pharmacotherapy did not exhibit hippocampal volumetric reductions, suggesting that antidepressants may have neuroprotective effects (Sheline, Gado, & Kraemer, 2003). Decreased hippocampal volume appears to be more evident based on cumulative recurrent depressive episodes, and hippocampal volumes inversely correlated with cumulative lifetime depression duration (Sheline, Sanghavi, Mintun, & Gado, 1999). More immediate recognition and treatment of depressive episodes is therefore important to diminish/prevent hippocampal damage from occurring with repeated MDD episodes.

The precise mechanisms underlying the decrease in hippocampal volume have not been fully determined (Banasr, Dwyer, & Duman, 2011). Volumetric reductions, however, seem to be driven by reductions in the neuropil (region of synaptic connections) and not gross cell death, and likely represent retraction of dendritic branches. Preclinical work has demonstrated that increased glucocorticoids, glutamate, and reduced BDNF likely contribute to these changes in hippocampal volume, as shortening and atrophy of hippocampal dendritic processes have been observed (Sapolsky, 2000). Additionally, animal research has found that neuroanatomical changes, including those to the neuropil, glia, dendritic complexity and neural apoptosis likely underlie the hippocampal volume reductions in MDD. McEwen et al. demonstrated that stress can have profound effects on the morphology of hippocampal neurons and proposed that the
hippocampus may be the first brain area to display observable structural changes because of its high propensity for neurogenesis (McEwen, 1999). Sustained stress has relevant adverse effects on hippocampal morphology including: retraction of dendritic processes, loss of neutrophil volume, in addition to loss of preexisting hippocampal neurons (Sapolsky, 2001). Additional systems, such as those involved in dendritic atrophy including glutamate release, N-methyl-d-aspartic acid (NMDA) receptors, gamma-aminobutyric acid (GABA) receptors, serotonin release, and circulating glucocorticoids have been postulated to play a role in observable human hippocampal atrophy in psychiatric illnesses (McEwen & Magarinos, 2001). It is most likely not one mechanism that is orchestrating changes in the hippocampus, but rather an intertwined concert of these mechanisms.

2.1.3.5 NAA in Major Depressive Disorder

N-acetyl-aspartate (NAA) is the second most abundant molecule in the brain after the amino acid glutamate. The largest concentration of NAA exists in the CNS with smaller amounts in the peripheral nervous tissue including: the superior cervical ganglion, dorsal root ganglion, dorsal root, ventral root, sciatic nerve, adrenal medulla, and splenic nerve (Birken & Oldendorf, 1989). Hardly any NAA, however, is found outside the nervous system (Birken & Oldendorf, 1989). Although the specific functions of NAA are unclear, early studies by Buniatian et al. demonstrated that NAA might act as an acetyl group donor to glucosamine and choline (Buniatian, Hovhannisian & Aprikian, 1965). Glucosamine is an amino sugar and a prominent precursor in the synthesis of glycosylated proteins and lipids while choline is a water-soluble essential nutrient. Both are important for proper body function. NAA is thought to primarily reflect neuronal density and integrity and is detected only in neurons (Maddock & Buonocore,
Closely correlated with mitochondrial energy metabolism, NAA synthesis is thought to reflect mitochondrial integrity (Clark, 1998); and NAA decreases are believed to reflect neuronal loss (Birken & Oldendorf, 1989; Clark, 1998; Gasparovic, Arfai, Smid, & Feeney, 2001).

H-MRS (see section 3.2.1.1) is an imaging method used to measure NAA, thus allowing researchers to indirectly examine neuronal alterations. In animal models of depression, some studies have noted decreased NAA concentration in the hippocampus (C. X. Li et al., 2008; Xi et al., 2011), suggesting decreased neural density in this region. Decreased NAA in several brain regions has also been reported in schizophrenia, bipolar disorder, and post-traumatic stress disorder (PTSD) (Maddock & Buonocore, 2012a; Steen, Hamer, & Lieberman, 2005). Some clinical studies (MacMaster, Moore, et al., 2008; Olvera et al., 2010) have found decreased NAA levels in medial temporal lobe structures in depression. In a study by MacMaster et al. 11-treatment naïve MDD case-control pairs (10–16 years of age) underwent H-MRS imaging (MacMaster, Moore, et al., 2008). NAA was lower in the left medial temporal cortex (27%) in MDD patients versus controls and it was suggested that this might reflect reduced neuronal viability. Furthermore, a study examining 16 healthy controls and 52 adult patients with MDD in different stages of the illness found that patients with treatment-resistant/chronic and remitted-recurrent depression had significantly lower NAA concentration than controls, especially in the right hippocampus (de Diego-Adelino et al., 2013). Additionally, it appears that NAA may be indicative of both state- and trait-dependent conditions in psychiatric disorders (Clark, 1998; Gasparovic et al., 2001).

Conversely, some studies have found increased NAA concentrations and other metabolites in the prefrontal and occipital cortices in MDD patients following successful
antidepressant treatment (Bellani et al., 2011; Gonul et al., 2006; Kaymak et al., 2009; Taylor et al., 2008). It appears that NAA may be indicative of both state- and trait-dependent conditions in psychiatric disorders (Clark, 1998; Gasparovic et al., 2001). In contrast, few studies have examined metabolite alterations in the hippocampi of patients with MDD. A study by Wang et al., found that after 12-weeks of treatment with a serotonin–norepinephrine reuptake inhibitor (SNRI) in first-episode, treatment-naive MDD patients, NAA/Cr (creatine) ratios increased significantly in the right hippocampus compared with pre-treatment values (Wang et al., 2012). Finally, various groups have proposed that hippocampal NAA changes may be related to illness trajectory, with repeated episodes causing a reduction in neuronal viability (MacMaster, Moore, et al., 2008; MacQueen et al., 2003; Sheline et al., 1999).

### 2.1.4 Antidepressant Treatment

#### 2.1.4.1 Overview

The clinical course of depression changes over time (Mezuk & Kendler, 2012) and no single treatment is effective for everyone (Fava et al., 2003). Because MDD can be life threatening due to the risk of suicide, it is of great importance to find reliable strategies to prevent and adequately treat this illness. The risk of suicide and level of functioning worsen as depressive symptoms become more severe; therefore, early intervention and effective treatment can decrease the burden of disease. In order to minimize the potential neurodegenerative course of MDD, as well as confounds of antidepressant treatment (e.g., treatment-resistance), the optimal time point to explore treatment-associated brain plasticity is in the early stages of MDD.
2.1.4.2 Standard Treatment for Major Depressive Disorder

A clinician may use pharmacotherapy in the treatment of MDD, prescribing medications such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), or monoamine oxidase inhibitors (MAOIs), among other types of pharmaceuticals. These drugs primarily act on the serotonin and/or norepinephrine systems by inhibiting the reuptake of serotonin and/or norepinephrine into the pre-synaptic neuron or by inhibiting the activity of monoamine oxidase (MAO). Inhibiting the activity of MAO prevents the breakdown of monoamine neurotransmitters and increases the availability of serotonin/norepinephrine in the synaptic cleft (Gelenberg et al., 2010).

Psychotherapy is a non-pharmaceutical treatment option currently available for MDD treatment. Psychotherapy encompasses approaches such as Cognitive Behavioural Therapy (CBT)- a form of ‘talk therapy’- Mindfulness Based Cognitive Behavioural Therapy (MCBT)- a form of 'mindfulness meditation'- and Interpersonal Therapy (IPT), which focuses on problems in personal relationships and the skills required to deal with these problems. These forms of therapy may be conducted by a registered psychologist or psychiatrist, or sometimes even online. The “active ingredient” in psychotherapy, however, still largely remains unknown and an evidence-based explanation is currently unavailable (Ekkekakis, 2013). Somatic therapies such as electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and vagus nerve stimulation are also used for the treatment of MDD. Studies suggest about 60% of young adults respond to these interventions and 40% achieve remission (Brent, 2009; Brent & Birmaher, 2006; Gelenberg et al., 2010).
In past years, the use of psychotherapy as treatment for depression has been steady or declining, whereas the use of pharmacotherapy has increased (Ekkekakis, 2013). The reasons for this may include factors such as increased direct-to-consumer advertising of psychotropic medications; affordability, as most individuals with insurance will cover pharmacotherapy; and a scarcity of psychotherapy resources (Ekkekakis, 2013). The success of an antidepressant therapy is typically indexed by a $\geq 50\%$ improvement from baseline (following an adequate course of intervention) on a recognized rating scale for depression symptoms, such as the Hamilton Rating Scale for Depression (HAMD$_{17}$) or the Beck Depression Inventory (BDI) (Shelton, 2006). Nevertheless, many patients with a $\geq 50\%$ reduction in HAMD$_{17}$ scores continue to experience significant residual symptoms and may still meet diagnostic criteria for MDD (Shelton, 2006). A partial responder to an antidepressant treatment ranges from 25%-49% and a non-responder would be indicative of a <25% decrease from baseline scores. Another common criterion for MDD remission is a HAMD$_{17}$ score $\leq 7$ (Shelton, 2006). This benchmark has been shown to provide the best differentiation between depressed and non-depressed individuals (Shelton, 2006). The optimal treatment is one that the patient prefers, will adhere to and helps.

2.1.4.3 Limitations and Need for Novel Interventions

Unfortunately, there is a scarcity of treatment options for depressed young adults, those who are most likely to experience their first major depressive episode. SSRIs are the only class of medications approved for treating MDD in adolescents; yet serious concerns exist with respect to increased risk of suicide during the initial treatment phase (Ekkekakis, 2013). Rates of remission following adequate SSRI treatment are variable and the majority of patients with MDD are expected not to achieve remission with a first antidepressant trial (Carvalho,
Cavalcante, Castelo, & Lima, 2007). Pharmaceuticals may cause adverse side effects such as decreased sexual desire, digestive problems, restlessness, constipation, weight gain, headaches and insomnia, increased blood pressure, among others (Chong, 2006). Furthermore, therapeutic onset is delayed as SSRIs typically take several weeks to become effective. As such, assessing the effectiveness of non-pharmacological antidepressant interventions in young adults with MDD is important. Unfortunately, it is common that patient adherence to pharmacotherapy is low and that rates of early discontinuation are high: 42.4% of patients discontinue antidepressant therapy within 30 days (Ekkekakis, 2013).

For individuals with non-severe MDD, the strategy of watchful waiting in clinical practice is often implemented as it is accepted by clinicians that treatment is not needed for mild and brief episodes (National Institute for Health and Clinical Excellence, 2007). Recently, a report by Patten et al (2012) indicated that sub-threshold MDD episodes have associated risk implications for later MDD episodes. Long-term monitoring of patients with preventive goals may be acceptable but requires additional investigation (Patten, Williams, Lavorato, Bulloch, & MacQueen, 2012).

Exercise is one such intervention that needs to be further explored. There are various barriers to effective MDD care including aspects such as inaccurate assessment, a lack of resources, the lack of trained health care providers, and social stigma associated with mental health disorders (World Health Organization, 2012). A recent meta-analysis suggested that there are minimal benefits of medication versus placebo for treating mild-moderate cases of depression (Fournier et al., 2010). As such, the role of non-pharmacological treatment options for depression becomes increasingly important. Exercise is one such therapy that has received considerable attention and will be discussed further in section 2.2.
2.2 Exercise

The terms “physical activity”, “exercise”, and “physical fitness” describe different concepts, however, they are often confused with one another and sometimes used interchangeably (Caspersen, Powell, & Christenson, 1985). Most broadly, physical activity is generally defined as any bodily movement produced by skeletal muscles that results in energy expenditure and can be categorized into occupational, sports, conditioning, household, or other activities (Caspersen et al., 1985). Exercise is a subset of physical activity and is planned, structured, and repetitive, with the objective of improving or maintaining physical fitness. Subsets of exercise are often referred to as either anaerobic or aerobic exercise, the latter being the focus of this thesis. Physical fitness is a set of attributes that are either health- or skill-related and can be measured by specific tests (Caspersen et al., 1985) (e.g., VO₂ max). Preclinical research generally refers to studies as being exercise-focused although animal physical fitness is typically not measured as an outcome variable.

2.2.1 Exercise and Major Depressive Disorder

Exercise as a therapy for depression has received considerable attention and been a popular research topic. Physical activity has shown promise in reducing depressive symptoms as well as in preventing depression episodes in the long term (Mammen & Faulkner, 2013). Furthermore, preliminary evidence shows that patients treated with exercise have a 9% risk of relapse, much lower than the 30% for patients treated with antidepressant medication (Babyak et al., 2000). Physical activity thus serves as a valuable preventative mental health promotion strategy as it decreases MDD risk (Mammen & Faulkner, 2013).
In contrast to other therapies, aerobic exercise in particular has the advantage of being a safe, socially acceptable, accessible, and relatively inexpensive intervention for young adults with MDD. Engaging in regular exercise does not carry a negative stigma and can be done outside standard medical settings. Furthermore, it offers a wide range of collateral benefits such as metabolic and cardiovascular health (Ekkekakis, 2013). These factors may make it an appealing early intervention for young people with a first onset of depressive symptoms or in the early stages of MDD. A review by Ekkekakis (2013) of physical activity as a mental health intervention in the era of managed care addresses some current ideas pertaining to exercise and depression. A few key points addressed include a naiveté from health care professionals regarding unfamiliarity with the current research regarding exercise and mental health, and how media can distort evidence, thereby negating opportunities for patients who may seek exercise as a treatment regime.

The majority of trials using exercise interventions for clinical depression have used either aerobic or anaerobic exercise, with aerobic exercise following the parameters of 60–80% of maximum heart rate for 30 minutes, three times per week, for an overall duration typically of 8 weeks (Perraton, Kumar, & Machotka, 2010). The exact mechanism by which exercise produces antidepressant effects has not been established. On a psychological level, several mechanisms have been proposed such as changes in body scheme and health attitudes and behaviors, learning and extinction, social reinforcement, experience of mastery, shift of external to more internal locus of control, and overall improved coping skills (Mammen & Faulkner, 2013). Better identification of what mechanisms are implicated in the antidepressant effects of exercise is important to ‘prescribe’ appropriate exercise interventions for treating MDD.
2.2.2 Exercise and Hippocampal Plasticity

2.2.2.1 Animal Models

Many of the biological mechanisms involved in the relationship between exercise, depression, and the brain are understood through experiments using animal models. Depression-like behaviors in animals, particularly rodents, are inferred from measures such as lack of sexual activity, excessive sleeping, weight gain, and lack of activity. Voluntary wheel running has been shown to increase neurogenesis in the hippocampus, neuronal spine density, synaptic plasticity, neurotrophin levels, and spatial memory function in mice (van Praag, 2008). More specifically, wheel-running has been found to increase cell proliferation and survival in the dentate gyrus of the hippocampus in young adulthood through old age (van Praag, Christie, Sejnowski, & Gage, 1999), perhaps contributing to changes in hippocampal volume. Unlike humans, rodents tend to be natural runners and will willingly run when put in an environment with a running wheel.

Preclinical studies investigating the effect of voluntary wheel running and how it would benefit mice that were sedentary until 19 months of age suggest that aerobic exercise stimulates hippocampal neurogenesis (van Praag, Shubert, Zhao, & Gage, 2005) and induces the release of proteins and peptides. These proteins and peptides are known to be related to improved health and survival of nerve cells. Although the exact mechanisms directly linking exercise with cell proliferation are still unknown, factors that participate in the modulation of adult neurogenesis include modulations in serotonin system function (Klempin et al., 2010), BDNF (Moon et al., 2012), vascular endothelial growth factor (VEGF) (Fabel et al., 2003), insulin-like growth factor (IGF-1) (Carro, Nunez, Busíguina, & Torres-Aleman, 2000), and endocannabinoids (Hill et al., 2010); activity in these systems tends to be upregulated following wheel-running.
BDNF plays a critical role in the brain throughout development and adulthood by promoting neuronal survival and regeneration. Higher serum levels of BDNF have also been associated with larger hippocampal volumes (Erickson et al., 2011). VEGF is a protein secreted from blood that acts on endothelial cells to stimulate blood vessel formation, and it is known to increase in people when they exercise (Schobersberger et al., 2000). Increased vasculature (and increased VEGF release) in the hippocampus has been associated with neurogenesis (Fabel et al., 2000). Exercise stimulates insulin-like growth factor (IGF-1), which is a trophic factor that circulates at high levels in the blood-stream (Carro et al., 2000). Exercise and intracarotid injection of IGF-I have been shown to produce similar effects in the brain including long-lasting changes in electrophysiological properties of neurons through modulation of ion channels (Carro et al., 2000). The endocannabinoid system is a neuromodulatory system composed of two receptors two ligands (Hill et al., 2010). Voluntary exercise in rats has shown to significantly increase endocannabinoid signaling within the hippocampus, and endocannabinoid signaling is necessary for voluntary exercise to increase proliferation of progenitor cells within the dentate gyrus (Hill et al., 2010). Overall, aerobic exercise in rodents has been shown to correlate with increased neural proliferation and survival in the hippocampus and surrounding tissue (van Praag et al., 2005).

2.2.2.2 Studies in Humans

Exercise has long been studied for its mood-enhancing effects, including in the context of MDD and in individuals with sub-threshold depression symptoms. Epidemiological studies suggest an association between physical inactivity and higher levels of depressive symptoms (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991). Physical activity has been found to
confer protective effects against the development of MDD in adolescent girls (Jerstad, Boutelle, Ness, & Stice, 2010). Moreover, studies in middle-aged and older adults report that aerobic exercise and higher baseline fitness levels are associated with antidepressant and mood-elevating effects. (Bjornebekk, Mathe, & Brene, 2005; Dimeo, Bauer, Varahram, Proest, & Halter, 2001; Dunn, Trivedi, Kampert, Clark, & Chambliss, 2005).

A study conducted by Dunn et al. (2005) performed an exercise intervention in a supervised laboratory setting with adults (N = 80) aged 20-45 years of age diagnosed with mild to moderate MDD. HAMD17 assessments indicated decreased depression symptoms. Importantly, the study found that aerobic exercise at a level consistent with public health recommendations is an effective treatment for patients with mild to moderate MDD. A 16-week intervention by Blumenthal et al. (1999) randomly assigned 156 participants into groups being treated with: (1) aerobic exercise, (2) antidepressants (sertraline hydrochloride – an SSRI) or (3) combined exercise and medication. This study showed that 16 weeks of exercise was equally effective in reducing depression in MDD as antidepressants. The study was conducted in older subjects, limiting the generalizability of results. Furthermore, the exercise was done in a group, which still leaves a question of whether social support was a factor influencing outcomes.

Despite extensive evidence suggesting the antidepressant effects of aerobic activity, little research has been devoted to the optimum type, frequency and duration of exercise in terms of alleviating depression symptoms. It is important to quantify the amount of exercise needed to reduce depressive symptoms so that recommendations for exercise prescription can be developed for better treating depression. The neurobiological mechanisms that underlie these mood-enhancing effects have not been well established, especially in the depressed young adult
population. It is unknown which mechanisms are involved in the antidepressant effects associated with aerobic exercise.

A few clinical studies indicate that the increased hippocampal volumes only emerge with long-term aerobic exercise (Erickson et al., 2011) (Pajonk et al., 2010). A randomized study in patients with schizophrenia assessed whether hippocampal volume would increase with exercise and whether this effect would be related to improved aerobic fitness (Pajonk et al., 2010). The study recruited a total of 24 subjects, 8 patients with schizophrenia and 8 healthy age and sex-matched controls who followed a 12-week aerobic exercise intervention (cycling). An additional 8 control patients played table soccer over 12-weeks. A 12 percent increase in hippocampal volume and 35 percent increase in hippocampal NAA/Creatine ratio in patients with schizophrenia post exercise intervention were observed. The study did not however see initial differences in hippocampal volume among the three groups or post-exercise changes in total brain volume or total grey matter. The change in hippocampal volume did however positively correlate with the change in VO$_2$max. Furthermore, this was associated with short-term memory improvements.

A prospective randomized controlled trial (Erickson et al., 2011) recruited 120 healthy older adults who were scanned at three time points: baseline, 6 months, and 1 year. This study found that those with aerobic exercise training exhibited a bilateral increase in anterior hippocampal volume, while other regions (posterior hippocampus, caudate nucleus and thalamus) remained unchanged. Conversely, anterior hippocampal volume was reduced in the stretching control group. Increased grey and white matter volume in prefrontal regions was found (Erickson et al., 2011). Little is known about whether the magnitude of aerobic fitness capacity improvement correlates with or drives the magnitude of hippocampal neuroplasticity and
affiliated mood changes. Based on the limited literature to date examining aerobic exercise in young adults with depression, this study appraised neurobiological variables of the hippocampus (volume & NAA) to better understand what mechanisms may be affiliated with mood changes.

2.2.3 Research Questions & Hypotheses

The following primary research questions were addressed:

1. **Will 12-weeks of structured aerobic exercise intervention improve cardiovascular fitness (as measured by VO_{2\max} changes) and decrease depressive symptoms (as measured by HAMD_{17} score changes) in relatively sedentary MDD participants?**

   We hypothesized that a structured 12-week aerobic exercise intervention would increase VO_{2\max} and decrease HAMD_{17} scores from baseline to week 12 post-exercise intervention in young adults with MDD.

2. **Will changes in hippocampal volume and NAA concentration increase after a structured 12-weeks aerobic exercise program in MDD patients?**

   We hypothesized that aerobic exercise would increase both hippocampal volumes and hippocampal N-acetyl aspartate (NAA) concentrations.

3. **Do changes in cardiovascular fitness (as measured by VO_{2\max} changes from baseline to week 12 positively correlate with changes in both hippocampal volume and NAA concentrations (from baseline to week 12)?**

   We hypothesized that a positive correlation between hippocampal volume and NAA concentration changes in depressed individuals with aerobic capacity (VO_{2\max}) increases after aerobic exercise training.
4. Do hippocampal volume and NAA concentration changes negatively correlate with changes in depressive symptoms (HAMD\textsubscript{17} scores) from baseline to week 12 (i.e., post-exercise intervention)?

We hypothesized that hippocampal volume and NAA concentration changes would inversely correlate with HAMD\textsubscript{17} score changes.

The following secondary research questions were also addressed:

5. Do differences exist in hippocampal volume and NAA concentration between MDD patients and healthy controls?

We hypothesized to see smaller hippocampal volumes and decreased NAA concentrations in patients when compared to healthy controls at baseline. After MDD patients completed the 12-week aerobic exercise intervention, we expected no differences between hippocampal volumes and NAA concentrations between MDD participants and controls.

The following exploratory research questions were also addressed:

6. Does aerobic exercise adherence (i.e., attendance and completion of 30 minutes of exercise in target HR zone) correlate with changes in depression scores (HAMD\textsubscript{17}; pre- to post-exercise)?

We hypothesized a positive correlation between aerobic exercise adherence and changes in depression scores.

7. Does aerobic exercise adherence (i.e., attendance and completion of 30 minutes of exercise in target HR zone) correlate with changes in hippocampal volume and NAA concentration pre- to post-exercise?

We hypothesized a positive correlation between aerobic exercise adherence and hippocampal volume, and between aerobic exercise adherence and NAA concentration.
Chapter Three: **Methods**

### 3.1 General Methods

#### 3.1.1 Participant Recruitment and Screening Overview

Unmedicated, relatively sedentary young adults (aged 18-24 years), with major depressive disorder [MDD; Hamilton Rating Scale for Depression (HAMD$_{17}$) (Hamilton, 1960) scores: minimum score of 14] were recruited from the Calgary community and the university student population. Demographically matched non-depressed healthy control participants were also recruited (Appendix A).

Explanation of the study’s aims, procedures and time commitments to interested potential participants was completed via email (Appendix B). Subsequently, an information and screening session was carried out by telephone to verify eligibility of both patients and controls (Appendix C & D). Interested and eligible participants were then assessed in-person using a semi-structured psychiatric interview (Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 2010) to ascertain MDD (as the primary diagnosis) or control status. The study psychiatrist confirmed the diagnosis and eligible participants were enrolled in the exercise intervention (12-weeks); only depressed individuals underwent the exercise intervention. Both depressed individuals and healthy controls underwent two sessions consisting of neuroimaging, neurocognitive and clinical assessments (baseline and 12-weeks later). MDD participants underwent a final fitness assessment (after 12-weeks of exercise intervention) while healthy controls were administered the International Physical Activity Questionnaire (IPAQ) at their 12-week assessment to ensure their physical activity levels did not drastically change from their pre-intervention assessment. The fitness assessments for the MDD participants occurred pre-intervention, at 8 weeks, and post-intervention (after 12-weeks). Regular clinical mood
assessments were also carried out for the depressed group throughout their 12-week exercise intervention (Figure 1 & Figure 4).

3.1.2 Telephone Pre-Screen

Participants were queried regarding demographic, fitness and mental health information. The BDI, a 21-item self-report scale, with higher scores indicating more severe depression, was administered (over the phone) to establish eligibility (min=12 for potential MDD participants; Appendix C: telephone screen of individuals regarding fitness and mental health). Appropriate and interested participants (i.e., those who passed the telephone-screen) were invited for an in-person assessment. Depressed individuals who scored in the severe range on the BDI (i.e., scores above 29), but were interested in participating in the study, were asked to come in for an in-person assessment as long as they were not experiencing significant suicidal ideation and expressed an interest in participating in the exercise training. Study inclusion was ultimately determined by the in-person psychiatric assessment and thus was at the discretion of the study psychiatrist.

3.1.3 Intake Session: In-Person Assessments and Screening

3.1.3.1 Baseline Clinical Assessments and Screening

Upon arrival to the laboratory, study procedures were re-explained, queries addressed and informed consent obtained (Appendix E & F). A semi-structured psychiatric assessment was conducted in addition to the following outcomes measures of interest. Hamilton Rating Scale for Depression (HAMD17) (Hamilton, 1960) is administered by a trained professional to assess MDD symptom severity. This interview style questionnaire captures some
atypical and somatic symptoms of the disorder. The scale contains 17 variables which are measured either on five-point or three-point scales. No distinction is made between intensity and frequency of symptoms. HAMD$_{17}$ scores of a minimum of 14 were required for study participation (for patients). However, interested participants with slightly lower HAMD$_{17}$ scored (i.e., 8-13: mild MDD severity) were considered for study inclusion on a case-by-case basis (at the discretion of the study psychiatrist). The following severity ranges using the HAMD$_{17}$ are typically used in indexing MDD severity: no depression symptoms (0–7); mild depression symptoms (8–16); moderate depression symptoms (17–23); and severe depression symptoms ($\geq 24$) (Zimmerman, Martinez, Young, Chelminsik, & Dalrymple, 2013).

**International Physical Activity Questionnaire (IPAQ)**

IPAQ assesses physical activity participation in everyday life.

**Physical Activity Readiness Questionnaire for Everyone (PAR-Q+)** (Bredin, Gledhill, Jamnik, & Warburton, 2013) Administered by a certified exercise physiologist (CEP) to determine the safety or possible risk of exercising for an individual based upon their answers to specific health history questions.

Participants meeting inclusion criteria after the in-person assessment met with the study psychiatrist (Dr. MacQueen) for a follow-up psychiatric evaluation. Potential participants and healthy controls then continued with the neurocognitive assessment.

3.1.3.2 Non-Depressed Control Group

Healthy, non-depressed control participants (Appendix D; BDI<10) were matched to patient participants on all relevant parameters, including age, weight and exercise history. They also underwent neuroimaging, cognitive testing pre and post-intervention, but did not partake in
exercise training. Participants were recruited through posters, advertisements around the University of Calgary, Craigslist, and word of mouth.

3.1.3.3 Inclusion and Exclusion Criteria

Pertinent patient and control inclusion and exclusion criteria are outlined in Tables 1 and Figure 1.

Table 1: Participant Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
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<tbody>
<tr>
<td><strong>MDD Participants</strong></td>
<td><strong>Healthy Controls</strong></td>
</tr>
<tr>
<td>• Current MDD as primary diagnosis (MINI-assessed)</td>
<td>• No MDD (MINI-assessed)</td>
</tr>
<tr>
<td>• Minimum score of 14 on HAMD\textsubscript{17}, established during in-person assessment*</td>
<td>• BDI below 10</td>
</tr>
<tr>
<td>• Males and females 18-24 years of age</td>
<td>• Life-time history of psychosis</td>
</tr>
<tr>
<td>Physically healthy (not obese: BMI&lt;35)</td>
<td>• Current (i.e., within 6 months) drug/alcohol abuse or dependence (except nicotine)</td>
</tr>
<tr>
<td>Relatively sedentary (not undergoing aerobic exercise training consistently 3X/week)</td>
<td>• Currently taking antidepressants, other psychoactive drugs or engaging in formal psychotherapy</td>
</tr>
<tr>
<td></td>
<td>• Life-time history of anorexia/bulimia</td>
</tr>
<tr>
<td></td>
<td>• Life-time history of seizure</td>
</tr>
<tr>
<td></td>
<td>• Unstable medical condition (i.e., inadequately stabilized for &gt;3months)</td>
</tr>
<tr>
<td></td>
<td>• Patients at significant risk for suicide</td>
</tr>
<tr>
<td></td>
<td>• Physical/medical condition presenting participation in aerobic exercise training</td>
</tr>
<tr>
<td></td>
<td>• MRI contraindications</td>
</tr>
<tr>
<td></td>
<td>• No immediate family (i.e., parents/siblings) history of depression – healthy controls only</td>
</tr>
</tbody>
</table>

* Individuals with mild MDD severity (scores of 8-13) were included at the discretion of our study psychiatrist

MDD: Major Depressive Disorder; HAMD\textsubscript{17}: Hamilton Rating Scale for Depression
Figure 2. Outline of participant recruitment, screening and enrolment

Hamilton Rating Scale for Depression (HAMD<sub>17</sub>), International Physical Activity Questionnaire (IPAQ), Physical Activity Readiness Questionnaire (PAR-Q+)
3.2 Specific Methods

3.2.1 Magnetic Resonance Imaging

3.2.1.1 Fundamentals of Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an ideal quantitative, non-invasive and safe way to obtain in vivo information about the brain. MRI uses principles of magnetic resonance, which entails combining magnetic fields and radiowaves to form discernable 3-D images. The body contains a large amount of water and different tissues have different amounts of water. The contrast between different soft tissues permits a highly detailed picture to be obtained. Each water molecule of has two spin-active $^1$H nuclei. When such a nucleus is placed in an external magnetic field, two different energy states emerge; a low-energy state and a high-energy state. A nucleus in an external magnetic field can absorb or emit electromagnetic radiation in transitioning between these two energy states. An MRI detects the emitted radio frequency signal from the appropriate excited hydrogen atoms, which forms the appropriate images as atoms return to their equilibrium state. Unlike computerized tomography (CT) scans, which use x-rays, an MRI scan does not expose a subject to ionizing radiation and is therefore considered safe, provided the subject does not have any metal on or in their body. This can be screened for in addition to inquiring if the subject may be claustrophobic as the space inside an MRI machine is fairly limited.

The images analyzed in this study were $T_1$-weighted, where $T_1$ is the spin-lattice relaxation time or the average time it takes for excited protons to emit electromagnetic energy and return to ground state. $T_1$ images allow considerable distinction between grey and white matter where grey matter appears grey, and white matter white. In contrast, $T_2$-weighted images, where $T_2$ is spin-spin relaxation time allows to differentiate between tissue and fluid. Because of this, $T_2$-weighted images are useful in identifying abnormal fluid accumulation in the brain.
3.2.1.2 Fundamentals of Proton Spectroscopy

Magnetic resonance spectroscopy (MRS) is a safe, non-ionizing and non-invasive imaging technique that directly assesses in vivo biochemistry within a specific brain region (Stanley, 2002). $^1$H-MRS is the most common type of MRS and is similar to MRI as it uses the same magnetic principles and equipment. $^1$H-MRS provides information about the concentrations of freely mobile metabolites contained in the fluid component of a specific region of interest in the brain (Maddock & Buonocore, 2012b). To be $^1$H-MRS-quantifiable, metabolites must be freely mobile (e.g., not bound to cell membrane or macromolecules), and present in high concentration (generally at least 1 millimolar). Although $^1$H-MRS can reliably quantify several neurochemicals, neurotransmitters of greatest interest in the study of mood disorders including monoamines (serotonin, norepinephrine, and dopamine), are present in the brain in concentrations far too low to be measured by MRS.

Data is presented in a spectrum format with a series of observable peaks, as seen in Figure 3. The horizontal axis, called chemical shift, reflects the proton resonant frequency, which is dependent on the structure of the molecule of interest (e.g., NAA). The area under the curve corresponds to the proton concentration at that given frequency (Ross & Bluml, 2001). NAA is generally the tallest peak observed on the spectrum.
Figure 3. A typical $^1$H-MRS spectrum from a voxel in the human brain

The horizontal axis displays the frequency of the protons in the structure of each molecule of interest, while the area under the peaks corresponds to the proton concentration at that frequency. Neural metabolites depicted here are as follows N-acetyl-aspartate (NAA), creatine (Cr), choline (Cho), myoinositol (mI), and glutamate and glutamine (Glu+Gln).
3.2.1.3 Data Acquisition

3.2.1.3.1 Anatomical MRI Sequence

MRI data was acquired pre- and post-exercise training (within a week of exercise completion for depressed participants) and after 12-weeks for control participants. Images were collected with a General Electric 750 3T scanner with a 24-channel high-resolution head coil at the Alberta Children’s Hospital under the supervision of trained MRI technicians.

A high-resolution T1-weighted anatomical scan in the axial orientation was obtained using the following anatomical imaging acquisition specifications: repetition time (TR) = 8.152ms, time to echo (TE) = 3.16ms, flip angle 10 degrees, 208 partitions, 256 X 256 matrix, field view (FOV) = 256, 0.8 mm slice thickness.

3.2.1.3.2 MRI Tracing

3.2.1.3.2.1 Overview

Isotropic MRI image files (NIfTI format) were loaded onto a PC workstation. Tracings were carried out using a stylus and interactive monitor (Wacom Cintiq 21UX, Vancouver, WA, USA) and Analyze Direct 10 software (Overland Park, KS, USA). All images were enlarged in the sagittal view to 2X magnification to reduce manual tracing errors. The volume of the hippocampus (mm$^3$) was determined. Hippocampal boundaries were determined by referring to neuroanatomical brain atlases as well as previous publications on hippocampal manual tracing techniques (Konrad et al., 2009). The hippocampus was defined anatomically as the hippocampus proper (Ammon’s horn: CA1, CA2, CA3 CA4), dentate gyrus and the subiculum. The fimbria and fornix were excluded from all tracings. Although all tracings were performed in the sagittal view, coronal and axial views were used to determine and verify hippocampal
boundaries (outlined below). A single trained rater, blind to any identifying information, carried out the hippocampal tracings. Intra-rater reliability was determined by re-tracing a random subset of the hippocampus (N=9). A second rater then completed a random selection of hippocampal tracings and measurements to ensure inter-rater reliability was adequate. Tracings were performed on MR images with subjects’ identities and diagnoses masked.

3.2.1.3.2.2 Hippocampal Tracing Specifications

Tracing commenced in the sagittal view in the most lateral slice where grey matter was first apparent within the lateral ventricle. White matter from the alveus and fimbria served as the landmark aiding in the identification of the superior border of the hippocampus whereas the white matter from the parahippocampal gyrus, below the subiculum, served as the inferior border. Hippocampal tracing were carried out within these white matter boundaries. The amygdala was used to identify the anterior boundary of the head of the hippocampus while the cerebral spinal fluid (CSF) was used to identify the tail of the hippocampus and the posterior borders (Figure 4, 5, 6).

Moving medially (sagittally), in some cases, the parahippocampal gyrus became quite “toothy” and it was important to avoid tracing any potential CSF. In most cases, the hippocampus head was no longer visible before tracing of the tail was completed. Medial boundaries were determined by using the coronal view where the posterior tail of the hippocampus was visible inferior to the crux of the fornix. While some segmentation protocols stop measuring the hippocampus when the crux of the fornix appears, others, including the procedure that was adopted for the current study, continued to trace the hippocampus posteriorly until the hippocampal ovoid gray matter was no longer visible (coronal view).
Hippocampal boundary demarcations are a potential source of error in volumetric MRI studies and vary across the literature (Konrad et al., 2009). The major points of discrepancy when tracing included: 1) the inclusion/exclusion of hippocampal white matter (alveus and fimbria) 2) the definition of the anterior hippocampal–amygdala border 3) the definition of the posterior border and the extent to which the hippocampal tail was included 4) the definition of the inferior medial border (Konrad et al., 2009).
Figure 4. Sagittal slice selection of human hippocampus.

Figure 5. Hippocampal demarcations: transverse (A), coronal (B), sagittal (C)
Figure 6. Anatomical boundaries used hippocampal tracing

Cerebral spinal fluid (CSF)
3.2.1.3.2.3 Intracranial Volume Tracing Specifications

Similarly to hippocampal tracings, intracranial volume (ICV) tracings were carried out with a semi-automated process using Analyze Direct 10. The skull was stripped away while the brain was kept intact (including cerebellum) and cerebral spinal fluid (CSF) was demarcated (CSF was not included in ICV measures). Each image slice was inspected and edited to ensure consistency and that proper ICV boundaries were correctly demarcated (Figure 7). Editing was performed in the transverse view using coronal and sagittal views as reference. ICV boundaries were determined by referring to standard neuroanatomical atlases. The cortex, cerebellum and brainstem were included while cerebrospinal fluid was excluded.

3.2.1.3.3 Proton Spectroscopy (MRS) Sequences

The short echo (TE = 30 msec, TR = 2000 msec) $^1$H-MRS protocol consists of voxels placed within the left and right hippocampi [6 cubic centimeters (cc), angulated to achieve better coverage, 128 averages, 256 total acquisitions, 2500 Hz spectral width, 2048 points] (Figure 8).

3.2.1.3.3.1 MRS analysis

Spectroscopy sequence analysis was conducted with LC Model (Provencher, 1993, 2001). LC Model software fits in vivo metabolite spectra by using model spectra previously acquired from similar scanning conditions from various compounds in phantom solutions and is operator independent. The operator receives approximate maximum-likelihood estimates of the metabolite concentrations and their uncertainties (Cramer-Rao lower bounds). LC Model normalizes the metabolite spectra obtained using an unsuppressed water peak as reference.
Figure 7. Transverse intracranial volume (ICV)
Example of inferior brain slice showing boundaries encompassing the cerebellum (A), mid brain (B), superior brain (C).
Figure 8. $^1$H-MRS spectrum voxel placement in the human hippocampus
3.2.2 Exercise Intervention

3.2.2.1 Baseline/Pre-intervention Physical Fitness Assessment Session and Screen

3.2.2.1.1 Initial Assessments

Prior to commencing the first exercise session, participants and healthy controls underwent a short fitness appraisal. To ensure their safety, they completed the Physical Activity Readiness Questionnaire for everyone (Brendin et al., 2013) and if required, the Physical Activity Readiness Medical Examination (PARmed-X+) (Brendin et al., 2013) questionnaire.

These questionnaires were administered at the time of the initial in-person assessment. All fitness assessments were conducted by an experienced certified exercise physiologist (CEP) following the standardized Canadian Physical Activity, Fitness & Lifestyle Approach Protocol (CPAFLA) (CSEP, 2003) guidelines and the American College of Sports Medicine Guidelines for Exercise Testing and Prescription (ACSM, 2010). The appraisal consisted of two components: a body composition portion, wherein the participants’ height, weight, body mass index (BMI) and waist circumference (WC) were measured, and a cardiovascular portion, during which time participants performed a sub-maximal incremental biking test, measuring their heart rate’s response to increasing workloads (Appendix I).

VO₂ max (or cardio-respiratory aerobic capacity/fitness), which reflects the maximum rate at which an individual consumes O₂ during maximal exertion on either a treadmill or cycle ergometer, is measured directly using a metabolic cart and measuring expired gases (ACSM, 2010). Predictive submaximal tests, as performed in this study, estimates VO₂ max based on the relatively linear relationship between VO₂ and HR. This study used the YMCA submaximal test, which employs a cycle ergometer to estimate VO₂ max (Golding, 1989; ACSM 2010).
3.2.2.2 Aerobic Exercise Intervention

Following the above assessments, the exercise intervention commenced. Participants engaged in an exercise training protocol for 12-weeks at the Kinetix Fitness & Wellness Centre (Teaching Research and Wellness building, University of Calgary) three times per week. Each session consisted of: a) 3-5 min of low-intensity warm-up exercises, b) 30-45 min of aerobic training, and c) 5-10 min cool down and stretching (Figure 9). During the 30 min of aerobic exercise, participants were permitted to select from an assortment of aerobic equipment including, but not limited to, cycling on a upright or reclined stationary bike, running on a treadmill, using an elliptical, rowing on an ergometer or engaging in a circuit of activities. Participants were allowed to change equipment during their session. Additionally, each participant wore his or her heart rate monitor throughout the session (Appendix: J & K).

3.2.2.2.1 Heart Rate Monitoring

Heart rate reserve (HRR) is the difference between the maximum heart rate of an individual and their resting heart rate. The target heart rate zone was 60–75% of the heart rate reserve (HRR: HRR = HRmax - HRrest) for the first 6 weeks of training and 70–85% HRR for the remainder of the exercise training intervention, consistent with the ACSM guidelines for aerobic exercise training zones. Steady-state HR during each aerobic exercise session was recorded. To help participants modify their intensity as needed to remain within their target zone, HR monitors were set to correspond with each individuals minimum and maximum heart rate for their designated zone. The HR monitor beeped if the participant fell outside of that designated HR range.
Following each training session, participants’ minute-by-minute heart rate data was downloaded onto a computer and the mean and maximum heart rate were recorded. Additionally, participants were asked to rate each session at the end (0=extremely unpleasant - 10=extremely pleasant).

3.2.2.2 Mood Assessments

Pre and post-exercise intervention mood assessments were carried out with the HAMD_{17} in order to evaluate changes from pre-intervention over the given exercise duration. Additionally, throughout the intervention, prior to exercise sessions on weeks 2, 4, 6, 8, and 10, mood/clinical symptoms were also assessed with the HAMD_{17} (Figure 9). This was performed in a structured interview by a trained rater.

3.2.2.3 Exercise Intervention Retention

The exercise intervention consisted of 36 sessions (3 sessions/week for 12-weeks). One of the major threats to the validity of this study was participant compliance. Study personnel monitored adherence by recording attendance at each training session. It is recognized that participating in this study required a significant time commitment. In order to maximize participant adherence and limit discontinuation, several measures were incorporated. First, the participants had the option to perform their training sessions using various exercise options/equipment (e.g., treadmill, bike, rowing ergometer, circuit). Second, participants were allowed to engage in other activities while performing their exercise (e.g., listening to music, watching TV).
Participants who did complete the three training sessions/week were encouraged to keep attending training sessions as frequently as possible and queried as to how training could be adapted to enhance their attendance; attempts were made to incorporate this feedback into the training schedule. Participants were reminded that the training sessions provided a unique opportunity to work with fitness experts and are a great way of improving physical health.
Figure 9. Aerobic exercise intervention outline and associated measures following MDD participant enrollment

Hamilton depression rating scale (HAMD_{17}); Heart Rate Reserve (HRR); Magnetic Resonance Imaging (MRI); Magnetic Resonance Spectroscopy (MRS)
3.2.3 Statistical Analyses Plan

For the purpose of this study, the primary outcome measures were baseline and week 12 neuroimaging indices (hippocampal volume and NAA levels), fitness measures (VO2max) and depression scores (HAMD17 scores). Additionally, percent changes in outcome measures of interest were carried out and adjusted for baseline scores (outlined in “iv” below).

A traditional hypothesis-testing approach involves testing a null hypothesis. Given the pilot nature of the study, the small sample sizes of our groups and the large individual variability on pertinent measures of interest, we felt that this approach was inappropriate. A failure to reject the null hypothesis could represent an actual lack of effect or a failure to detect an effect due to a lack of statistical power (Type II error); given our sample size and anticipated effect size, we were underpowered to detect group differences for our measures of interest. For this reason, the analyses presented includes descriptive and basic statistics (one-way analyses of variance [ANOVAs] or t-tests).

IBM SPSS Statistics for Macintosh (Version 20.0.0. Armonk, NY: IBM Corp) and Microsoft Word Excel for Macintosh (Version 14.3.9) were used to carry out all analyses. The following information pertains to how variables of interest were calculated and how data analyses were carried out (the same approach was applied for all variables of interest). Significance level was <0.05 for the t-tests, one-way ANOVAs, and correlations.

i. Descriptive results (means, standard deviations) were used to present baseline, week 12, as well as changes in hippocampal volume, NAA concentration, VO2max, and HAMD17 scores. Results are typically represented per group (i.e., MDD and healthy controls).

ii. Descriptive results were also used to present exercise treatment responders versus non-responders on all pertinent outcome measures. Exercise responders were defined as those
with a ≥5% increase in their VO\textsubscript{2}max levels from pre- to post-exercise intervention (as determined by a median split of the change in VO\textsubscript{2}max scores in the MDD cohort).

iii. Descriptive results were also presented for treatment responders versus non-responders. Treatment responders were defined as MDD individuals who exhibited a minimum of a 50% decrease in HAMD\textsubscript{17} scores from baseline to week 12.

iv. T-tests were used to compare MDD and control groups on specific demographic and clinical variables (i.e., age, years of education, HAMD\textsubscript{17} scores). Chi-square tests were used to examine whether the distribution between the genders differed between the groups (i.e., MDD versus healthy controls).

v. T-tests were used to compare cardiorespiratory fitness measures (VO\textsubscript{2}max) between the control and MDD group at baseline; VO\textsubscript{2}max was assessed for the MDD group pre and post exercise intervention using paired t-tests.

vi. Exercise adherence was expressed as a percent and calculated based on the number of sessions attended out of the maximum number of exercise sessions ([X number of sessions attended/36]*100).

vii. Each participant’s “exercise effort” was also calculated. This was a percentage of the total minutes the participant exercised below and in (or above) their target HR zone.

viii. In addition to reporting baseline and post-exercise intervention values for each measure of interest (i.e., hippocampal volume, NAA levels, depression scores, VO\textsubscript{2}max), percent changes in measures of interest were reported and adjusted for baseline scores (i.e., ((baseline score - week 12 score)/baseline score)*100). In the analyses presented, a positive percent change represents an increase in a particular measure of interest from baseline to week 12, while a negative percent change represents a decrease.
ix. Spearman’s correlations were completed for the following in order to evaluate exploratory hypotheses (significance was set at .01 to minimize false positives; all change scores are expressed as a percent):

a. Changes in VO₂max (from baseline to week 12) and attendance (expressed as a percent).

b. Changes in VO₂max and duration in HR zone (expressed as a percent).

c. Changes in VO₂max and changes in HAMD₁₇ scores (from baseline to week 12).

d. Changes in HAMD₁₇ scores and attendance.

e. Changes in hippocampal volumes and changes in VO₂max.

f. Changes in NAA concentration and changes in VO₂max.

g. Changes in hippocampal volume and changes in HAMD₁₇ scores.

h. Changes in NAA concentration and changes in HAMD₁₇ scores.
4.1 Results: Overview

The primary purpose of this study was to assess changes in neurobiological variables in the hippocampus (volume and NAA levels) in relation to changes in cardiovascular fitness (measured by VO$_2$max) and depression severity (HAMD$_{17}$ scores) in young depressed adults pre-to post-aerobic exercise intervention. Additionally, we examined the differences in neural, clinical and fitness levels between MDD participants and healthy controls at baseline and after 12-weeks.

In brief, we hypothesized that hippocampal volume and NAA levels would increase after aerobic exercise intervention in individuals with MDD and that these increases would correlate with increases in VO$_2$max and with MDD symptom reductions. Between MDD participants and healthy controls, we expected to see smaller hippocampal volumes and decreased NAA concentrations in the MDD group at baseline. We also expect that these variables would be similar to healthy controls after MDD participants completed the 12-week aerobic exercise intervention.

4.1.1 Data Screening

4.1.1.1 Normative Data

Data was recorded, stored, checked for outliers (2.5 standard deviations [SD] above the mean), and any errors using graphical techniques and by viewing the descriptive statistics (in addition to inspection of the raw data). No collected data was excluded apart from one NAA value that was recorded but could not be physiologically possible.
4.1.2 Participant demographics

A total of 23 participants were recruited for the study (n=13 healthy controls; n=10 MDD participants). There were no significant differences (Chi-square) in the distribution of the sexes between the MDD and healthy control groups; age, and years of education also did not differ between the two groups (t-test) (Table 2).

Out of the 10 MDD participants, 5 had previously tried medication, 8 had previously experienced previous episodes of depression, and 8 had a comorbidity of some form of anxiety. According to the HAMD17, 7 MDD participants were classified as mild and 3 were classified as moderately depressed.

Table 2: Mean demographic characteristics of healthy controls and MDD participants at baseline

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Sex</th>
<th>Ethnicity</th>
<th>Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>21.2 ±1.8</td>
<td>7M/6F</td>
<td>6 Caucasian; 4 East Asian; 3 Asian</td>
<td>15.2 ±1.5</td>
</tr>
<tr>
<td>(n=13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD (n=10)</td>
<td>21.4 ±1.7</td>
<td>6M/4F</td>
<td>8 Caucasian; 2 Asian</td>
<td>14.7 ±1.8</td>
</tr>
<tr>
<td>p value</td>
<td>0.61</td>
<td>0.59</td>
<td>---</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Age and education reported in years (mean±SD). MDD: Major Depressive Disorder; M: male; F: female.

p values are the results of one-way ANOVAs and t-tests
4.1.3 Cardiorespiratory fitness ($VO_2$max)

No significant differences in $VO_2$ max were noted between the control and MDD groups at baseline ($p=0.27$). Within the MDD group, a trend towards $VO_2$max increase was observed from pre- to post-exercise intervention ($p=0.054$) (Figure 10).

Figure 10: Mean $VO_2$max scores of the healthy control group at baseline and major depressive disorder (MDD) group pre- and post- 12-week exercise intervention. Means±SDs are presented.
Participants in the MDD group, with the exceptions of two, displayed increased VO2\text{max} by week 12 of exercise intervention. Figure 11 shows VO2\text{max} changes throughout the exercise period (at weeks 0, 8 and 12) per participant. Overall, there was a 6% increase in VO2\text{max} (n=9) from baseline to week 12.

**Figure 11:** Individual VO2\text{max} (ml/kg/min) measures in MDD patients throughout 12-weeks of aerobic exercise intervention.

VO2\text{max} was assessed at pre-intervention (Pre), Week 8 (W8) and post-intervention (Post – Week 12). Each line corresponds to a different MDD participant (n=10).
4.1.4 Exercise adherence and effort

Aerobic exercise adherence and effort for each MDD participant are presented in Table 3. Percentage of sessions attended for all MDD participants ranged from 69% to 100% with the mean sessions attended at 85%. The percentage of time spent below the target HR zone (X minutes/total minutes attended exercising), ranged from 12% to 32%. The percentage of time spent in their designated target HR zone (X minutes/total minutes attended exercising) ranged from 68-95%. The time spent in the target HR zone (expressed as a percentage) is a measure of “effort”. Exercise responders and non-responders (MDD group only) were classified based on a median-split of VO$_{2\text{max}}$ changes pre- to post-exercise intervention (n=9). This yielded a median of a 5% change in VO$_{2\text{max}}$ levels; four individuals had changes greater than 5% and were classified as responders and five individuals (with changes below 5%) were classified as non-responders.
Table 3: MDD participants’ exercise intervention adherence and effort in designated HR zone (expressed as percent), percent VO$_2$max change pre- to post-exercise intervention, exercise responders, and depression score response

<table>
<thead>
<tr>
<th>Participant</th>
<th>Sessions attended</th>
<th>Below target HR zone</th>
<th>In target HR zone</th>
<th>Change VO$_2$max</th>
<th>Exercise Responder</th>
<th>% Change HAMDI$_{17}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>69.4</td>
<td>12.2</td>
<td>87.8</td>
<td>2.71</td>
<td>No</td>
<td>-75</td>
</tr>
<tr>
<td>2</td>
<td>86.1</td>
<td>26.02</td>
<td>73.98</td>
<td>-6.73</td>
<td>No</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>83.3</td>
<td>22.46</td>
<td>77.54</td>
<td>7.89</td>
<td>Yes</td>
<td>-78</td>
</tr>
<tr>
<td>4</td>
<td>94.4</td>
<td>23.25</td>
<td>76.75</td>
<td>1.61</td>
<td>No</td>
<td>-31</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>18.07</td>
<td>81.93</td>
<td>15.94</td>
<td>Yes</td>
<td>-86</td>
</tr>
<tr>
<td>6</td>
<td>83.3</td>
<td>31.86</td>
<td>68.14</td>
<td>11.78</td>
<td>Yes</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>75</td>
<td>4.2</td>
<td>95.8</td>
<td>-1.99</td>
<td>No</td>
<td>-78</td>
</tr>
<tr>
<td>8</td>
<td>86.1</td>
<td>11.75</td>
<td>88.25</td>
<td>16.77</td>
<td>Yes</td>
<td>-47</td>
</tr>
<tr>
<td>9</td>
<td>83.3</td>
<td>17.49</td>
<td>82.51</td>
<td>4.93</td>
<td>No</td>
<td>-79</td>
</tr>
</tbody>
</table>

HR: Heart Rate; Exercise responder status based on a median-split of the VO$_2$max changes. HAMDI$_{17}$: Hamilton Depression Scale (17 item version)
The mean percentage of total possible sessions that participants exercised below their target HR zone was 66%, while the mean percentage of total possible sessions participants exercised in their target HR zone (for the 30 minute duration) was 34% (Figure 12). This was calculated on a binary approach of each participant either completing the expected exercise prescription when they attended (>30 minutes in HR zone) or not completing the expected exercise prescription (<30 minutes in HR zone, or they did not attend).

**Figure 12: Mean percent of exercise adherence (sessions attended), exercise effort (time below and in heart rate [HR] zone), expressed as a percent (%) of total sessions.** Means±SDs are presented.
Within the MDD group, in 34% of the total possible sessions attended, participants completed the desired exercise prescription of 30 minutes in their target HR zone. In 23% of the sessions attended, MDD participants exercised between 25-30 minutes, and 28% of the time, MDD participants exercised less than 25 minutes (Figure 13).

![Figure 13: Breakdown of mean percent session adherence exercising in appropriate heart rate (HR) zone when less than prescribed amount.](image)

Means±SDs are presented.
4.1.5 Depression measures

As expected, MDD participants had greater HAMD\textsubscript{17} at baseline relative to healthy controls (Table 4). After 12-weeks, no significant differences between the MDD and controls group were observed for HAMD\textsubscript{17} scores ($p = .06$). Within the MDD participants, significantly decreased HAMD\textsubscript{17} scores from pre- to post-exercise intervention were observed.

### Table 4: Mean Hamilton depression rating scale (HAMD\textsubscript{17}) scores for control and major depressive disorder (MDD) groups pre- and post- 12-weeks.

<table>
<thead>
<tr>
<th></th>
<th>HAMD\textsubscript{17} Scores</th>
<th></th>
<th>Within group $p$ value &amp; CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-</td>
<td>Post-</td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>1.4±1.7 (n=13)</td>
<td>2.3±2.6 (n=8)</td>
<td>0.573</td>
</tr>
<tr>
<td>MDD</td>
<td>14.1±3.7 (n=10)</td>
<td>7.4±6.9 (n=9)</td>
<td>0.010</td>
</tr>
<tr>
<td>Between Group $p$ value &amp; CI</td>
<td>$&lt;0.001$ [3.9, 9.9]</td>
<td>0.06 [2.0, 8.0]</td>
<td></td>
</tr>
</tbody>
</table>

HAMD\textsubscript{17}: Hamilton Depression Scale (17 item version); MDD: Major Depressive Disorder; means±SDs are presented; CI: 95% confidence interval
Based on a $\geq 50\%$ decrease in baseline HAMD$_{17}$ scores, 5 responders and 4 non-responders were identified post-exercise intervention (Tables 5).

**Table 5: Mean Hamilton depression rating scale (HAMD$_{17}$) scores in MDD responders and non-responders pre- and post- 12-weeks of exercise intervention, as well as change scores.**

<table>
<thead>
<tr>
<th>MDD Responder/Non-Responder Status</th>
<th>HAMD$_{17}$ Pre</th>
<th>HAMD$_{17}$ Post</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Responders (3M/2F)</td>
<td>11.6±2.5</td>
<td>2.4±0.5</td>
<td>-79.0±4.0</td>
</tr>
<tr>
<td>4 Non-responders (2M/2F)</td>
<td>15.5±1.9</td>
<td>13.8±5.5</td>
<td>-11.5±32.5</td>
</tr>
</tbody>
</table>

Responders/non-responders were categorized based on a $\geq 50\%$ decrease in HAMD scores.

HAMD$_{17}$: Hamilton Depression Scale (17 item version); MDD: Major Depressive Disorder; means±SDs are presented.

Individual HAMD$_{17}$ changes over the 12-week exercise intervention are presented in Figure 14. Most individuals, with the exception of two, who completed the exercise intervention, exhibited decreased HAMD$_{17}$ scores by week 12 relative to baseline.
Figure 14: Individual Hamilton depression rating scores ($\text{HAMD}_{17}$) in MDD patients throughout 12-weeks of an aerobic exercise intervention. Assessment time points include pre-intervention (week 0/W0), post-intervention (week 12/W12) and every 2 weeks in-between (W2, 4, 6, 8, and 10). Each line corresponds to a different MDD participant.
4.1.6 Hippocampal volume measures

Raters blinded to subject diagnosis carried out hippocampal measurements. Intra-class correlations (ICC), used to measure inter- and intra-rater reliability (a measure of the degree of agreement between raters and reliability over repeated tracing sessions by the same tracer, respectively) revealed an ICC of 0.93 for inter-rater reliability (n=9 different hippocampi traced by 2 raters) and 0.87 for intra-rater reliability (9 re-traced hippocampi by one person).

Left and right hippocampal measures were adjusted for whole brain volume. No significant differences between groups (MDD versus healthy controls) at baseline or week 12 were observed in hippocampal volumes (Table 6). Additionally, no differences existed in hippocampal volumes pre- to post-week 12 within groups and no group differences were noted in change scores (Table 7).

Table 6: Hippocampal volume (adjusted for whole brain volume) measures pre- and post-12-weeks in control and MDD groups

<table>
<thead>
<tr>
<th></th>
<th>Left HC</th>
<th></th>
<th>Right HC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Within group p value &amp; CI</td>
<td>Pre</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>1.80±0.20 (n=13)</td>
<td>1.77±0.21 (n=7)</td>
<td>0.768 [-0.13, 0.10]</td>
<td>1.88±0.24 (n=13)</td>
</tr>
<tr>
<td>MDD</td>
<td>1.84±0.17 (n=10)</td>
<td>1.79±0.23 (n=9)</td>
<td>0.581 [-0.14, 0.24]</td>
<td>1.86±0.17 (n=10)</td>
</tr>
<tr>
<td>Between Group p value &amp; CI</td>
<td>0.64 [1.73, 1.90]</td>
<td>0.84 [1.67, 1.90]</td>
<td>0.82 [1.78, 1.95]</td>
<td>0.52 [1.75, 2.0]</td>
</tr>
</tbody>
</table>

MDD: Major Depressive Disorder; HC: Hippocampus; means±SDs are presented; CI: 95% confidence interval
Table 7: Percent change in hippocampal volume (adjusted for whole brain volume) pre- to post-12-weeks in control and MDD groups

<table>
<thead>
<tr>
<th>HC volume change</th>
<th>Left</th>
<th>Right</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy controls</td>
<td>0.7±6.8</td>
<td>4.0±13.9</td>
</tr>
<tr>
<td></td>
<td>(n=7)</td>
<td>(n=7)</td>
</tr>
<tr>
<td>MDD</td>
<td>-0.3±12.6</td>
<td>1.0±10</td>
</tr>
<tr>
<td></td>
<td>(n=9)</td>
<td>(n=9)</td>
</tr>
<tr>
<td>Between Group p</td>
<td>0.61</td>
<td>0.53</td>
</tr>
<tr>
<td>value &amp; CI</td>
<td>[-6.46, 4.68]</td>
<td>[-5.36, 8.45]</td>
</tr>
</tbody>
</table>

MDD: Major Depressive Disorder; HC: Hippocampus; means±SDs are presented; CI: 95% confidence interval

4.1.7 NAA Concentrations

T-tests revealed no significant differences between control and MDD groups in NAA levels at pre- or post- 12-weeks (Table 8). Changes in left and right hippocampal NAA levels from pre- to post- 12-weeks (expressed as a percent) also revealed no significant difference between healthy control and MDD groups (Table 9).

Table 8: Mean hippocampal N-acetyl aspartate concentrations (NAA) in control and MDD groups at pre- and post-12-weeks.

<table>
<thead>
<tr>
<th>HC NAA concentration (mmol/kg wet weight)</th>
<th>Left HC</th>
<th>Right HC</th>
<th>Within group p value &amp; CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre</td>
<td>Post</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>8.3±1.2</td>
<td>8.1±0.8</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>(n=6)</td>
<td>(n=8)</td>
<td>[-0.84, 1.23]</td>
</tr>
<tr>
<td>MDD</td>
<td>8.4±1.2</td>
<td>8.4±1.5</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>(n=8)</td>
<td>(n=8)</td>
<td>[-1.14, 0.98]</td>
</tr>
<tr>
<td>Between Group p value &amp; CI</td>
<td>0.98</td>
<td>0.34</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>[7.85, 8.94]</td>
<td>[7.35, 8.86]</td>
<td>[7.77, 8.62]</td>
</tr>
</tbody>
</table>

NAA: N-acetyl-aspartate; MDD: Major Depressive Disorder; HC: Hippocampus; means±SDs are presented; CI: 95% confidence interval
Table 9: Percent change in hippocampal N-acetyl aspartate concentrations from pre- to post- 12-weeks in control and MDD groups

<table>
<thead>
<tr>
<th></th>
<th>Percent change in HC NAA levels</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Left</td>
<td>Right</td>
<td></td>
</tr>
<tr>
<td>Healthy controls</td>
<td>-2.1±11.8 (n=6)</td>
<td>5.5±15.5 (n=4)</td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>1.0±12.4 (n=6)</td>
<td>3.6±8.8 (n=6)</td>
<td></td>
</tr>
<tr>
<td>Between group p</td>
<td>0.66 [-7.95, 6.86]</td>
<td>0.81 [-3.64, 12.3]</td>
<td></td>
</tr>
</tbody>
</table>

NAA: N-acetyl-aspartate; MDD: Major Depressive Disorder; HC: Hippocampus; means±SDs are presented; CI: 95% confidence interval

4.1.8 Correlations

In order to assess our primary research questions, (Do VO$_2$max changes positively correlate with hippocampal volume and NAA concentration changes? Do hippocampal volume and NAA concentration changes correlate with HAMD$_{17}$ score changes?) and exploratory questions (Does aerobic exercise adherence correlate with HAMD$_{17}$ score changes? Does aerobic exercise adherence correlate with hippocampal volume and NAA concentration?) Spearman’s correlations were conducted (Table 10). Adherence was based on percent attendance and percent time spent in the target HR zone. No significant correlations were noted.
Table 10: Spearman’s correlations between VO\textsubscript{2}max, time in target HR zone, and HAMD\textsubscript{17} score changes (expressed as a percent from baseline to week 12) and changes in hippocampal volume and N-acetyl aspartate (NAA) levels.

<table>
<thead>
<tr>
<th></th>
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HC: hippocampus; NAA: N-acetyl-aspartate; HR: Heart Rate
Chapter Five: Discussion

5.1 Primary Findings

The primary purpose of this study was to test the effects of a 12-week aerobic exercise intervention and accompanying changes in cardiovascular fitness (measured by VO\(_2\)max) on neurobiological variables in the hippocampus (volume and NAA levels) and related depression severity (HAMDi7 scores) changes in young sedentary depressed adults. This was accomplished in the following ways: first, we examined if enhancing VO\(_2\)max with aerobic exercise would be associated with decreased HAMDi7 scores in young adults with MDD. Next, we examined if decreased HAMDi7 scores were associated with hippocampal volume and NAA concentration changes. Lastly, we examined if differences in these measures existed between MDD participants and matched controls. Overall, we found decreased HAMDi7 scores in MDD participants following the exercise intervention; a trend towards increased VO\(_2\)max scores was also observed. Although depression scores declined, this was not observed to be linked to increases in VO\(_2\)max changes or exercise compliance. No changes in either hippocampal volume or NAA concentration were observed pre- to post-exercise in the MDD group. Examining MDD participants in comparison to controls also revealed no significant differences in either hippocampal volume or NAA concentration. Large individual variability was noted in all aspects of this study and the relatively small sample size may have limited the findings, including the detection of hippocampal plasticity effects.

5.2 Statistical Analyses

Small sample sizes are associated with a greater risk of Type II errors, that outliers can have a disproportionate effect on the results, and the possibility that sampling bias plays a larger role in the outcome measures. In an attempt to avoid biasing statistical analyses, planned analysis
of outcomes was based on the intention-to-treat principle. Statistical analyses were therefore conducted based on assumptions that the sample size was sufficient to see statistically significant changes in outcome variables. Although, strictly speaking, not all the assumptions were met for parametric statistical testing, t-tests were used to compare groups (MDD vs. controls) while rmANOVAs were used to assess pre- to post- measures. Within-subject assessments (e.g., longitudinal assessments) are generally more robust statistical approaches because changes can be assessed in the same person and minimize variability. This can be viewed as a strength of this study.

Confidence intervals (CI) were important to include because our sample population was small (thus, caution should be exercised when interpreting all outcomes of this study). CIs provided a measure of the spread of our estimates of the parameters of interest. The inclusion of CIs allows those interested in translating and applying our findings to young adult MDD populations to better understand variability in the measures of interest in a larger sample. CIs allow us to better assess our outcome measures (HAMD$\text{17}$, VO$_{\text{2max}}$, hippocampal volume and NAA concentration) and how they may have contributed to our mainly null findings. As such, the results presented in this thesis do not necessarily provide evidence that aerobic exercise has no impact on our measures of interest; instead, it may be failing to provide evidence that exercise is the reason for change. This leads us to question what other variables may be important.

5.3 Participant demographics and recruitment

Although recruitment was widespread across Calgary for a period of 1.5 years, our sample size was relatively small. Generally, depression is associated with a lack of motivation. As such, recruiting depressed participants for this exercise intervention was an onerous task. The
stigma of mental illness is a potential cause for reluctance to seek help for mental problems (Schomerus, Matschinger, & Angermeyer, 2009), and could have contributed to some of the challenges associated with participant recruitment for this study. In addition, part of the challenge with clinical research and a longitudinal, intervention-based study includes the risk of participants not attending sessions and dropping out of the study. All MDD participants that met recruitment criteria and started the exercise intervention did, however, complete the 12-week aerobic exercise intervention. Complete datasets (including all measures of interest) were not available for some participants. Methodological issues (i.e. scanner and data transfer problems) and inability to follow up with participants (i.e. no longer interested in the study or unable to contact, in the case of a handful of controls) contributed to missing data.

A strength of this study is that young adult MDD patients were our target population. Studying this population eliminated some potential confounding factors such as increased burden of disease in an older population and long medication/intervention history. Additionally, it allowed the recruitment of some participants who were experiencing their first depression episode. Exercise intervention at this stage in life, in particular, could yield other health benefits and lead to healthy lifestyle changes in a population at greatest risk for encountering depression again later in life. Adolescents with sub-clinical levels of depression symptoms show higher rates of early-adulthood depression, substance misuse and adverse psychological and social functioning (Aalto-Setala, Marttunen, Tuulio-Henriksson, Poikolainen, & Lonnqvist, 2002). Furthermore, reductions in hippocampal volume may not precede illness onset, but decreased hippocampal volume has been proposed to occur at the greatest rate in the early years after illness onset (MacQueen et al., 2003). Studying this young cohort provided an opportunity to potentially mitigate some of the negative outcomes for our subjects, while at the same time
studying the neurobiological changes that may be associated with the neural advantages of exercise. Furthermore, this study adds to the existing literature, which is limited in younger population with MDD.

Selection bias is inherent in this type of study. Our sample consisted of volunteers who responded to study advertisement and consisted largely of university students. Presumably, the patients in our study believed exercise to be a credible treatment for depression, were favourably inclined to participate, and available to commit to a time intensive intervention. It is likely that exercise-mediated amelioration of depression symptoms may be explained by synergistically acting psychological and physiological mechanisms. This may include existing theories of depression such as the distraction hypothesis (Craft, 2005), which suggests that physical activity serves as a distraction from worries and depressing thoughts. Exercise has also been proposed to be linked with enhanced self-efficacy, the belief that one possesses the necessary skills to complete a task as well as the confidence that the task can actually be completed with the desired outcome obtained (Craft, 2005).

5.4 Outcome measures

5.4.1 Maximal aerobic capacity (VO₂max scores) and exercise compliance

A key component of this study was that the 12-week aerobic exercise intervention used was specifically designed to improve maximal aerobic capacity (VO₂max). Our VO₂max analysis showed a trend towards an increase in scores post- versus pre-exercise intervention in the MDD cohort (Figure 5). Studies with larger cohorts have shown increases in VO₂max with a 12-week aerobic exercise program (Krogh et al., 2014; Pajonk et al., 2014); therefore, with an increased sample size, we would presumably also see a significant change. When compared to both continuous moderate- and continuous vigorous-intensity exercise, near-maximal-intensity
exercise has been found to produce a significant improvement in VO$_2$\text{max} (Gormley et al., 2008). A possible reason why we did not observe larger VO$_2$\text{max} changes in MDD participants may be because only an average of 34% of the total sessions were completed exactly as prescribed - exercising a minimum of 30 minutes in the designated target HRR zone. If MDD participants completed anything less than 30 minutes, this fell short of the aerobic cut off. Furthermore, it is important to recognize that the exercise intensity in our study increased after the first 6 weeks in an attempt to continue to elicit VO$_2$ changes. Overall, it appears the exercise intervention was too challenging for participants to maintain during the prescribed 30 minute time duration.

Most exercise studies examining changes in depression scores based on an exercise intervention fail to provide a comprehensive breakdown of exactly how the intervention was conducted or details as to how adherence was assessed and evaluated. This is a significant limitation in the literature to date, not only because it makes study replication difficult, but also because analyses following the exercise intervention presume that the outcome measures are based on adherence to the prescribed exercise program (which may not be the case). In this study, we quantified the exercise intensity of each participant through HR monitoring to ensure they were in their target HR zone for the prescribed duration (Figure 7). Because only 34% of the total sessions were completed exactly as prescribed, the percentage of sessions where participants did not spend 30 minutes exactly in their HR zone was important to quantify (Figure 8). For future studies, instructing participants to exercise for 45 minutes may allow collection of 30 minutes in the prescribed HR zone. Few studies have quantified the “dose” of exercise and the decrease/remission of depression symptoms.
Other exercise intervention studies do not report exact adherence to the protocol, but merely indicate if participants completed 75% of the sessions (e.g., attendance). When participants in this study did attend their exercise sessions, they spent 68-95% of the time in their designated target HR zone (see Table 3). All MDD participants who were enrolled in our exercise program completed it (attendance range 69-100%). No data was lost due to dropout, indicating that the program was an effective way for getting depressed young people to exercise. Dropout may have been mitigated due to precautions taken during enrollment, which ensured that participants were aware of the time commitment prior to participating. Tailoring the exercise program so that it was based on participants’ timetable may have also helped maintain adherence. Finally, having each session supervised and the HR monitor accessible to the participants likely also contributed to adherence.

A comparable study by Déry et al, examined a cohort of young adults (non-depressed, sedentary, but otherwise healthy individuals - 4 males, 8 females; mean age = 21.83) who participated in an exercise intervention (Dery et al., 2013). Their intervention involved high-intensity interval training (HIIT) at levels near maximal-intensity for six weeks. Their study participants also varied widely in their response to the intervention, ranging from no change to 29% improvement in VO$_2$ scores. Our submaximal VO$_2$ scores ranged from a decrease in VO$_2$ max (-7%) to an increase of 17%. Déry et al also observed increased performance on their visual pattern separation task, a task that recruits the hippocampus. Incorporating a functional task, which may be more sensitive to hippocampal brain changes (as opposed to hippocampal volumetric and NAA concentration changes) may be worthwhile in future research. Functional neuroimaging during a hippocampus-dependent task has, in fact, been carried out in this cohort pre- and post-intervention, but is beyond the scope of this thesis and will not be discussed.
A submaximal VO$_2$ assessment (i.e. an indirect assessment of VO$_2$ levels), such as was done in this study, is based on certain assumptions. The primary assumption is that both HR and VO$_2$ increase linearly with increasing workload. If HR and VO$_2$ are not actually linear, over- or under-prediction errors can occur. If participants in this study were overly anxious, which can cause HR fluctuations this could have contributed to over- or under-estimations of VO$_2$ max (Figure 6). Given that MDD with a comorbidity of anxiety is significantly associated with HR variability (Chang et al., 2013), this may have been an issue in the current study. A submaximal VO$_2$ test therefore may not be as reliable as directly measuring the exchange of O$_2$ and CO$_2$ gas while the participant is on a treadmill or stationary bike.

The question as to whether aerobic exercise was the reason for decreased depression scores and neuroplastic changes in the brains of young adults will need to be settled with further studies. Future comparable studies should include control trials, where participants with MDD do not undergo the aerobic exercise intervention. Additional longitudinal studies, where patients are tracked over the course of the disease and where follow-up after an exercise intervention is conducted are also needed. This will help us continue to understand knowledge gaps pertaining to the MDD course of illness and how exercise might be involved in mitigating some negative symptoms and changing neurobiology of the human brain. Pajonk et al conducted a study where MDD participants were in both the control and in the exercise intervention group (Pajonk et al., 2010). Depression symptoms in this study ameliorated in spite of no statistically significant changes in VO$_2$ max. This suggests that VO$_2$ max may not be the best method for assessing fitness improvements and that other factors (e.g., endorphin release, lactate concentration, increased blood flow) may also have played a role in antidepressant effects.
5.4.2 Depression scores

Depression scores, as measured by the HAMD$_{17}$, improved in our MDD participants post-exercise. While this change may be due to neurobiological effects of the aerobic exercise that we were simply unable to detect (and/or did not measure), other factors may have also contributed to this antidepressant effect. The mere act of coming in for the exercise intervention may have caused changes in HAMD$_{17}$ scores via the Hawthorne (or observer) effect. This refers to a phenomenon whereby participants improve or alter an aspect of their behavior in response to an environment change, rather than in response to the nature of the change itself (McCarney et al., 2007). Furthermore, as MDD is an episodic condition subjects may have improved regardless of the exercise intervention. Treatment approaches, including both pharmacological and non-pharmacological, commonly take 4-8 weeks to become effective (Patten, 2001). According to the Canadian National Population Health Survey, the number of weeks men and women 18-24 years of age reported being depressed in the past 52 weeks was a mean duration of 6 weeks (Patten, 2001). This implies that the average MDD episode may potentially resolve during a 3-month intervention, such as the one conducted in this study. Additionally, because depression can be seasonal, it is important to note that recruitment was conducted on a rolling basis and participants started the intervention at different times throughout a nearly two-year span. As most participants were students, external stressors such as exams could have contributed to depression scores. This was observed in one healthy control that attributed higher HAMD$_{17}$ scores to exam stress. MDD participants had regular clinical assessments, were seen by a psychiatrist, and interacted with the designated exercise team regularly. All of these interactions could also have contributed to improvement.
A next step may be to evaluate if MDD participants who were considered exercise responders (those with higher VO$_2$max changes) were most likely to show HAMD$_{17}$ changes. Because of the small sample size we did not have the power to answer this question. Contrary to our hypothesis, greater adherence was not significantly associated with lower depression scores. This is consistent with the work of Dunn et al. who recruited 80 adults with MDD and divided them into various exercise intensity categories (Dunn et al., 2005). They did not see a significant correlation between decreased HAMD$_{17}$ scores and adherence, despite significant HAMD$_{17}$ improvement after the exercise intervention. In the current study, cardiorespiratory fitness (i.e., VO$_2$max) was likewise not associated with reductions in depressive symptoms.

5.4.3 Hippocampal volume

A meta-analysis indicated that aggregate hippocampal volumes were lower in patients with MDD compared to age- and sex-matched controls (McKinnon et al., 2009). This same meta-analysis, however, also found that the difference between patients and controls was most apparent in those with a recurrent or chronic form of the illness (>2 years duration or more than 1 illness episode). Differences in hippocampal volume were detectable in children, middle-aged and older adults with MDD, but not in young adults. Thus, during late adolescence and early adulthood, differences in hippocampal volume may be less robust, or absent compared to healthy controls. Contrary to our hypothesis, and yet consistent with the results of the meta-analysis, there were no observable differences in hippocampal volumes between MDD and healthy control young adults assessed in this thesis work (Table 4). It is possible that submaximal VO$_2$ measurements and neurobiological measurements lack the sensitivity to detect correlations among the variables of interest. Furthermore, these non-significant correlations may indicate a potential lag between mood changes and changes in the neurobiology of the brain. Illness
duration and number of episodes are important factors to consider when analysing hippocampal volume, and may be contributing factors as to why no differences in this outcome measure were seen in this cohort. Studies have indicated that antidepressant medication use may protect against hippocampal volume loss (Sheline et al., 2003). This may perhaps be a contributing factor as to why no differences were seen between MDD participants and controls in this cohort as five MDD patients had previously tried medication.

Pereira et al. suggested that exercise in humans selectively targets the dentate gyrus of the hippocampus (Pereira et al., 2007). This is likely because neurogenesis is known to occur when neural progenitor cells in the subgranular zone, located in the dentate gyrus, undergo mitosis. Future analyses may warrant subdividing the hippocampus into the head, body, and tail in order to see if these subregions reveal volumetric differences. Smaller hippocampal volume has been observed to be most prominent in the posterior hippocampus in medication-free, remitted subjects with recurrent MDD (Neumeister, 2005). The dentate gyrus however is located mainly in the body of the hippocampus.

Neurogenesis may be one explanation accounting for changes in hippocampal volume - synaptogenesis or synaptic restructuring may be another. Exercise also seems to benefit glial cells, both astrocytes (Li et al., 2005) and oligodendrocytes (Krityakiarana et al., 2010). Astrocytes help provide brain structure and provide vascular support, while oligodendrocytes help support synaptic transmission and ensheathe neural fibers with myelin. The neural benefits associated with exercise may be driven in part by increased blood flow to the brain. In people, exercise has been shown to alter brain vasculature by stimulating the growth of new capillaries from pre-existing brain vessels and improving resting cerebral blood flow (Ainslie et al., 2008). This, in turn, enhances brain oxygen delivery and neural metabolic activity. Increased levels of
physical fitness have also been associated with greater cerebrovascular reserve and improved cognitive function (Brown et al., 2010).

It is important to recognize that other training tasks, apart from exercise, can also influence hippocampal volume. A series of famous studies by Maguire et al. on London taxi drivers documented changes in hippocampal structure associated with acquiring the knowledge of London’s layout (Maguire, Frackowiak, & Frith, 1997; Maguire, Gadian, Johnsrude et al., 2000; Woollett & Maguire 2011). Taxi drivers are generally relatively sedentary, yet volumetric differences (typically increases) were observed in the hippocampus with spatial training. Furthermore, preclinical studies have demonstrated that exposure to an enriched environment elicits positive hippocampal changes, including increased numbers of dendritic branches and spines, enlargement of synapses as well as increased increased glial numbers (Rosenzweig & Bennett, 1996; Brown et al., 2003). More hippocampal neurons are also observed in adult mice living in enriched environments (Kempermann, Kuhn, & Gage, 1997). Therefore, environmental enrichment alone may elicit hippocampal changes.

High field-strength scanners (3T and 7T) are becoming more common and accessible to researchers and recent studies using higher field strength scanners have indeed shown subregion-specific changes in the human hippocampus, such as in the tail (Ho, Hooker, Sahay, Holt, & Roffman, 2013). Currently, in vivo imaging does not enable cellular resolution and may not be sensitive enough to reveal microscopic hippocampal changes. Although this study used a 3T scanner and we did not find differences in hippocampal volume between groups or over time, other studies using 1.5T scanners have found hippocampal differences (Frodl et al., 2008). It is important to recognize that although increased field strength can provide better resolution, it is
more susceptible to motion artefacts which could negate the positive contributions of increased field strength.

Significant inter-individual variability in hippocampal volume has been observed in healthy young adults (Lupien et al., 2007). This has been proposed to arise from both genetic (e.g., BDNF Val^66^ Allele (Bueller et al., 2006) and experiential/environmental factors (e.g., enriched environment, nutritional factors, stressful situations) (Lupien et al., 2007) – though this is mainly based on animal work. Furthermore, inter-subject variability in hippocampal volume was more pronounced in young compared to older adults (Lupien et al., 2007). Since previous studies evaluating the effect of exercise on hippocampal volume have predominantly been conducted in middle-aged and older adults, this may explain why significant hippocampal differences were noted in older adults with MDD and matched controls. What other studies have observed to be smaller hippocampal volume in MDD participants when compared to controls may merely be the results of pre-determined inter-individual differences (Lupien et al., 2007). Smaller hippocampal volume may be what makes individuals more susceptible to mental disorders, such as depression, (Lupien et al., 2007) as opposed to depression being the reason for changes in hippocampal volume.

Methodological issues may also contribute to variability in reports of hippocampal volume in the context of mental illness. The delineation of hippocampal boundaries from adjacent regions varies substantially among studies (Ho et al., 2013) making it challenging to directly compare hippocampal values among them. Furthermore, some studies correct for whole brain volume while others do not, further complicating the direct comparison between studies.
### 5.4.4 NAA concentration

Similar to the null hippocampus volume results, and contrary to our hypothesis, no differences were observed in NAA concentration at baseline between controls and MDD participants or after exercise intervention in MDD participants. This non-significance could in part be explained by the small sample sizes (see section 5.2 Statistical Analysis). Due to technical challenges, NAA values were unavailable for 11 hippocampus recordings accounting for a smaller sample size than other outcome variables (Table 6). However, Pajonk et al noted an increase pre- to post-exercise intervention in hippocampal NAA levels in a sample size of only 8 patients with schizophrenia (Pajonk et al., 2010). Comparing our results with those of Milne et al. who evaluated NAA concentration in first-episode MDD patients (n=14) as well as multiple-episode patients (n=14) in mainly middle-aged adults (mean age = 47.3), NAA concentrations in our MDD cohort were slightly higher than they reported (Milne, MacQueen, Yucel, Soreni, & Hall, 2009). Higher NAA concentrations in our healthy control cohort versus their control group were also noted. These differences may be explained by differences in MRS hippocampal voxel placement. In the current study, much of the hippocampal tail was included whereas in Milne et al. less of it appears to have been included and greater hippocampal surrounding regions appeared to have been incorporated (Milne et al., 2009).

### 5.5 Limitations

As mentioned in other sections (5.2 and 5.3), there are some study limitations that should be acknowledged. A primary limitation is the small sample size, which limited statistical power and the appropriateness of certain statistical approaches. Additional limitations include the potential self-selection bias of healthier and more active individuals recruited for this study, who were interested in an exercise program and believed that exercise would be a positive
intervention for their depression. The current study was also limited by the lack of a control
groups for comparison purposes. Furthermore, adherence to the exercise protocol (as described
in section 5.4.1) may have impacted the outcome measures, as the prescribed “exercise dose”
was generally not achieved. Moreover, the length of the exercise intervention (12-weeks) may
not have been long enough to illicit structural and chemical hippocampal changes even though
mood changes were observed.

5.6 Future directions

Future research might consider a number of changes based upon findings from the
present study. First and foremost, adding control groups (i.e., non-depressed individuals as well
as depressed individuals not engaged in exercise) would provide a basis of comparison for
evaluating whether enhanced mood in MDD participants was indeed from changes in increased
aerobic fitness rather than merely from other aspects of the study. For example, this may include
an MDD group who completed 12-weeks of an intervention where sessions were not designed to
elicit changes in aerobic fitness (e.g., stretching classes). Furthermore, a healthy control group
who engaged in the 12-weeks of aerobic exercise training would allow us to assess whether
neuroplastic changes are more pronounced within the context of depression. In comparable
future research, investigators should include follow-up questionnaires a few weeks post
intervention. This may allow examination of various exercise maintenance strategies that could
provide insight on health behavior changes and maintenance of exercise regimes for individuals
suffering from MDD.

Other brain regions (e.g., prefrontal cortex, amygdala) may also warrant investigation as
they may also exhibit observable changes with exercise intervention. Using a brain region other
than the hippocampus as a control area to further investigate changes in NAA concentration may
also be warranted.

Other factors that may have influenced our results and should be considered carefully in future work include modulations in neurotrophines such as BDNF, VEGF, and IGF-1. Further research should evaluate changes in these chemicals in order to better understand the underlying mechanisms that may be involved in volumetric changes in the hippocampus. Furthermore, genetic tests may also be warranted to better evaluate how specific genetic variants (e.g., TrkB receptors) may also influence treatment and exercise outcomes. Furthermore, as the hippocampus is involved in cognition and memory, evaluating neurocognitive tests that recruit the hippocampus may also prove interesting. Future studies may also choose to include a nutrition component in order to try and control for confounding factors in this domain, which may affect outcome variables of interest.

5.7 Conclusions and implications

Overall, depression scores as measured by the HAMD_{17} decreased, while VO_{2max} measures showed an increased trend following the exercise intervention. Accumulating animal evidence indicates that exercise plays a role in hippocampal plasticity. Contrary to our hypotheses, we found no differences following exercise intervention in hippocampal neurobiological measures (volume and NAA). However, results from this study should not be interpreted as evidence that aerobic exercise has no effect on neurobiological measures, as our power to detect statistical differences was limited. Nevertheless, understanding brain neuroplasticity in young adults with MDD is an important component of understanding the substrates upon which treatments may work. Characterizing neurobiological profiles in MDD are important to better understand the disorder and target interventions.
MDD treatment options are limited and, from a clinical perspective, aerobic exercise may represent an attractive alternative to pharmacotherapy for treating young adults with MDD. Failure to intervene in early and less severe MDD episodes can leave individuals susceptible to recurrent and more severe depression episodes later in life (Patten et al., 2012). The advantages of an aerobic exercise regime are well known. In addition to exercise potentially limiting depression reoccurrence, its inclusion in standard care – particularly with respect to mental illness - can also be used to decrease the overall burden on the healthcare system.
Chapter Six: References


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Sapolsky, R. M. (2001). Depression, antidepressants, and the shrinking hippocampus.

*Proceedings of the National Academy of Sciences of the United States of America, 98*(22), 12320-12322.


Currently suffering from depression or suspect that you may be depressed?

You may be eligible to participate in a research study on the possible beneficial effects of 12 weeks of exercise training on mood, brain structure & function in depression.

Eligible Participants:

- Females & males 18-24 yrs old
- Physically healthy
- Suffering from suspected/diagnosed depression
- Not currently taking antidepressant or undergoing treatment
- Not suffering from other psychiatric illness

In addition to aiding in understanding depression, potential benefits include:

- Comprehensive psychiatric evaluation
- 12 weeks of exercise training (3x/week) under care of fitness experts & researchers
- Compensation for time & effort

For further information, please contact:

brain.neuroboost@gmail.com

This study has been approved by the Conjoint Health Research Ethics Board (Ethics ID# 24612)
Interested in getting an MRI and assisting with Mental Health research?

You may be eligible to participate in a research study evaluating the effects of fitness on mood, brain structure & function in depression.

Eligible Participants:

- Females & males 18-24 yrs old
- Physically healthy
- Not exercising regularly (more than 3X/week of vigorous/challenging aerobic/cardiac activity)
- No history of depression in a 1st degree relatives (mom/dad/siblings)
- Not currently taking antidepressant or undergoing treatment
- Not suffering from other psychiatric illness

In addition to aiding in understanding depression, potential benefits include:

- Comprehensive psychiatric evaluation
- Compensation for time & effort
- Exposure to research facilities at both Foothills Hospital and Alberta Children’s Hospital

For further information, please contact:

brain.neuroboost@gmail.com

This study has been approved by the Conjoint Health Research Ethics Board (Ethics ID# 24612)
APPENDIX B: PRELIMINARY EMAIL COMMUNICATION

To:__________________

From: brain.neuroboost@gmail.com

Hi ______,

My name is Allegra. I'm a University of Calgary student working in conjunction with researchers at the Alberta Children’s Hospital and Mathison Centre for Mental Health Research & Education (Foothills Hospital).

Thanks for your interest in assisting with this study! Here is some additional information.

We are trying to understand the effects of exercise on the brain in individuals with depression. Exercise has been shown to promote brain health and to alleviate symptoms of depression. We are trying to recruit controls and participants who may fit our criteria for participation in this research study.

For PATIENTS:

We are looking for individuals with depression (or suspected depression) to participate in this study. Participants should be: 18-22 years of age, not exercising regularly (i.e., more than 3X/week of vigorous/challenging aerobic/cardiac activity), not claustrophobic and not currently taking antidepressants or engaged in formal psychotherapy.

Participation would require a 3-month commitment during which time you would be participating in aerobic (i.e., cardio) intervention (3X/week ~1hr/session) - this would occur at an exercise facility (Kinetix Center) at the Foothills Hospital under the supervision of exercise physiologists and fitness specialists/trainers. We would try to organize the exercise sessions at times that would be most convenient for you. Additionally, before the exercise intervention, you would need to come in for a psychiatric/mood assessment, complete some simple cognitive tasks as well as provide blood (if you are comfortable with that). All of this would occur at the Foothills Hospital (~2-2.5 hr). You would also need to come in for a brain scan (called an MRI), which would occur on a different day at the Alberta Children's Hospital (not far from the Foothills Hospital: ~1.5 hr). You would also be required to meet with our study psychiatrist for a short clinical evaluation. You would be compensated for the initial assessments but not for the exercise intervention. After the 3-month exercise intervention, we would do the same assessments as at the beginning (psychiatric, cognitive and brain imaging) - you will again be compensated for these.
For CONTROLS:

We are looking for healthy controls (no physical or psychiatric conditions) who are: 18-24 years of age, not exercising regularly (more than 3X/week of vigorous/challenging aerobic/cardiac activity), not claustrophobic and have no history of depression in a 1st degree relatives (mom/dad/siblings).

Participation would include coming in for a psychiatric evaluation, completing simple cognitive tasks as well a a blood draw (~2-2.5 hr). On a second session you would be involved in a 1.5 hr neuroimaging session. This entire process wold be repeated 12 weeks later. You will be compensated for your time. Your information would be compared with information gathered from depressed individuals before and after they complete an intense exercise intervention program.

If you are interested and think you fit the criteria, we would like to organize a phone conversation with you. This will take ~20 min and we would ask you a series of questions to determine if you are indeed eligibility for (and still interested in) the study, explain the study in further detail and answer any questions you may have. All of your information would be kept confidential.

Please let us know what number I can reach you at and an assortment of times that may work best for me to call you.

Your interest and involvement is of great importance to us and you would be greatly helping advance our understanding in this area. We are working with state of the art equipment, facilities, and faculty and are keen to have you onboard.

Looking forward to hearing from you.

Cheers,

Allegra Courtright

Study Supervisor:

Frank MacMaster
Cuthbertson and Fischer Chair in Paediatric Mental Health
Departments of Psychiatry and Paediatrics, University of Calgary
Behavioural Research Unit, Alberta Children's Hospital
2888 Shaganappi Trail NW, Calgary AB T3B 6A8

twitter.com/FrankMacMaster
facebook.com/RethinkChildMentalHealth
APPENDIX C: PATIENTS PHONE SCREENING SCRIPT

Name: ______________________________ Sex: M or F (circle) Age: ____________

Employment: ______________________________ Highest Level of Education:_________________________

Telephone: (h) ___________ (c) ___________ E-mail:_________________________________

Hello (INSERT INDIVIDUAL’S NAME)
My name is (FIRST NAME) and I am a(n) (POSITION) at the University of Calgary, Department of Psychiatry. I am calling with regard to the depression study that you had expressed interest in. **OR** Thank you for calling us to find out more about our research regarding depression.

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine if mood and brain function and structure change after exercise training in young adults with depression symptoms. We also want to measure if specific biological markers can help us to predict who is the most likely to have positive mood effects from exercise training.

This study involves several components. First, you would come in for an in-person screen, complete some questionnaires and simple cognitive tasks. Afterward, should you still qualify and want to participate, you would be scheduled to come in for an MRI scan during which time you would complete a simple memory task. If you are comfortable with it, we would also collect a blood sample. After these tests you will have a follow-up with Dr. MacQueen - an investigator and psychiatrist involved in this study.

After completing this, you would be enrolled in an exercise training program. This would involve about an hour-long exercise session, three times a week for 12 weeks under the supervision of fitness experts at the Faculty of Kinesiology. During this exercise training, we would occasionally re-assess your psychiatric state and mood. After completing training, we would ask you to come in for a re-assessment. You would again complete the cognitive tasks and undergo a second brain scan and blood collection.

Are you still interested in participating in this study and continuing with the phone screen?

[IF NO]: Thank you very much for your interest.
- Would you like us to keep your name on file to contact you regarding any other studies in the Department of Psychiatry? YES NO

-Is this a good time to do the phone screen – it should take ~20 min.?
[IF NO]: Set up a time to call back: Date: ______________________ Time: ______________________

Before bringing you in for an in-person screen, we need to ask you a few questions to determine if you are eligible for the study. This information is personal in nature so if any questions make you feel uncomfortable, please let me know. You can choose not to answer any questions. The information that I receive from you today will be destroyed if you do not qualify for the study or choose not to participate. Is it alright if I proceed?

[IF NO]: Thank you very much for your time.
- Would you like us to keep your name on file to contact you regarding any other in the Department of Psychiatry? YES NO

1. DEMOGRAPHICS/PHYSICAL HEALTH

I am now going to ask you some questions on your physical and mental health and other general information.

- What is your current age (must be 18-24 for inclusion – preferably 18-22)? Employment status? Highest education level completed? (Fill out on 1st page)
*If they just turned 25 (within 1-2 months), continue with screen. If older, thank them for their time and interest, but inform them that they do not meet the strict criteria for inclusion in the current study.

**If older than 25**: INELIGIBLE Would you like us to keep your name on file to contact you about other studies in the Department of Psychiatry? YES NO

*IF YES to questions below: INELIGIBLE.* If not sure, ask Dr. MacQueen. Inform participant that you will call them back regarding whether they qualify for the study OR (if ineligible) thank them for their time/interest, but inform them that they do not meet the strict criteria for inclusion in the current study.

1. Has your doctor ever said that you have a heart condition or high blood pressure?
   YES NO [IF YES]: INELIGIBLE

2. Has your doctor ever said that you should only do medically supervised physical activity?
   YES NO [IF YES]: INELIGIBLE

3. Do you feel chest pain at rest, during your daily activities, OR when you do physical activity?
   YES NO [IF YES]: INELIGIBLE Heavy breathing with physical activity should not be confused with chest pain.

4. Do you lose balance because of dizziness or have you suddenly lost consciousness in the last 12 months?
   YES NO [IF YES]: INELIGIBLE ELIGIBLE If dizziness was associated with over-breathing (e.g., during vigorous exercise)

5. Have you ever had a concussion?
   YES NO [IF YES]: INELIGIBLE If unconscious for >10 min_______________________________________

6. Have you been diagnosed with or are currently treated for serious major medical problem/s? Do you have any chronic medical conditions or disabilities?
   YES NO [IF YES]: INELIGIBLE cardiac problems, asthma, physical disability (preventing exercise training)

7. Are you currently taking medications regularly for chronic health problems? e.g. blood pressure, cholesterol, thyroid, diabetes
   YES NO [IF YES]: INELIGIBLE (depending on medications) What medications are you taking?__________________________ ELIGIBLE contraception, occasional use of sedatives, inhalers for allergies/asthma

8. Are you involved in varsity athletics, or engage in strenuous exercise 3 or more X/week? e.g. running, strength training, soccer, swimming (if 1X/week – OK or if mild-moderate exercise max. 3X/week or a combo of the two, e.g. 1X strenuous, 1-2X mild per week).
   YES NO [IF YES]: INELIGIBLE This study is looking at changes associated with aerobic exercise; these changes are not likely to be seen in people that already exercise regularly.

9. Do you have a bone or joint problem that could be made worse by becoming more physically active?
   YES NO ELIGIBLE If past bone/joint problems, which do not limit current ability to be physically active

10. Do you have neurological or neuromuscular problems? e.g. seizures, brain cysts/tumors/surgery, MS, ALS
    YES NO [IF YES]: INELIGIBLE Anything preventing participation in exercise or brain pathology.

11. Have you ever been diagnosed with developmental problems/learning disabilities? e.g. autism, Asperger’s, mental retardation (word choice), dyslexia
    YES NO [IF YES]: INELIGIBLE Anything preventing carrying out tasks; dyslexia, to the extent that reading is very impaired.

12. Can you tell me your approximate height and weight? Ht _____ Wt ______
    Metric Units: BMI = Weight (kg) / (Height (m))²: ______
    English Units: BMI = Weight (lb) / (Height (in))² x 703: ______ (1 foot = 12 inches) [IF BMI >35]: INELIGIBLE
2. MRI COMPATIBILITY

These next questions are to determine if you can participate in the MRI/brain scanning component of the study:

1. Have you ever had an MRI scan before?
   YES  NO  [IF YES] What was it for? ______________________________________________

2. Are you claustrophobic? Feel very uncomfortable/anxious/panicky in enclosed spaces?
   YES  NO  [IF YES]: INELIGIBLE (depending on severity)________________________________________

3. Are you right handed, left handed, or do you use both? _____________________________

4. Do you have any metal in your body? e.g. pacemakers, surgical/aneurysm clips, implanted metal plates, screws or pins, ear implants, braces on your teeth other metal objects?
   YES  NO  [IF YES]: ELIGIBLE Most surgically implanted things are titanium (MRI-safe); small braces/retainers are usually OK – check with MRI Center.

5. As far as you know, is there a chance that you may be pregnant (females)?
   YES  NO  [IF YES]: ELIGIBLE

3. PSYCHIATRIC ASSESSMENT – GENERAL

I am now going to ask you some questions regarding your emotional/mental wellbeing.

1. Have you ever had a problem with alcohol or drug abuse or dependence?
   YES  NO  [IF YES] Current? _____________________________________________________________
   INELIGIBLE if currently (last 6 months) abusing or dependent on alcohol or illicit drugs.
   ELIGIBLE if more than 6 months ago, occasional alcohol/drug use.

2. Have you ever suffered from, or been diagnosed with, any psychiatric or emotional problems?
   YES  NO  [IF YES] Which? _________________________________________________________________
   INELIGIBLE if bipolar disorder, sz, eating disorder, currently abusing/dependent on alcohol or illicit drugs.
   ELIGIBLE If depression, anxiety disorders & alcohol/drug abuse if over 6 months ago.

   [IF YES] ask:
   3. When were you diagnosed? ___________________________________________________________________

4. Have you taken/are you taking medication for (the disorder)?
   YES  NO  [IF YES] What? When? _____________________________________________________________
   INELIGIBLE if currently taking psychoactive meds.

5. Have you received treatment/therapy for psychiatric or for emotional problems?
   YES  NO  [IF YES] What? When? _____________________________________________________________
   INELIGIBLE if currently in psychotherapy. Past therapy/psychological visits OK

4. DEPRESSION

- Was there a time in your life when, for 2 weeks or more, everyday, most of the day you felt depressed, sad, unhappy, or it was hard for you to cheer up?  YES  NO

- Was there a time in your life when, for 2 weeks or more, you lost interest in things or were unable to enjoy most things that you used to enjoy?  YES  NO

Are you currently experiencing thoughts/feelings of depression?  YES  NO
[IF YES] How long have you been experiencing these thoughts/feelings this time?______________
[IF YES] How many episodes like this have you had in your lifetime (best guess)?______________
I will now ask you a series of questions related to depression. Please remember that you can choose not to answer any of the questions. Of the following statements, choose the one which best suits you:

1. **Sadness:**
   0 I do not feel sad.
   1 I feel sad much of the time.
   2 I feel sad all the time.
   3 I am so sad or unhappy that I can’t stand it.

2. **Pessimism:**
   0 I am not discouraged about my future.
   1 I feel more discouraged about my future than I used to be.
   2 I do not expect things to work out for me.
   3 I feel my future is hopeless and will only get worse.

3. **Past Failure:**
   0 I do not feel like a failure.
   1 I have failed more than I should have.
   2 As I look back, I see a lot of failures.
   3 I feel I am a total failure as a person.

4. **Loss of Pleasure:**
   0 I get as much pleasure as I ever did from the things I enjoy.
   1 I don’t enjoy things as much as I used to.
   2 I get very little pleasure from the things I used to enjoy.
   3 I can’t get any pleasure from the things I used to enjoy.

5. **Guilty Feelings:**
   0 I don’t feel particularly guilty.
   1 I feel guilty over many things I have done or should have done.
   2 I feel guilty most of the time.
   3 I feel guilty all the time.

6. **Punishment Feelings:**
   0 I don’t feel I am being punished.
   1 I feel I may be punished.
   2 I expect to be punished.
   3 I feel I am being punished.

7. **Self-Dislike:**
   0 I feel the same about myself as ever.
   1 I have lost confidence in myself.
   2 I am disappointed in myself.
   3 I dislike myself.

8. **Self-Criticalness:**
   0 I don’t criticize or blame myself more than usual.
   1 I am more critical of myself than I used to be.
   2 I criticize myself for all of my faults.
   3 I blame myself for everything bad that happens.

9. **Suicidal Thoughts or Wishes:**
   0 I don’t have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

10. **Crying:**
    0 I don’t cry anymore than I used to.
    1 I cry more than I used to.
    2 I cry over every little thing.
    3 I feel like crying, but I can’t.

11. **Agitation:**
    0 I am no more restless or wound up than usual.
    1 I feel more restless or wound up than usual.
    2 I am so restless or agitated that it’s hard to stay still.
    3 I am so restless or agitated that I have to keep moving or doing something.

12. **Indecisiveness:**
    0 I make decisions about as well as ever.
    1 I find it more difficult to make decisions than usual.
    2 I have much greater difficulty in making decisions than I used to.
    3 I have trouble making any decisions.

13. **Worthlessness:**
    0 I do not feel I am worthless.
    1 I don’t consider myself as worthwhile and useful as I used to.
    2 I feel more worthless as compared to other people.
    3 I feel utterly worthless.

14. **Loss of Energy:**
    0 I have as much energy as ever.
    1 I have less energy than I used to have.
    2 I don’t have enough energy to do very much.
    3 I don’t have enough energy to do anything.

15. **Changes in Sleeping Pattern:**
    0 I have not experienced any change in my sleeping pattern.
    1a I sleep somewhat more than usual.
    1b I sleep somewhat less than usual.
    2a I sleep a lot more than usual.
    2b I sleep a lot less than usual.
    3a I sleep most of the day.
    3b I wake up 1-2 hours early and can’t get back to sleep.

16. **Irritability:**
    0 I am no more irritable than usual.
    1 I am more irritable than usual.
    2 I am much more irritable than usual.
    3 I am irritable all the time.

17. **Changes in Appetite:**
    0 I have not experienced any changes in my appetite.
    1a My appetite is somewhat less than usual.
    1b My appetite is somewhat greater than usual.
    2a My appetite is much less than before.
    2b My appetite is much greater than usual.
    3a I have no appetite at all.
    3b I crave food all the time.

18. **Concentration Difficulty:**
    0 I can concentrate as well as ever.
    1 I can’t concentrate as well as usual.
    2 It’s hard to keep my mind on anything for very long.
    3 I find I can’t concentrate on anything.

19. **Tiredness or Fatigue:**
    0 I am no more tired or fatigued than usual.
    1 I get more tired or fatigued more easily than usual.
    2 I am too tired or fatigued to do a lot of the things I used to do.
    3 I am too tired or fatigued to do most of the things I used to do.

20. **Loss of Interest in Sex:**
    0 I have not noticed any recent change in my interest in sex.
    1 I am less interested in sex than I used to be.
    2 I am much less interested in sex now.
    3 I have lost interest in sex completely.

**Total** (sum)
***ELIGIBLE: Scores 10-29***
If the individual scores higher than 30 or exhibits suicidal thoughts, say the following:
- Based on your responses to the questionnaire, it seems that you may be experiencing rather severe depressive (or suicidal) thoughts. Do you have a family physician?
  [IF YES] Is it possible for you to contact them immediately? I recommend booking an appointment with them as soon as possible.
  [IF NO] Are you a student at the University of Calgary? [If yes] I recommend calling the Wellness Centre and speaking with a counselor there. You can contact them at 403.210.9355; they are located on the 3rd floor of the MacEwan Student Centre in Room 370.
  [If not a UofC student]: You may also contact the Distress Centre at 403.266.1605 or the Calgary suicide and Crisis line at 403.266.0700.
- If scores are within appropriate range, continue.

5. MANIA

- Was there a period in your life when, for at least one week:
  - You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?  YES  NO
  - You became impulsive in a way that was unusual for you (e.g. spent a lot of money, had sexual indiscretions)?  YES  NO
  - You needed less sleep but did not feel tired?  YES  NO
  [IF YES TO ANY OF THE ABOVE] Are you currently experiencing any of these feelings?  YES  NO
  INELIGIBLE if yes to any. Strongly advise making appointment with a healthcare professional.

6. PSYCHOSIS

- Hallucinations: Has there ever been a time in your life when you believed you saw things that were not really there or heard voices or other sounds that were not real?  YES  NO
- Delusions: Have you ever had a time in your life when you believed people were following you, out to get you, trying to hurt you or that you had special powers?  YES  NO
  [IF YES] to any of above: INELIGIBLE. Strongly advise making an appointment with a healthcare professional.

Alright, we are all done. Based on this preliminary screen, you seem like a great candidate for the study. Are you still interested in participating?

[IF YES]: I would like to schedule you to come in for the in-person screen. We will not know if you qualify for the study itself until that is completed. For the in-person screen, you will be reimbursed $20 for completing the clinical assessment, which will take about an hour. And, if you qualify, you will receive another $20 for completing a neurocognitive test battery after the clinical assessment. In total, the in-person clinical assessment and cognitive tasks should last ~2-2.5 hours. Is that alright?

Appointment booked for: ______________________________________
I will confirm your appointment 24 hours in advance. Would you prefer to be contacted via email or by phone?
**Confirm email address or phone number**

Thank you for taking the time to do this phone screen, we appreciate your participation. I will see you on (Date of appointment)
APPENDIX D: HEALTHY CONTROL PHONE SCREENING SCRIPT

Hello (INSERT INDIVIDUAL’S NAME)

My name is (FIRST NAME) and I am a(n) (POSITION) at the University of Calgary, Department of Psychiatry. I am calling with regard to study that you had expressed an interest in participating in as a control. **OR** Thank you for calling us to find out more about our research.

Do you have a moment so that I can explain the study to you?

The purpose of our study is to examine if mood and brain function and structure change after exercise training in young adults with depression symptoms. We also want to measure if specific genetic markers can help us to predict who is the most likely to have positive mood effects from exercise training. Our patients will engage in 12 weeks of aerobic exercise training. However, we are also testing non-depressed controls to see what the stability of brain activity and structure, as well as of certain biomarkers, is over a 12 week period without any exercise intervention. As a control participant, you would come in for an in-person screen, complete some questionnaires and simple cognitive tasks. Afterward, should you still qualify and want to participate, you would be scheduled to come in for an MRI scan during which time you would complete a simple memory task. If you are comfortable with it, we would also collect a blood sample. You would also participate in a physical assessment session during which time we would collect information about your weight, height and physical fitness levels. Subsequently, you would come in 12 weeks later to do these same things.

Are you still interested in participating in this study and continuing with the phone screen?

[IF NO]: Thank you very much for your interest.
- Would you like us to keep your name on file to contact you regarding any other studies in the Department of Psychiatry? YES NO

- Is this a good time to do the phone screen – it should take ~20 min.?
[IF NO]: Set up a time to call back: Date: ______________________         Time: ________________________

Before bringing you in for an in-person screen, we need to ask you a few questions to determine if you are eligible for the study. This information is personal in nature so if any questions make you feel uncomfortable, please let me know. You can choose not to answer any questions. The information that I receive from you today will be destroyed if you do not qualify for the study or choose not to participate. Is it alright if I proceed?

[IF NO]: Thank you very much for your time.
- Would you like us to keep your name on file to contact you regarding any other in the Department of Psychiatry? YES NO

1. DEMOGRAPHICS/PHYSICAL HEALTH

I am now going to ask you some questions on your physical and mental health and other general information.

- What is your current age (must be 18-24 for inclusion)? Employment status? Highest education level completed? (Fill out on 1st page)
* If they just turned 25 (within 1-2 months), continue with screen. If older, thank them for their time and interest, but inform them that they do not meet the strict criteria for inclusion in the current study.
Would you like us to keep your name on file to contact you about other studies in the Department of Psychiatry?

- YES
- NO

*IF YES* to questions below: INELIGIBLE. If not sure, ask Dr. MacQueen. Inform participant that you will call them back regarding whether they qualify for the study OR (if ineligible) thank them for their time/interest, but inform them that they do not meet the strict criteria for inclusion in the current study.

1. Has your doctor ever said that you have a heart condition or high blood pressure?
- YES
- NO  [*IF YES*: INELIGIBLE]

2. Has your doctor ever said that you should only do medically supervised physical activity?
- YES
- NO  [*IF YES*: INELIGIBLE]

3. Do you feel chest pain at rest, during your daily activities, OR when you do physical activity?
- YES
- NO  [*IF YES*: INELIGIBLE; Heavy breathing with physical activity should not be confused with chest pain.]

4. Do you lose balance because of dizziness or have you suddenly lost consciousness in the last 12 months?
- YES
- NO  [*IF YES*: INELIGIBLE; ELIGIBLE if dizziness was associated with over-breathing (e.g., during vigorous exercise)]

5. Have you ever had a concussion?
- YES
- NO  [*IF YES*: INELIGIBLE; If unconscious for >10 min.]

6. Have you been diagnosed with or are currently treated for serious major medical problem/s? Do you have any chronic medical conditions or disabilities?
- YES
- NO  [*IF YES*: INELIGIBLE cardiac problems, asthma, physical disability (preventing exercise training)]

7. Are you currently taking medications regularly for chronic health problems? e.g. blood pressure, cholesterol, thyroid, diabetes
- YES
- NO  [*IF YES*: INELIGIBLE (depending on medications) What medications are you taking?]

8. Are you involved in varsity athletics, or engage in strenuous exercise 3 or more X/week? e.g. running, strength training, soccer, swimming (if 1X/week – OK or if mild-moderate exercise max. 3X/week or a combo of the two, e.g. 1X strenuous, 1-2X mild per week). 
- YES
- NO  [*IF YES*: INELIGIBLE This study is looking at changes associated with aerobic exercise; these changes are not likely to be seen in people that already exercise regularly.]

9. Do you have a bone or joint problem that could be made worse by becoming more physically active?
- YES
- NO  [*IF YES*: ELIGIBLE If past bone/joint problems, which do not limit current ability to be physically active]

10. Do you have neurological or neuromuscular problems? e.g. seizures, brain cysts/tumors/surgery, MS, ALS
- YES
- NO  [*IF YES*: INELIGIBLE Anything preventing participation in exercise or brain pathology.]

11. Have you ever been diagnosed with developmental problems/learning disabilities? e.g. autism, Asperger’s, mental retardation (word choice), dyslexia
- YES
- NO  [*IF YES*: INELIGIBLE Anything preventing carrying out tasks; dyslexia, to the extend that reading is very impaired.]

12. Can you tell me your approximate height and weight? Ht _____ Wt _____
- Metric Units: BMI = Weight (kg) / (Height (m))^2: _____
- English Units: BMI = Weight (lb) / (Height (in))^2 x 703: _____ (1 foot = 12 inches) [*IF BMI >35*: INELIGIBLE]
2. MRI COMPATIBILITY

These next questions are to determine if you can participate in the MRI/brain scanning component of the study:

1. Have you ever had an MRI scan before?
   YES   NO   [IF YES] What was it for?

2. Are you claustrophobic? Feel very uncomfortable/anxious/panicky in enclosed spaces?
   YES   NO   [IF YES]: INELIGIBLE (depending on severity)

3. Are you right handed, left handed, or do you use both?

4. Do you have any metal in your body? e.g. pacemakers, surgical/aneurysm clips, implanted metal plates, screws or pins, ear implants, braces on your teeth other metal objects?
   YES   NO   [IF YES]: ELIGIBLE Most surgically implanted things are titanium (MRI-safe); small braces/retainers are usually OK – check with MRI Center.

5. As far as you know, is there a chance that you may be pregnant (females)?
   YES   NO   [IF YES]: ELIGIBLE

3. PSYCHIATRIC ASSESSMENT – GENERAL

I am now going to ask you some questions regarding your emotional/mental wellbeing.

1. Have you ever had a problem with alcohol or drug abuse or dependence?
   YES   NO   [IF YES] Current?
   INELIGIBLE if currently (last 6 months) abusing or dependent on alcohol or illicit drugs.
   ELIGIBLE if more than 6 months ago, occasional alcohol/drug use.

2. Have you ever suffered from, or been diagnosed with, any psychiatric or emotional problems?
   YES   NO   [IF YES] Which?
   INELIGIBLE if diagnoses occurred.

4. DEPRESSION

- As far as you know, have any of your 1st degree relatives (mother, father, siblings) suffered from depression (clinically-diagnosed, sustained episode)?  YES   NO
- Was there a time in your life when, for 2 weeks or more, everyday, most of the day you felt depressed, sad, unhappy, or it was hard for you to cheer up?  YES   NO
- Was there a time in your life when, for 2 weeks or more, you lost interest in things or were unable to enjoy most things that you used to enjoy?  YES   NO

Are you currently experiencing thoughts/feelings of depression?  YES   NO
INELIGIBLE if yes to any of the above.

I will now ask you a series of questions related to depression. Please remember that you can choose not to answer any of the questions. Of the following statements, choose the one which best suits you:
| 1. Sadness:                      | 2 I am so restless or agitated that it's hard to stay still. |
| 0 I do not feel sad.            | 3 I am so restless or agitated that I have to keep moving or doing something. |
| 1 I feel sad much of the time.   |                                                   |
| 2 I feel sad all the time.      |                                                   |
| 3 I am so sad or unhappy that I can't stand it. |                                                   |
| 2. Pessimism:                   |                                                   |
| 0 I am not discouraged about my future. |                                                   |
| 1 I feel more discouraged about my future than I used to. |                                                   |
| 2 I do not expect things to work out for me. |                                                   |
| 3 I feel my future is hopeless and will only get worse. |                                                   |
| 3. Past Failure:                |                                                   |
| 0 I do not feel like a failure.  |                                                   |
| 1 I have failed more than I should have. |                                                   |
| 2 As I look back, I see a lot of failures. |                                                   |
| 3 I feel I am a total failure as a person. |                                                   |
| 4. Loss of Pleasure:            |                                                   |
| 0 I get as much pleasure as I ever did from the things I enjoy. |                                                   |
| 1 I don't enjoy things as much as I used to. |                                                   |
| 2 I get very little pleasure from the things I used to enjoy. |                                                   |
| 3 I can't get any pleasure from the things I used to enjoy. |                                                   |
| 5. Guilty Feelings:             |                                                   |
| 0 I don't feel particularly guilty. |                                                   |
| 1 I feel guilty over many things I have done or should have done. |                                                   |
| 2 I feel guilty most of the time. |                                                   |
| 3 I feel guilty all the time.    |                                                   |
| 6. Punishment Feelings:         |                                                   |
| 0 I don't feel I am being punished. |                                                   |
| 1 I feel I may be punished.      |                                                   |
| 2 I expect to be punished.       |                                                   |
| 3 I feel I am being punished.    |                                                   |
| 7. Self-Dislike:                |                                                   |
| 0 I feel the same about myself as ever. |                                                   |
| 1 I have lost confidence in myself. |                                                   |
| 2 I am disappointed in myself.   |                                                   |
| 3 I dislike myself.              |                                                   |
| 8. Self-Criticalness:           |                                                   |
| 0 I don't criticize or blame myself more than usual. |                                                   |
| 1 I am more critical of myself than I used to be. |                                                   |
| 2 I criticize myself for all of my faults. |                                                   |
| 3 I blame myself for everything bad that happens. |                                                   |
| 9. Suicidal Thoughts or Wishes: |                                                   |
| 0 I don't have any thoughts of killing myself. |                                                   |
| 1 I have thoughts of killing myself, but I would not carry them out. |                                                   |
| 2 I would like to kill myself.   |                                                   |
| 3 I would kill myself if I had the chance. |                                                   |
| 10. Crying:                     |                                                   |
| 0 I don't cry anymore than I used to. |                                                   |
| 1 I cry more than I used to.     |                                                   |
| 2 I cry over every little thing. |                                                   |
| 3 I feel like crying, but I can't. |                                                   |
| 11. Agitation:                  |                                                   |
| 0 I am no more restless or wound up than usual. |                                                   |
| 1 I feel more restless or wound up than usual. |                                                   |
| 12. Indecisiveness:             |                                                   |
| 0 I make decisions about as well as ever. |                                                   |
| 1 I find it more difficult to make decisions than usual. |                                                   |
| 2 I have much greater difficulty in making decisions than I used to. |                                                   |
| 3 I have trouble making any decisions. |                                                   |
| 13. Worthlessness:              |                                                   |
| 0 I do not feel I am worthless.  |                                                   |
| 1 I don't consider myself as worthwhile and useful as I used to. |                                                   |
| 2 I feel more worthless as compared to other people. |                                                   |
| 3 I feel utterly worthless.      |                                                   |
| 14. Loss of Energy:             |                                                   |
| 0 I have as much energy as ever. |                                                   |
| 1 I have less energy than I used to have. |                                                   |
| 2 I don't have enough energy to do very much. |                                                   |
| 3 I don't have enough energy to do anything. |                                                   |
| 15. Changes in Sleeping Pattern:|                                                   |
| 0 I have not experienced any change in my sleeping pattern. |                                                   |
| 1a I sleep somewhat more than usual. |                                                   |
| 1b I sleep somewhat less than usual. |                                                   |
| 2a I sleep a lot more than usual. |                                                   |
| 2b I sleep a lot less than usual. |                                                   |
| 3a I sleep most of the day.      |                                                   |
| 3b I wake up 1-2 hours early and can't get back to sleep. |                                                   |
| 16. Irritability:               |                                                   |
| 0 I am no more irritable than usual. |                                                   |
| 1 I am more irritable than usual. |                                                   |
| 2 I am much more irritable than usual. |                                                   |
| 3 I am irritable all the time.   |                                                   |
| 17. Changes in Appetite:        |                                                   |
| 0 I have not experienced any changes in my appetite. |                                                   |
| 1a My appetite is somewhat less than usual. |                                                   |
| 1b My appetite is somewhat greater than usual. |                                                   |
| 2a My appetite is much less than before. |                                                   |
| 2b My appetite is much greater than usual. |                                                   |
| 3a I have no appetite at all.    |                                                   |
| 3b I crave food all the time.    |                                                   |
| 18. Concentration Difficulty:   |                                                   |
| 0 I can concentrate as well as ever. |                                                   |
| 1 I can't concentrate as well as usual. |                                                   |
| 2 It's hard to keep my mind on anything for very long. |                                                   |
| 3 I find I can't concentrate on anything. |                                                   |
| 19. Tiredness or Fatigue:       |                                                   |
| 0 I am no more tired or fatigued than usual. |                                                   |
| 1 I get more tired or fatigued more easily than usual. |                                                   |
| 2 I am too tired or fatigued to do a lot of the things I used to do. |                                                   |
| 3 I am too tired or fatigued to do most of the things I used to do. |                                                   |
| 20. Loss of Interest in Sex:    |                                                   |
| 0 I have not noticed any recent change in my interest in sex. |                                                   |
| 1 I am less interested in sex than I used to be. |                                                   |
| 2 I am much less interested in sex now. |                                                   |
| 3 I have lost interest in sex completely. |                                                   |
**ELIGIBLE: Scores <10 (or so – use discretion)**
If the individual scores higher than 30 or exhibits suicidal thoughts, say the following:
- Based on your responses to the questionnaire, it seems that you may be experiencing rather severe depressive (or suicidal) thoughts. Do you have a family physician?
[IF YES] Is it possible for you to contact them immediately? I recommend booking an appointment with them as soon as possible.
[IF NO] Are you a student at the University of Calgary? [If yes] I recommend calling the Wellness Centre and speaking with a counselor there. You can contact them at 403.210.9355; they are located on the 3rd floor of the MacEwan Student Centre in Room 370.
[If not a UofC student]: You may also contact the Distress Centre at 403.266.1605 or the Calgary suicide and Crisis line at 403.266.0700.
- If scores are within appropriate range, continue.

5. MANIA
- Was there a period in your life when, for at least one week:
  - You were so happy/excited/energized that other people thought you were not your normal self and/or this was abnormal for you?  YES  NO
  - You became impulsive in a way that was unusual for you (e.g. spent a lot of money, had sexual indiscretions)?  YES  NO
  - You needed less sleep but did not feel tired?  YES  NO
[IF YES TO ANY OF THE ABOVE] Are you currently experiencing any of these feelings?  YES  NO
INELIGIBLE if yes to any. Strongly advise making appointment with a healthcare professional.

6. PSYCHOSIS
- Hallucinations: Has there ever been a time in your life when you believed you saw things that were not really there or heard voices or other sounds that were not real?  YES  NO
- Delusions: Have you ever had a time in your life when you believed people were following you, out to get you, trying to hurt you or that you had special powers?  YES  NO
[IF YES] to any of above: INELIGIBLE. Strongly advise making an appointment with a health care professional.

Alright, we are all done. Based on this preliminary screen, you seem like a great candidate for the study. Are you still interested in participating?
[IF YES]: I would like to schedule you to come in for the in-person screen. We will not know if you qualify for the study itself until that is completed. For the in-person screen, you will be reimbursed $20 for completing the clinical assessment, which will take about an hour. And, if you qualify, you will receive another $20 for completing a neurocognitive test battery after the clinical assessment and blood draw – if you are OK with that. In total, the in-person clinical assessment and cognitive tasks should last ~2-2.5 hours. Is that alright?
Appointment booked for:___________________________________________________________

I will confirm your appointment 24 hours in advance. Would you prefer to be contacted via email or by phone?
**Confirm email address or phone number**
Thank you for taking the time to do this phone screen, we appreciate your participation. I will see you on (Date of appointment)!
APPENDIX E: PATIENT CONSENT TO PARTICIPATE IN EXERCISE AND DEPRESSION STUDY

PATIENT CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Effects of Aerobic Exercise on Mood and Hippocampal Plasticity and Function in Young Adults with Mild Major Depressive Disorder (MDD)

INVESTIGATORS:
Principal Investigator: Dr. Frank MacMaster, PhD. (Phone: 403.955.2784)
Co-investigators: Dr. Glenda MacQueen, MD., PhD.
Dr. Matthew Hill, PhD.
Dr. Nicole Culos-Reed, PhD.
Dr. Andrea Protzner, PhD.
Dr. Signe Bray, PhD.

Study Coordinators: Dr. Natalia Jaworska, MSc., PhD.
Devin Mahnke, MSc.
Allegra Courtright, BSc.

PRIMARY CONTACT: Natalia Jaworska

FUNDING SOURCES: Investigator-initiated study

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more information or require clarification about anything in the document, please ask. Please take the time to carefully read and understand the content of this document. A copy of this document will be provided to you.

BACKGROUND & PURPOSE:
Major depressive disorder (MDD), or depression, is a common mental illness in which negative emotions and accompanying physical and behavioral effects can greatly interfere with normal function. Mild forms of depression are seldom diagnosed and treated, and tend to be “self-managed.” While this is often appropriate, the possible progression of depression into more severe forms of MDD constitutes a large threat in young adults because treatment of this population is particularly problematic. The most commonly used antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs), have been linked with increased risk of suicide in young adults (18-24 years of age). As such, other forms of antidepressant treatment in young adults are needed.
The purpose of this study will be to examine the effects of long-term (12 week) exercise of moderate intensity on physical and mental health in mildly depressed young adults. Evidence suggests that long-term exercise has positive effects on the brain, specifically a structure called the hippocampus, which is often negatively affected by MDD. We will study if long-term exercise induces brain plasticity (changes in brain structure, particularly the hippocampus), which, in turn, will result in a positive impact on mood, cognition, and brain function. These measures will be obtained using computerized tasks, paper-and-pencil questionnaires and brain imaging using magnetic resonance imaging (MRI). We will also look at whether specific genes predict who is most likely to have an antidepressant response to exercise. The genetic information will be obtained using collected blood.

Young adult (aged 18-24) males and females with a mild form of depression, and not currently obtaining any antidepressant treatment(s) and who will not commence antidepressant medication during this study (if deemed an appropriate course of action by the psychiatrist), will be asked to participate in: 1. **Intake Session:** This will consist of an in-person psychiatric assessment and subsequent meeting with a psychiatrist (not on the same day). You will also perform simple cognitive tasks. 2. **Baseline Brain Imaging and Blood Collection.** 3. **Exercise Training:** You will complete a 12-week aerobic intervention program (3 times/week). 4. **Post-Training Reassessments:** The same clinical and cognitive assessments will be carried out as in the Intake Sessions. 5. **Post-Training Brain Imaging and Blood Collection.**

We expect to enroll 70 young adults with mild depression (35 males and 35 females; aged 18-24). This study involves 12 weeks of moderate-intensity exercise training and four separate visits before and after completing training for neuroimaging, blood collection as well as mood/clinical and cognitive assessments. All assessments will be carried out at facilities at the Teaching, Research and Wellness (TRW) building at the Foothills Medical Center; neuroimaging sessions will be carried out at the Alberta Children's Hospital. Exercise training will occur on the main campus of the University of Calgary or TRW building.

**STUDY PROCEDURES**

After reading and signing this informed consent document, the intake session (Parts A & B) will start:

1. **Intake Session - Part A: Clinical Assessments (~1hr):** A psychiatric assessment will be carried out by the study coordinators. This is a scripted interview that will inquire about your thoughts and feelings. Questions on personal and familial psychiatric history will also be asked. Several questionnaires probing mood, physical health and hand preference will be administered. Participants meeting inclusion criteria after this intake interview will meet with the study psychiatrist (Dr. Glenda MacQueen) at a later date for a follow-up psychiatric evaluation (~30 min). Participants found to have moderate to severe depression based on this clinical assessment and questionnaires will be scheduled to meet with the psychiatrist as soon as possible. Appropriate clinical steps will be undertaken in consultation with the psychiatrist. Participants with no or clinically insignificant
depression symptoms as determined by the assessment will not be included in any further assessments or this study.

Several questionnaires probing quality of life and anxiety will also be given to participants to fill out at their own leisure (hard-copy or e-mailed) and returned to study coordinators (~15min).

2. Intake Session - Part B: Cognitive Assessments (~1hr): After completing the clinical assessment, a series of computerized and paper-and-pencil based tests will be administered. These simple tests examine cognitive domains such as attention and processing speed, executive function as well as learning and memory. If it is not possible to carry out the cognitive assessments after the clinical assessment (i.e., on the same day), an alternate time will be arranged.

After the intake session (Parts A & B), a date for brain imaging and blood collection (carried out on the same day) will be established.

3. Brain Imaging (Baseline; ~2 hr total): Prior to the brain scan, you will meet with the study coordinators who will administer a memory task.

After completing the memory task outside of the scanner, you will be taken to the scanner. There, you will change into comfortable hospital scrubs and robe and will then be assisted into the scanner. Once inside the scanner, you will lie still; sometimes you will be asked to open or close your eyes. You will also complete a memory task. If time permits, you may be asked to view silent clips from a popular TV show (10 min). Afterward, you would complete a brief memory task regarding these video clips. Instructions regarding the tasks will be provided prior to entering the scanner. This will occur at the Alberta Children’s Hospital scanner.

*MRI Information*

MRI provides information on brain structure while functional MRI (fMRI) measures brain activity. fMRI/MRI is a safe and non-invasive procedure. The MRI image looks similar to an X-ray image, but does not use radiation. It allows us to “see” the hippocampus and other brain areas that may be altered in depression. Comparing these images before and after exercise intervention will allow us to determine if brain structure changes with long-term exercise. Baseline brain MRI images may also help us to predict who will be most likely to benefit from the antidepressant effects of exercise. fMRI helps us to understand how the brain functions in depression and determine if function changes with exercise.

MRI/fMRI images are collected using a large and strong magnet. Therefore, participants with any magnetic material (i.e., most metals) in their bodies that cannot be removed cannot participate in this study. An MRI technician will ensure whether that it is safe for you to enter the scanner. During the scan, you will lie on a table that will be moved into the scanner (total scan time: ~1 hr). During scanning, you will be asked to lie as still as possible (legs and head will be supported by pillows) because movement blurs brain images. The scanner makes loud, banging sounds, therefore, you will wear protective earplugs. You will be able to communicate with the technician/study coordinator(s) during
the scan. Since scanning involves lying with the head and neck inside the scanner, some participants may become anxious and experience claustrophobia (fear of enclosed spaces). If this occurs, the scan can be interrupted or terminated at any time by squeezing a squeeze-ball that you will hold during the scan.

4. **Blood Sample (Baseline; ~10 min):** After the scan, a blood sample will be collected by trained personnel into three tubes (~4 teaspoons). Blood collection will allow us to examine if specific genetic factors involved in controlling brain structure and function are associated with specific clinical (e.g., depressed mood) and brain changes (e.g., smaller hippocampus). These measures may also help us determine who is most likely to show antidepressant benefits from exercise training.

5. **Exercise Training (12 weeks, 3 times/week):** Within a week of completing the baseline neuroimaging session and blood collection, you will be enrolled in long-term aerobic exercise training under the direction of trained fitness personnel and researchers (Culos-Reed Health & Wellness Laboratory, Faculty of Kinesiology, University of Calgary, main campus). The training will occur in small groups and will be scheduled in accordance with your availability.

   A. **Intake Session: Physical Assessment:** During the intake session of the exercise training, fitness personnel will administer several questionnaires. Measures of physical health and fitness such as weight and height, waist circumference, resting blood pressure and heart rate, will also be obtained. Additionally, baseline aerobic capacity, which measures maximum oxygen consumption (VO₂max), will be calculated. If the fitness personnel carrying out these assessments determine that you may be in some sort of physical danger by participating in long-term exercise training (e.g., heart rate abnormalities), you will not be allowed to participate in this study. Should this be the case, you will also be directed to appropriate medical professionals.

   B. **Exercise Training:** You will carry out the aerobic exercise training for 12 weeks, at a frequency of three times a week. Each session will last a maximum of 1 hour and consist of: a) 3-5 min of low-intensity warm-up exercises on a treadmill or stationary bicycle; b) 3-5 min of stretching; c) 30 min of aerobic training (cycling, treadmill running, StairMaster climbing or elliptical trainer); d) 5-10 min cool down and stretching. During training, heart rate and blood pressure will be monitored and occasionally aerobic capacity will be re-assessed.

6. **Clinical Assessments During Exercise Training:** At various time points during exercise training, mood and clinical symptoms will be re-assessed using standardized questionnaires. These assessments will be conducted by study coordinators, who will meet with you before your exercise sessions.

7. **Clinical and Cognitive Re-Assessment (Post-Exercise Training):** Within a week after completing exercise training, the clinical and cognitive assessments will be re-administered in the same manner as outlined for the intake session.
8. Brain Imaging and Blood Connection (Post-Exercise Training): Within 1-2 weeks after completing exercise training, brain imaging and blood collection procedures will again be carried out.

POTENTIAL RISKS
Mental Health Assessments:
- Psychiatric assessments may cause distress in some participants. However, each of the assessment measures used in this study have been administered extensively in young adults with no or minimal adverse effects. Additionally, the study researchers are trained in administering clinical and mood assessments in a way that will minimize discomfort. Psychiatric assessments may be terminated at any time and you have the right not to answer questions. Strict procedures for record keeping will also be followed to ensure confidentiality.

Medical/Physical Risks:
- Blood collection may cause local discomfort or slight bruising, which should diminish in several days.
- During the fitness intake session and exercise training, you will be closely monitored. If you over-exert yourself and this leads to strong physical discomfort (e.g. nausea, sense of passing out) and/or abnormal cardiac activity, you will be told to slow down or discontinue the session, and be monitored closely by study personnel.

Brain Imaging:
- Due to the strong magnetic field, any metallic objects on/within the body constitute a potential hazard in the scanner. You will be thoroughly screened for metallic content by trained technicians before entering the scanner. If you have metallic content that cannot be removed from the body, you may not be able to participate in this study.
- You may feel frustrated while performing the memory task in the scanner and cognitive assessments outside the scanner. However, there is no penalty for imperfect performance and you will simply be asked to do your best during these tasks.
- It is unknown whether the scanner magnet poses any risk to a fetus, therefore, pregnant females or those who suspect they may be pregnant will not be allowed to participate in the current study.
- The MRI machine/scanner is loud and may cause some auditory discomfort; you will be required to wear earplugs while inside the scanner.
- The space inside the MRI machine is fairly limited, so some participants may feel claustrophobic. If this occurs, you can squeeze a squeeze-ball that will interrupt or terminate the scan.
- MRI scans are not intended to screen for medical conditions. In the unlikely event that a brain abnormality is detected, the scans will be referred to a specialist for further examination. Should these be of any concern, you as well as your family physician will be informed of these results. The scans obtained during this research study will not become part of your hospital records.
POTENTIAL BENEFITS
Direct benefits include a comprehensive psychiatric assessment by trained personnel and the study psychiatrist. A comprehensive evaluation by an experienced psychiatrist may help you to better understand your mental health needs. Furthermore, should any participant be identified as having a significant mental illness that requires immediate attention, the appropriate care will be provided.

Exercise training, under the care of fitness experts and researchers at a fully equipped facility and at no monetary cost, will provide you with an opportunity to improve your physical health under safe conditions. Previous research suggests potential benefits of long-term exercise training on depression symptoms, overall mental well-being, cognitive function, and brain structure and function. The knowledge gained from this study will help in understanding the brain processes associated with the mood-elevating effects of exercise. Additionally, it will help us determine which brain and genetic factors are useful in predicting if exercise training will have positive mood effects.

PARTICIPATION
Participation in this study is voluntary and withdrawal from the study is possible at any time. You will be asked to inform the research personnel if you choose to withdraw from the study.

COMPENSATION
For your time and effort, you will be compensated $40.00 CDN after completing the intake session (i.e., clinical and cognitive assessments). You will be compensated again after completing the first neuroimaging scan and blood collection ($40.00 CDN). The same compensation will again be provided after clinical and cognitive re-assessment ($40.00 CDN) and the second neuroimaging scan and blood collection ($40.00 CDN), which will occur after completing exercise training (i.e., after 12 weeks). Participants who withdraw from the study will be compensated for any completed components.

In the unlikely event that you suffer injury as a result of participating in this research, no additional compensation will be provided to you by the University of Calgary or the study researchers/personnel. You still have all your legal rights and nothing stated in this consent alters your right to seek damages.

CONFIDENTIALITY
Your personal information will not be available to anyone not directly involved in this study. Additionally, all your information will be coded with a unique identification code (i.e., series of letters and numbers). Only the study coordinators will maintain a participant identification list to enable record identification and retrieval. All hardcopy data will be stored in a secured cabinet. Computerized data will be stored on a password-protected computer.

University policy requires that participant research records be kept for a minimum of five years after final publication of the study results. These records will not contain any personal identifiers. Participant identification lists will be stored in a separate and secure location. No identifying information will be used in any publications/presentations of results stemming from this research.
Representatives of the University of Calgary Conjoint Health Research Ethics Board and the Health Protection Branch of Canada may inspect participant records to verify the collected information (i.e., in the case of an audit). Should this occur, all personal information made available for inspection will be handled with strict confidence and in accordance with local data protection laws.

The University of Calgary Conjoint Health Research Ethics Board has approved this research study. Ethics ID # 24612 A signed copy of this consent form has been given to you to keep for your records and reference.
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Effects of Aerobic Exercise on Mood and Hippocampal Plasticity and Function in Young Adults with Mild Major Depressive Disorder (MDD)

INVESTIGATORS:
Principal Investigator: Dr. Frank MacMaster, PhD. (Phone: 403.955.2784)
Co-investigators: Dr. Glenda MacQueen, MD., PhD.
Dr. Matthew Hill, PhD.
Dr. Nicole Culos-Reed, PhD.
Dr. Andrea Protzner, PhD.

Study Coordinators: Dr. Natalia Jaworska, MSc., PhD.
Devin Mahnke, MSc.
Allegra Courtright, BSc.
Dr. Signe Bray, PhD.

PRIMARY CONTACT: Natalia Jaworska

Your signature on this form indicates that you satisfactorily understand the information regarding your participation in this research project and agree to participate. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw from this study at any time. If you have further questions concerning matters related to this research, please contact Natalia Jaworska or Frank MacMaster.

If you have any questions concerning your rights as a possible participant in this research, please contact The Chair of the Conjoint Health Research Ethics Board, University of Calgary, at 403-220-7990.

SIGNATURES

Name of Participant (printed) ____________________________ Signature of Participant ____________________________ Date

Name of Investigator_/ (printed) ____________________________ Signature of Investigator_/ ____________________________ Date
Research Personnel Research Personnel

Name of Witness (printed) ____________________________ Signature of Witness ____________________________ Date

The University of Calgary Conjoint Health Research Ethics Board has approved this research study. A signed copy of this consent form has been given to you to keep for your records and reference.
APPENDIX F: HEALTHY VOLUNTEER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

HEALTHY VOLUNTEER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Effects of Aerobic Exercise on Mood and Hippocampal Plasticity and Function in Young Adults with Mild Major Depressive Disorder (MDD)

INVESTIGATORS:
Principal Investigator: Dr. Frank MacMaster, PhD. (Phone: 403.955.2784)
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Dr. Natalia Jaworska, MSc., PhD.
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Allegra Courtright, BSc.

PRIMARY CONTACT: Natalia Jaworska:

FUNDING SOURCES: Investigator-initiated study

This consent form is only part of the process of informed consent. It should give you the basic idea of what the research is about and what your participation will involve. If you would like more information or require clarification about anything in the document, please ask. Please take the time to carefully read and understand the content of this document. A copy of this document will be provided to you.

BACKGROUND & PURPOSE:
Major depressive disorder (MDD), or depression, is a common mental illness wherein negative emotions and accompanying physical and behavioral effects can greatly interfere with normal function. Mild forms of depression are seldom diagnosed and treated, and tend to be “self-managed.” While this is often appropriate, the possible progression of depression into more severe forms of MDD constitutes a large threat in young adults because treatment of this population is particularly problematic. The most commonly used antidepressant drugs, the selective serotonin reuptake inhibitors (SSRIs), have been linked with increased risk of suicide in young adults (18-24 years of age). As such, other forms of antidepressant treatment in young adults are needed.
The purpose of this study will be to examine the effects of long-term (12 week) exercise of moderate intensity on physical and mental health in mildly depressed young adults. Evidence suggests that long-term exercise has positive effects on the brain, specifically a structure called the hippocampus, which is often negatively affected by MDD. We will study if long-term exercise induces changes in brain structure, particularly the hippocampus, which will induce a positive impact on mood, cognition, and brain function. These measures will be obtained using computerized tasks, paper-and-pencil questionnaires and brain imaging using magnetic resonance imaging (MRI). We will also look at whether specific genes predict who is most likely to have an antidepressant response to exercise. The genetic information will be obtained using collected blood.

We will also carry out neuroimaging, cognitive testing, and blood draws in healthy volunteers (i.e., you) without any psychiatric illness (i.e., non-depressed) at baseline and after 12 weeks. Healthy control volunteers will not partake in exercise training. Data from healthy volunteers will be collected to gain information on the stability of brain structure and function over a 12-week period. This will help us understand the extent to which aerobic exercise induces brain, behavioral and mood changes in depressed individual above and beyond passage or time (or other factors).

We expect to enroll 16 healthy, non-depressed adults (8 males and 8 females; aged 18-24). In total, you will participate in four separate visits – two before and two after 12 weeks. These visits will include neuroimaging, mood/clinical and cognitive assessments as well as blood collection. All assessments will be carried out at facilities at the Teaching, Research and Wellness (TRW) building at the Foothills Medical Center; neuroimaging sessions will be carried out at the Alberta Children’s Hospital.

**STUDY PROCEDURES**

After reading and signing this informed consent document, the intake session (Parts A & B) will start:

1. **Intake Session - Part A: Clinical Assessments (~30 min):** A psychiatric assessment will be carried out by the study coordinators. This is a scripted interview that will inquire about your thoughts and feelings. Questions on personal and familial psychiatric history will also be asked, though you are free not to answer any questions that make you feel uncomfortable. Several questionnaires probing mood, physical health, quality of life and hand preference will also be administered. In the rare case that a healthy volunteer meets diagnostic criteria for a psychiatric illness, he/she will be referred to the study psychiatrist (Dr. Glenda MacQueen) and all further assessments will cease. Appropriate clinical steps will be undertaken in consultation with the psychiatrist, if necessary.

2. **Intake Session - Part B: Cognitive Assessments (~1hr):** After completing the clinical assessment, a series of computerized and paper-and-pencil based tests will be administered. These simple tests examine cognitive domains such as attention and processing speed, executive function as well as learning and memory.
After the intake session (Parts A & B), a date for brain imaging and blood collection (carried out on the same day) will be established.

3. Baseline Brain Imaging (~2 hr): Prior to the brain scan, you will meet with the study coordinators who will administer a memory task (~25 min). Afterward, you will change into comfortable hospital scrubs and robe and will then be assisted into the scanner. Once inside the scanner, you will lie still with your eyes open and closed as well as complete a memory task. If time permits, you may be asked to view silent clips from a popular TV show (10 min). Afterward, you would complete a brief memory task regarding these video clips. Instructions regarding the tasks will be provided prior to entering the scanner. This will occur at the Alberta Children’s Hospital’s Hospital scanner.

MRI Information

MRI provides information on brain structure while functional MRI (fMRI) measures brain activity. fMRI/MRI is a safe and non-invasive procedure. MRI images look similar to X-ray images, but do not use radiation. MRIs allow us to “see” the hippocampus and other brain areas that may be altered in depression. Your brain images (i.e., from non-depressed volunteers) will be compared with brain images from depressed individuals to assess how depression alters brain structure and function. More importantly, your brain structure and function will be examined before and after a 12-week period to establish the normal degree of variability in brain structure/function over such a time frame. This information will allow us to determine the extent to which brain changes can be attributed to aerobic exercise intervention in depressed individuals.

MRI/fMRI images are collected using a large, strong magnet. Therefore, participants with any magnetic material (i.e., some metals) in their bodies that cannot be removed may not be able to participate in this study. During the scan, you will lie on a table that will be moved into the scanner (total scan time: ~1 hr). During scanning, you will be asked to lie as still as possible (legs and head will be supported by pillows) because movement blurs brain images. The scanner makes loud, banging sounds, therefore, you will wear protective earplugs. You will be able to communicate with the technician/study coordinator(s) during the scan. Since scanning involves lying with the head and neck inside the scanner, some participants may become anxious and experience claustrophobia (fear of enclosed spaces). If this occurs, the scan can be interrupted or terminated by squeezing a squeeze-ball that you will hold during the scan.

4. Blood Sample (Baseline; ~10 min): After the scan, a blood sample will be collected by trained personnel into three tubes (~4 teaspoons). Blood collection will allow us to examine if specific genetic factors involved in controlling brain structure and function are associated with specific clinical (e.g. depressed mood) and brain changes (e.g. smaller hippocampus). These measures may also help us determine who is most likely to show antidepressant benefits from exercise training. You will be asked to sign a separate consent form indicating whether you choose to participate in the blood collection.

5. Clinical and Cognitive Re-Assessment: After 12 weeks, the clinical and cognitive assessments will be re-administered in the same manner as outlined for the intake session.
6. Brain Imaging and Blood Connection (Post-Exercise Training): After 12 weeks, brain imaging and blood collection procedures will again be carried out.

POTENTIAL RISKS

Mental Health Assessments:
- Psychiatric assessments may cause distress in some participants. However, each of the assessment measures used in this study has been administered extensively in young adults with minimal to no adverse effects. Additionally, the study researchers are trained in administering clinical and mood assessments in a way that will minimize discomfort. Psychiatric assessments may be terminated at any time and you have the right not to answer any questions asked. Strict procedures for record keeping will also be followed to ensure confidentiality.

Medical/Physical Risks:
- Blood collection may cause local discomfort or slight bruising, which should diminish in several days.

Brain Imaging:
- Due to the strong magnetic field, any metallic objects on or within the body constitute a potential hazard in the scanner. You will be thoroughly screened for metallic content by trained technicians before entering the scanner. If you have metallic content that cannot be removed from the body, you may not be able to participate in this study.
- You may feel frustrated while performing the memory task in the scanner and cognitive assessments outside the scanner. However, there is no penalty for imperfect performance and you will simply be asked to do your best during these tasks.
- It is unknown whether the scanner magnet poses any risk to a fetus; therefore, pregnant females or those who suspect they may be pregnant will not be allowed to participate in the current study.
- The MRI machine/scanner is loud and may cause some auditory discomfort; you will be required to wear earplugs while inside the scanner.
- The space inside the MRI machine is fairly limited, so some participants may feel claustrophobic. If this occurs, you can squeeze a squeeze-ball that will interrupt or terminate the scan.
- MRI scans are not intended to screen for medical conditions. In the unlikely event that a brain abnormality is detected, the scans will be referred to a specialist for further examination. Should these be of any concern, you as well as your family physician will be informed of these results. The scans obtained during this research study will not become part of your hospital records.

POTENTIAL BENEFITS

The knowledge gained from this study will help in understanding the stability of neural measures over a 12-week period and in better understanding the brain modulations association with depression.

PARTICIPATION
Participation in this study is voluntary and withdrawal from the study is possible at any time. You will be asked to inform the research personnel if you choose to withdraw from the study.

COMPENSATION
For your time and effort, you will be compensated $40.00 CDN after completing the intake session (i.e., clinical and cognitive assessments). You will be compensated again after completing the first neuroimaging scan and blood collection ($40.00 CDN). The same compensation will again be provided after clinical and cognitive re-assessment ($40.00 CDN) and the second neuroimaging scan and blood collection ($40.00 CDN) after 12 weeks. Participants who withdraw from the study will be compensated for any completed components.

In the unlikely event that you suffer injury as a result of participating in this research, no additional compensation will be provided to you by the University of Calgary or the study researchers/personnel. You still have all your legal rights and nothing stated in this consent alters your right to seek damages.

CONFIDENTIALITY
Your personal information will not be available to anyone not directly involved in this study. Additionally, all your information will be coded with a unique identification code). Only the study coordinators will maintain a participant identification list to enable record identification and retrieval. All hardcopy data will be stored in a secured cabinet. Computerized data will be stored on a password-protected computer.

University policy requires that participant research records be kept for a minimum of five years after final publication of the study results. These records will not contain any personal identifiers. Participant identification lists will be stored in a separate and secure location. No identifying information will be used in any publications/presentations of results stemming from this research.

Representatives of the University of Calgary Conjoint Health Research Ethics Board and the Health Protection Branch of Canada may inspect participant records to verify the collected information (i.e., in the case of an audit). Should this occur, all personal information made available for inspection will be handled with strict confidence and in accordance with local data protection laws.

The University of Calgary Conjoint Health Research Ethics Board has approved this research study. Ethics ID # 24612. A signed copy of this consent form has been given to you to keep for your records and reference.
HEALTHY VOLUNTEER CONSENT TO PARTICIPATE IN A RESEARCH STUDY

TITLE: Effects of Aerobic Exercise on Mood and Hippocampal Plasticity and Function in Young Adults with Mild Major Depressive Disorder (MDD)

INVESTIGATORS:
Principal Investigator: Dr. Frank MacMaster, PhD. (Phone: 403.955.2784)
Co-investigators: Dr. Glenda MacQueen, MD., PhD.
Dr. Matthew Hill, PhD.
Dr. Nicole Culos-Reed, PhD.
Dr. Andrea Protzner, PhD.
Dr. Signe Bray, PhD.

Study Coordinators: Dr. Natalia Jaworska, MSc., PhD.
Devin Mahnke, MSc.
Allegra Courtright, BSc.

PRIMARY CONTACT: Natalia Jaworska:

Your signature on this form indicates that you satisfactorily understand the information regarding your participation in this research project and agree to participate. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw from this study at any time. If you have further questions concerning matters related to this research, please contact Natalia Jaworska or Frank MacMaster.

If you have any questions concerning your rights as a possible participant in this research, please contact The Chair of the Conjoint Health Research Ethics Board, University of Calgary, at 403-220-7990.

SIGNATURES

Name of Participant (printed) ___________________ Signature of Participant ___________________ Date ________________

Name of Investigator/ Research Personnel (printed) ___________________ Signature of Investigator/ Research Personnel ___________________ Date ________________

Name of Witness (printed) ___________________ Signature of Witness ___________________ Date ________________

The University of Calgary Conjoint Health Research Ethics Board has approved this research study. A signed copy of this consent form has been given to you to keep for your records and reference.
November 28, 2013

Hi:

We are set to meet for your in person screen on **Monday at 4:00pm** In total, the testing should take about ~2-2.5 hours.

I will meet you in **4D74 on the 4th Floor of TRW** (Teaching Research and Wellness (please see directions below).

Please do not hesitate to phone us at (403) 210-6430 should you have any problems finding our location or send us an email at **brain.neuroboost@gmail.com**

**Preliminary Instructions:**

The testing will consist of two components: a clinical assessment and neurocognitive test. For the in person screen, you will be reimbursed $20 for completing the clinical assessment which will take about an hour. And if you qualify, you will receive another $20 for completing a neurocognitive test battery after the clinical assessment.

If for some reason you are unable to make the testing day, please notify us within 12 hours prior. We may reschedule the testing to a later date.

**Directions/Parking:**

**TRW Building**
3280 Hospital Dr. NW

If you are coming from 16th Ave:
- turn south on 29th St.
- turn right on Hospital Dr (first set of lights)
- proceed straight through 4way stop sign
- take bend to the left

From Memorial Dr/Parkdale Blvd:
- turn north on 29th St.
- head up the hill
- turn left at second set of lights at top of hill
- proceed straight through 4way stop sign
- take bend to left

From both directions, for parking:

Turn right onto ramp leading to Lot 14. This is the parking lot under the TRW building - which is the building we are in. Parking costs $2.25/half hour and can be paid in advance at any of the pay stations located on floors P2, P1 and G – please remember your stall number.

---

4th Floor, TRW Building, 3280 Hospital Drive N.W., Calgary, Alberta, Canada  T2N 4N1
November 28, 2013

Hi:

We are set to meet for a Fitness Appraisal on **Friday June 7 at 1:45pm**. In total, the testing should take no longer than 45 minutes to complete. I will meet you at the front desk of Kinetix Fitness & Wellness Centre (please see directions below).

**Preliminary Instructions:**
Here is a list of preliminary instructions for the Fitness Appraisal that I need you to follow before we meet to ensure standardization of the testing:

- no food within 2 hours prior to our appointment
- no smoking tobacco products within 2 hours prior to our appointment
- no heavy exercise, alcoholic beverages, or **caffeinated beverages** within 6 hours prior to our appointment.

The testing will consist of two components: a body composition portion, in which we will measure your height, weight, Body Mass Index and waist circumference; and a cardiovascular portion, where you will perform a sub-maximal, incremental biking test, measuring your heart rate’s response to increasing workloads.

As you will be exercising, please bring or come changed (change rooms are located on-site for your convenience) wearing gym attire, including shorts, a loose fitting t-shirt, as well as comfortable running shoes.

If for some reason you are unable to adhere to the above instructions, or you are feeling ill the day of the testing, we will have to reschedule the testing to a later date.

**Directions/Parking:**
Our address is:
Kinetix Fitness & Wellness Centre
Suite 101, Floor 1, TRW Building
3280 Hospital Dr. NW

If you are coming from 16th Ave:
- turn south on 29th St.
- turn right on Hospital Dr (first set of lights)
- proceed straight through 4way stop sign
- take bend to the left

From Memorial Dr/Parkdale Blvd:
- turn north on 29th St.
- head up the hill
- turn left at second set of lights at top of hill
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From both directions, for parking:
Turn right onto ramp leading to Lot 14. This is the parking lot under the TRW building - which is the building we are in. Parking costs $2.25/half hour and can be paid in advance at any of the pay stations located on floors P2, P1 and G – please remember your stall number.

From the underground lot, take the elevators up to the ground floor, transfer elevators and take the second elevator to the 1st floor - we're just around the corner. ....or, you may also take the stairs directly to the 1st floor.

I've included a link to a map if you need:
http://www.ucalgary.ca/kinetix/files/kinetix/Main%20Map%201.pdf

Other than that, if you have any questions/comments/concerns or need to reschedule, please feel free to give me a call at (403) 220-4196 or send me an email at cdgordon@ucalgary.ca

*Please note that at least 24hrs notice is required to cancel any appointment. Cancellations within this time are subject to forfeiture of that session.

Best Regards,

Chris Gordon BSc. Kin, CSEP-CEP
Manager, Kinetix Fitness and Wellness Centre

Allegra Courtright BSc. Kin
Staff, Kinetix Fitness and Wellness Centre
Neuroscience Graduate Student
Hotchkiss Brain Institute, University of Calgary
Mathison Centre for Mental Health Research & Education
# Appendix I: MDD Fitness Assessment Record Sheets

<table>
<thead>
<tr>
<th></th>
<th>Pre-term (BASELINE) Appraisal</th>
<th>Mid-term (WEEK 8) Appraisal</th>
<th>Post-term (WEEK 12) Appraisal</th>
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Date:
APPENDIX J: AEROBIC EXERCISE INTERVENTION RECORD SHEETS

Name: ___________________ Date of Birth: ___________________ Subject ID: ___________________

EXERCISE INTERVENTION
WEEK 1 SESSION #1 (W1.S1)  DATE: ___________________
___Pre-exercise: 17-item Hamilton rating scale for depression (HAMD), Montgomery-Åsberg Depression Rating Scale (MADRS) & Multidimensional Outcome Expectations for Exercise Scale (MOEES)

<table>
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<th>W1.S2 date:</th>
<th>W1.S3 date:</th>
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<td>Notes: Rate Session (pleasant) (0-10)</td>
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WEEK 2 (W2)

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___***Clinical assessment ~20-30 min before start of W2.S3 (HAMD & MADRS)
DATE: ___________________
### WEEK 3 (W3)

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Notes:
Rate Session (pleasant) (0-10)

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Notes:
Rate Session (pleasant) (0-10)

***Clinical assessment ~20-30 min before start of W4.S3 (HAMD & MADRS)

DATE:_________________
### WEEK 5 (W5)

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Notes:
Rate Session
(pleasant)
(0-10)

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Notes:
Rate Session
(pleasant)
(0-10)

***Clinical assessment ~20-30 min before start of W6.S3 (HAMD & MADRS)
DATE:__________________________
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**Notes:**
Rate Session (pleasant) (0-10)

## WEEK 8 (W8): RE-ASSESSMENT

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**Notes:**
Rate Session (pleasant) (0-10)

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***Clinical assessment ~20-30 min (HAMD & MADRS) before start of W8.S3
DATE: _______________
***Fitness assessment
### WEEK 9 (W9)

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- Rate Session (pleasant) (0-10)

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### WEEK 10 (W10)

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Notes:
- Rate Session (pleasant) (0-10)

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***Clinical assessment ~20-30 min before start of W10.S3 (HAMD & MADRS)

DATE:___________________
### WEEK 11 (W11)

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### WEEK 12 (W12)

<table>
<thead>
<tr>
<th>Week 12</th>
<th>W12.S1/Physical Re-assessment** date:</th>
<th>W12.S2 date:</th>
<th>W12.S3 date***:</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–60% of HRRes</td>
<td></td>
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<td></td>
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<tr>
<td>HR Max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR Min</td>
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<tr>
<td>HR Mean</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise of choice &amp; duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Notes: Rate Session (pleasant) (0-10)</td>
<td></td>
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</tr>
</tbody>
</table>

***Clinical assessment ~20-30 min after completing exercise intervention
DATE:_________________
**Final Fitness assessment
APPENDIX K: POLAR HEART RATE MONITOR, KINETIX EXERCISE FACILITY, MRI & MRS SCANNING