

Mechanisms by which exercise promotes cognitive
function in both depressed and non-depressed individuals

by

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Abstract

Major depressive disorder (MDD) is a debilitating disease characterized by low mood, memory deficits, poor sleep quality and alterations in biochemical markers associated with neuroplasticity. Less than half of MDD patients receive an efficacious treatment, warranting the need for novel treatment strategies. Exercise as an add-on therapy is a promising approach shown to improve mood, however, its mechanism of action remains unknown. To advance our understanding of the mechanisms by which exercise affects brain function this thesis studied both healthy and MDD individuals. Study One used a functional magnetic resonance imaging (fMRI) subsequent memory paradigm to investigate the effects of an eight-week exercise intervention on neural function in healthy and MDD groups. FMRI results showed significant deactivation in the hippocampus and across several memory-associated regions in both groups suggesting a potential increase in neural efficiency. Study Two evaluated exercise as an add-on to antidepressant medication (ADM) and cognitive behavioural group therapy (CBGT) for MDD. Exercise led to a robust decrease in depression scores ($p=0.007$, $d=2.06$), with 75% of the patients achieving either response or remission compared to 25% of those who received ADM and CBGT only. Exercise also led to greater improvements in sleep quality ($p=0.046$, $d=1.28$), cognitive function ($p=0.046$, $d=1.08$) and plasma brain-derived neurotrophic factor (BDNF), $p=0.003$, $d=6.46$. Furthermore, BDNF was positively correlated with improvements in depression ($p=0.002$, $R^2 = 0.50$) and sleep quality ($p=0.011$, $R^2 = 0.38$). Study Three found that exercise for healthy, young adults did not improve cognitive performance or biomarkers, despite the neural changes seen in the fMRI study. Overall, this thesis demonstrates that exercise promotes neuroplasticity

in both healthy and MDD patients, substantially improving mood and cognitive performance in MDD. Plasma BDNF levels and sleep quality appear to be good indicators of treatment response and potential biomarkers associated with the clinical recovery of MDD.

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Statement of Contributions

This thesis presents the research of Joanne Gourgouvelis in collaboration with her thesis supervisors Dr. Bernadette Murphy and Dr. Paul Yelder. The sum of this work resulted in the following contributions to the literature.

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Tables of contents

Abstract.....	i
Acknowledgements	iii
Statement of Contributions.....	v
Tables of contents.....	vi
List of Figures.....	ix
List of Tables	xi
List of abbreviations	xii
Chapter 1 - Introduction	1
1.1 Statement of the problem and general thesis objectives	1
1.2 Review of the literature.....	4
1.2.1 Depression statistics	4
1.2.2 Major Depressive Disorder	5
1.2.3 Depression and cognitive impairment.....	6
1.2.4 Neural correlates of episodic memory	11
1.2.5 Alterations in brain structure and function in MDD	17
1.2.6 Mechanisms associated with depression.....	20
1.2.7 Current therapies for depression	36
1.2.8 Effects of exercise	39
1.3 Conclusions.....	46
1.4 Research objectives: research questions and hypotheses	48
1.4.1 Study 1: Research objectives, questions and hypotheses	48
1.4.2 Study 2: Research objectives, question and hypotheses.....	50
1.4.3 Study 3: Research objectives, questions and hypotheses	52
Chapter 2: Exercise Promotes Neuroplasticity in Both Healthy and Depressed Brains: An fMRI Pilot Study	54
2.1 Abstract.....	54
2.2 Introduction.....	55
2.3 Materials and Methods.....	57
2.3.1 Participants	57
2.3.2 Psychometric Evaluation.....	58
2.3.3 Fitness Assessment.....	58
2.3.4 Exercise Intervention.....	59
2.3.5 Statistical Analysis	61
2.3.6 Associative Memory Task.....	61
2.3.7 fMRI Scanning Parameters	63
2.3.8 fMRI Analysis	64
2.4 Results.....	65
2.4.1 Baseline Characteristics	65
2.4.2 Psychometric, memory and fitness results	66
2.4.3 fMRI results.....	67
4. Discussion.....	72

5. Limitations	77
6. Future Research	78
2.8 References.....	81
Connecting statement I.....	94
Chapter 3: Exercise leads better clinical outcomes in those receiving medication plus cognitive behavioural therapy for major depressive disorder.....	96
3. 1 Abstract.....	96
3.2 Introduction.....	98
3.3 Methods	103
3.3.1 Participants	103
3.3.2 Psychometric measures: anxiety, depression, sleep quality	104
3.3.3 Cognitive measures	105
3.3.4 Plasma collection.....	106
3.3.5 Fitness assessment.....	106
3.3.6 Exercise intervention.....	107
3.3.7 Statistical analysis	109
3.4 Results.....	109
3.4.1 Baseline characteristics between MDD and healthy groups	109
3.4.2 Baseline characteristics between MDD groups.....	111
3.4.3 Pre-post measures for MDD groups	111
3.5 Discussion.....	117
3.6 Limitations	120
3.7 Conclusion	121
3.8 Conflict of interest disclosure	122
3.9 Acknowledgments	122
3.10 References.....	123
Connecting statement II	135
Chapter 4: You can't fix what isn't broken: Effects of eight weeks of exercise on cognitive function and biochemical markers in young and healthy adults	136
4.1 Abstract.....	136
4.2 Introduction.....	137
4.3 Methods	141
4.3.1 Participants	141
4.3.2 Neuropsychological measures	141
4.3.3 Plasma collection.....	143
4.3.4 Fitness assessment.....	144
4.3.5 Exercise prescription	144
4.3.6 Statistical analysis	146
4.4 Results.....	146
4.4.1 Baseline characteristics between groups	146
4.4.2 Pre-post measures.....	147
4.5 Discussion.....	149
4.6 Limitations	152
4.7 Conclusion	153
4.8 Conflict of interest disclosure	153

4.9 Acknowledgments	153
4.10 References.....	154
Chapter 5: General Discussion	162
5.1 Limitations	166
5.2 Future directions	167
5.3 Clinical implications	168
5.4 Qualitative observations	169
References.....	172
Appendix 1: BDI	211
Appendix 2: HADS	213
Appendix 3: MoCA.....	214
Appendix 4: PSQI	215
Appendix 5: Saliva collection instructions.....	219
Appendix 6: Resistance exercises	220
Appendix 7: Pre-scanning questionnaire.....	225
Appendix 8: MRI safety form.....	226
Appendix 9: Par-Q & You	227
Appendix 10: ParMED-X.....	228
Appendix 11: Consent forms	229

List of Figures

- Figure 1. 1 - Anatomy of the medial temporal lobe (MTL): This represents a sagittal segmented MTL: amygdala (blue), hippocampus (brown), anterior parahippocampus (dark brown), posterior parahippocampus (gold), perforant path (white) Adapted from: (Seidman, Rosso et al. 2014). 12
- Figure 1. 2 - Histology-derived volumetric annotation of the human hippocampal subfields in postmortem MRI. Abbreviations: CA=cornu ammonis; DG=dentate gyrus; SUB=subiculum; SRLM-HS=stratum radiatum, lacunosum-moleculare, and hippocampal sulcus (Adler, Pluta et al. 2014)..... 12
- Figure 1. 3 - Schematic illustration of the medial temporal lobe memory system. The perirhinal and parahippocampal cortices receive projections from unimodal and polymodal regions in the frontal, temporal, and parietal lobes. Two-thirds of the cortical input to the entorhinal cortex is received from the perirhinal and parahippocampal cortices which are the main source of cortical input to the hippocampal formation. The entorhinal cortex also receives other direct inputs from orbital frontal cortex, cingulate cortex, insular cortex and superior temporal gyrus (Adapted from Zola-Morgan, Squire & Ramus, 1994). 13
- Figure 1. 4 - Schematic illustration of the unidirectional trisynaptic neural circuitry involved for the processing of information processing by the hippocampus. The main input to the hippocampus is from the entorhinal cortex that projects to the DG and CA3 pyramidal neurons via the perforant path. CA3 neurons receive input from the DG via the mossy fibres. The CA3 projects to the CA1 pyramidal cells via the Schaffer collateral pathway. CA1 neurons receive input from the perforant path and project back to the entorhinal cortex forming a loop..... 15
- Figure 2. 1 - (A) During the encoding task, participants viewed 240 face name pairs over two nine minute fMRI runs. Participants were asked if they thought the name suited the face and responded using a response box. Each run included 120 face name pairs presented for a duration of 3000 ms, jittered with 34 fixation crosses ranging from 3000-9000 ms in increments of 3000 ms. (B) The retrieval task was then performed on a laptop computer outside the MR scanner. Participants were instructed to choose which of the two names was originally paired with the face shown and then asked if they were confident with their choice. This was used to identify the correct successful encoding trials as remembered (correct) vs lucky guesses..... 63
- Figure 2. 2 - (A) Regions within the hippocampus found to be active in the correct > incorrect contrast for both Healthy and MDD at baseline, used as an ROI to extract Beta values for an analysis of activity in the hippocampus. (B) Beta values for correct > incorrect from both groups at pre-treatment and post-treatment. Both groups showed a reduction in hippocampal activity within the bilateral ROI following exercise. Error bars represent standard error..... 70

Figure 2. 3 - Pre to post changes in neural activity in the correct > incorrect contrast (parried-samples t-test). Decreases in activity following exercise were noted in several regions, irrespective of group. 71

Figure 2. 4 - Pre-post changes found a negative relationship between changes in depression scores and activation in the right occipital, left occipital/fusiform and left precentral gyrus, irrespective of group. 72

Figure 3. 1 - Individual group plots illustrating pre-post changes for (A) BDI depression scores, (B) PSQI scores and (C) BDNF levels. Abbreviations: CBGT=cognitive behavioural group therapy; BDI=Beck Depression Inventory; PSQI=Pittsburgh Sleep Quality Inventory; BDNF=brain-derived neurotropic factor..... 116

Figure 3. 2 Responders, non-responders and remissive MDD patients at 8 weeks for each group. Benefit of exercise was greater as defined by treatment response and remission (N=6) compared to (N=2) in the non-exercise group. Responders represent patients with a greater than or equal to a 47% reduction BDI score at 8 weeks compared to baseline and remission represents patients with a BDI score less than or equal to 11. Abbreviation: CBGT=cognitive behavioural group therapy 117

Figure 3. 3 A) Linear regression of pre-post changes for BDI and PSQI scores against BDNF change, irrespective of group. (A) A significant negative correlation was found for (A) BDI scores and BDNF levels ($p=0.002$, $R^2 = 0.50$) and (B) PSQI scores and BDNF levels ($p=0.011$, $R^2 = 0.38$) indicating that improvements in depression and sleep quality scores are associated with an increase in BDNF levels. Abbreviations: BDI, Beck Depression Inventory, BDNF, brain-derived neurotropic factor, PSQI, Pittsburgh Sleep Quality Index 117

Figure 4. 1 - Group plots illustrating pre-post biomarker changes for (A) plasma BDNF concentrations, (B) plasma CTHB concentrations. Abbreviations: BDNF=brain-derived neurotropic factor; CTHB=cathepsin B 148

Figure 4. 2 - Group plots illustrating pre-post CANTAB changes for (A) DMS, (B) PAL, (C) SRM, (D) IED. Abbreviations: DMS=delayed matching to sample; PAL=paired associates learning; SRM= spatial recognition memory; IED= intra-extra dimensional set shift 149

Figure 5. 1 - Converging mechanisms associated with MDD and exercise on neural function: Previous and current findings149

List of Tables

Table 2. 1 - Baseline characteristics of participants	66
Table 2. 2 - Results of pre-post changes for depression scores, cognitive assessment, memory performance, body mass index and fitness	69
Table 2. 3 - Brain regions showing pre-post changes in activity for the correct > incorrect, irrespective of group	71
Table 2. 4 - Regions showing decreased activation associated with depression, irrespective of group	72
Table 3. 1 - Baseline characteristics of depressed patients and healthy controls	113
Table 3. 2 - Baseline characteristics of depressed groups	114
Table 3. 3 - Pre-post changes for depressed groups.....	115
Table 4. 1 - Baseline characteristics of participants	147
Table 4. 2 - Pre-post changes for BMI and VO ₂ max	147

List of abbreviations

ADM	Antidepressant medication
ACTH	Corticotropin hormone
AVP	Vasopressin
BBB	Blood-brain barrier
BDI-II	Beck Depression Inventory – second edition
BDNF	Brain-derived neurotrophic factor
BOLD	Blood oxygenation level-dependent
CA	Cornu ammonis
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBT	Cognitive behavioural therapy
CBGT	Cognitive behavioural group therapy
CRH	Corticotropin-releasing hormone
CTHB	Cathepsin B
CBGT	Cognitive behavioural group therapy
CAR	Cortisol awakening response
CNS	Central nervous system
DG	Dentate gyrus
DMS	Delayed matching to sample
ECT	Electroconvulsive therapy
ELISA	Enzyme-linked immunosorbent assay
EPI	Echo-planar image
ERN	Error-related negativity
ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
FOV	Field of view
GABA	Gamma-aminobutyric acid
GAIN-SS	Global Appraisal of Individual Needs – Short Screener
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale - Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression

HC	High-confidence
HR	Heart rate
HPA	Hypothalamic-pituitary-adrenal
IED	Intra–extra dimensional set shift
IGF	Insulin growth factor
IL-1 β	Interleukin 1 beta
IL-1ra	Interleukin 1 receptor antagonist
IL-6	Interleukin 6
IL-10	Interleukin 10
IFN- γ	Interferon gamma
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen activated protein kinase
MDD	Major depressive disorder
MDE	Major depressive episode
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NFTA	Nuclear factor of activated T-cells
NMDA	N-methyl-D-aspartate
P75 ^{NTR}	Pan-neurotrophin receptor 75
PAL	Paired associates learning
PAR-Q	Physical Activity Readiness Questionnaire
PARmed-X	Physical Activity Readiness Medical Examination
PFC	Prefront cortex
PSQI	Pittsburgh Sleep Quality Index
PVN	Paraventricular nucleus
REB	Research ethics board
ROI	Region of interest
RPE	Rating of Perceived Exertion
SCID-I	Structural Clinical Interview for DSM-IV Axis I Disorders

SOS	Salimetrics® Oral Swab
SPM	Statistical parametric mapping
SRM	Spatial recognition memory
SSRI	Selective serotonin reuptake inhibitor
SWA	Slow-wave activity
TE	Echo time
TR	Repetition time
TNF- α	Tumor necrosis factor alpha
VEGF	Vascular endothelial growth factor
VO2 max	Maximal oxygen uptake

Chapter 1 - Introduction

1.1 Statement of the problem and general thesis objectives

The effects of Major Depressive Disorder (MDD) are profound and far-reaching, being one of the leading contributors to the global burden of disease (WHO, 2008). MDD is a common (Patten, Williams et al. 2015), costly (Patten and Beck 2004), and highly recurrent disorder (Belsher and Costello 1988), that is associated with significant morbidity and mortality rates (Wells, Stewart et al. 1989, Fawcett 1993, Harris and Barraclough 1998, Ustun, Rehm et al. 1999). Despite many efforts to develop effective antidepressant therapies, depression remains a severely undertreated and under recognized disorder in the primary care setting (Shelton 2006). It has been estimated that only half of depressed Canadians seek medical treatment and of those, less than half receive an efficacious treatment (Andrews, Sanderson et al. 2000, Patten and Beck 2004). Moreover, a recent meta-analysis raised the possibility that the side effects associated with antidepressant medication (ADM) may outweigh the small therapeutic effects in many individuals (Jakobsen, Katakam et al. 2017). As such, the role of a non-pharmacologic treatment option for depression in becoming increasingly important.

Exercise is a treatment option with proven benefits in the treatment of MDD, however, its mechanism of action remains unknown. To fully understand the magnitude of effects of exercise and to capitalize on the full treatment potential of exercise in depressed populations, we must first identify physiological mechanisms that are specific to depression. Currently, there is a shortage of reporting sedentary behaviour, physical activity levels and cardiovascular fitness parameters in the depression literature. As such,

some of the physiological differences observed in studies comparing depressed individuals to healthy controls might be confounded by an inactive lifestyle, which is more prevalent in depressed populations (Appelhans, Whited et al. 2012). There is an extensive body of literature from both elderly humans and animals that have identified mechanisms associated with neuroplasticity and cognitive function that are also associated with the onset and recovery of MDD. It is therefore critical that we understand the impact of physical activity and cardiorespiratory fitness levels on neural function in those with MDD as well as healthy individuals in order to delineate physiological mechanisms unique to depression and independent of physical activity levels. Once we understand why and how exercise works to alleviate symptoms in MDD, we will be able to better prescribe exercise, identify patients who will benefit from exercise, and develop more efficacious ADMs or combination of pharmaceutical agents that target these mechanisms.

The primary goal of this PhD thesis was to determine the mechanisms by which exercise as an add-on therapy to ADM and cognitive behavioural group therapy (CBGT), improves the symptoms of those with MDD. To identify unique biomarkers associated with MDD, independent of physical activity and fitness variables, this study investigated the effects of exercise in both MDD patients and healthy individuals who were considered low active and cardiorespiratory unfit. This study will add further insight into the pathophysiology of MDD as well as indicators that are associated with treatment response from exercise. Accordingly, this study used a multidisciplinary approach using a combination of neuroimaging, biochemical analyses and behavioural assessments to measure the effects of exercise on depressive symptoms, neural function, cognitive

function and sleep quality, and to identify putative biomarkers related to treatment response. This study also explored the neural effects of exercise in young and healthy adults who were considered low active and with low levels of cardiorespiratory fitness, to provide normative values for comparison and to contribute knowledge to this sparse area in the literature.

This thesis research will significantly advance knowledge, as it is the first to use a combination of functional neuroimaging, biochemical analyses and behavioural measures to measure changes in brain function following a structured, supervised exercise intervention in people with MDD undergoing antidepressant therapy. By correlating changes in neural activity with clinical changes, and changes in biochemical markers shown to be altered in MDD, it will add to our understanding of which biomarkers are most predictive of improved cognitive function. This study will also distinguish which biomarkers change with ADM plus psychotherapy plus exercise versus ADM plus psychotherapy. Importantly, this research will begin to elucidate how exercise affects young and healthy adults and will help determine whether exercise has an effect on brain function before the onset of any age-related neurodegeneration.

Overall, this research project will create a more solid literature base for multi-disciplinary research approaches in the future. Ideally, it may be possible to use a patient's biochemical and clinical signature to determine which combination of exercise, pharmacotherapy and/or psychological interventions are required to maximize treatment outcomes. This work has the potential to provide a tool to improve exercise prescription and to guide the development of a holistic treatment approach to optimize clinical outcomes for MDD in Canada.

1.2 Review of the literature

1.2.1 Depression statistics

Major depressive disorder (MDD) is an international public-health problem and considered the most prevalent and most cumbersome to treat of all psychiatric disorders. Depression is currently the second leading cause of disability worldwide and is projected to be the leading cause by the year of 2020 (Ferrari, Charlson et al. 2013). The economic burden of depression in Canada has been estimated at over 32 billion dollars annually (Stonebridge and Sutherland, 2016), and is associated with an approximately 50% increase in healthcare costs when comorbid with a chronic medical illness (Katon 2003). The lifetime prevalence rate of a major depressive episode (MDE) is 11%, with the rate for women nearly double the rate for men (Patten, Williams et al. 2015). Depression is associated with negative health habits, such as smoking, substance abuse, poor diet, a physically inactive lifestyle and noncompliance with medical treatment (Farmer, Locke et al. 1988, Patton, Carlin et al. 1998, DiMatteo, Lepper et al. 2000, Hasin, Goodwin et al. 2005, Appelhans, Whited et al. 2012). There is also strong evidence that depression plays a role in the aetiology of other medical illnesses including coronary heart disease (Whang, Kubzansky et al. 2009), type 2 diabetes (Pan, Lucas et al. 2010), decreased bone density (Williams, Bjerkeset et al. 2011), peptic ulcers (Scott, Alonso et al. 2013), obesity (Onyike, Crum et al. 2003) and death due to unnatural causes (Wulsin, Vaillant et al. 1999). Furthermore, depression when comorbid with other chronic diseases has been shown to worsen health outcomes compared with any combination of chronic diseases without depression (Moussavi, Chatterji et al. 2007).

Depression is a severely undertreated and under recognized disorder in the primary care setting (Diverty and Beaudet 1997). It seems that many patients feel the stigma of seeking treatment is greater than the stigma of living with the disorder (Mojtabai and Olfson 2006). It has been estimated that only 56% of depressed Canadians seek medical treatment (Patten and Beck 2004). Of those patients who so seek medical help for their depression, only 32% receive an efficacious treatment (Andrews, Sanderson et al. 2000). It has also been estimated that over 40% of depressed patients who do achieve partial or full remission of their disease, continue to experience residual symptoms putting them at greater risk for relapse (Fava et al., 2006; Paykel et al., 1995). Taken together, it is critical that depression is a considered public-health priority that must consider innovative and more cost-effective interventions to lessen its burden (Ferrari, Charlson et al. 2013).

1.2.2 Major Depressive Disorder

MDD is characterized by a wide range of behavioral, emotional, and cognitive symptoms, including depressed mood, anhedonia, feelings of worthlessness or guilt, suicidal ideation, changes in body weight or appetite, sleep disturbance, lack of energy, psychomotor agitation or retardation and decreased ability to think or concentrate. The Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-V) defines a MDE as a period greater than two weeks characterized by five or more of these symptoms and at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure (APA and DSM-IV 2000).

1.2.3 Depression and cognitive impairment

Cognitive impairment is present in approximately 90% of patients with MDD and is associated with poorer treatment response (Story, Potter et al. 2008, Conradi, Ormel et al. 2011). It has been reported that nearly half of the patients who achieve remission continue to experience cognitive impairment as a residual symptom of MDD (Conradi, Ormel et al. 2011) revealing an independent relationship between cognition and depression severity. The DSM-V recognizes and incorporates cognitive impairment as “diminished ability to think or concentrate” in the diagnostic criteria for MDD (APA and DSM-IV 2000). Cognitive impairments in depression are most apparent during tasks that require effortful processing and executive control (Hartlage, Alloy et al. 1993). Several meta-analyses have reported deficits in executive function, attention, cognitive processing speed, visual learning and memory in depressed populations (Zakzanis, Leach et al. 1998b, Lee, Hermens et al. 2012, Snyder 2013). However, the magnitude of cognitive impairment associated with MDD is unknown due to the variability of effects sizes and methodological inconsistencies across studies. To address these drawbacks in the literature, a recent systematic review and meta-analysis investigated the degree of cognitive impairment in patients with depression during both symptomatic and remitted states. To increase interstudy homogeneity, researchers included studies that used a specific neuropsychological test battery called the Cambridge Neuropsychological Test Automated Battery (CANTAB), to examine a broad range of cognitive domains. Results showed significant moderate effect sizes (Cohen's *d*) for deficits in executive function, memory and attention, ranging from -0.34 to -0.65 in patients experiencing depressive episodes compared to healthy controls. Results also showed significant moderate effect

sizes for deficits in attention and executive function that range from -0.52 to -0.61 , and small to moderate effect sizes for deficits in memory that range from -0.22 to -0.54 , in patients who were considered remitted (Rock, Roiser et al. 2013). These results suggest that cognitive impairment is a core and clinically important feature of depression that persists beyond symptoms of low mood. These findings also suggest there to be an underlying mechanism that is associated with cognitive function independent of depressive mood.

Behavioural evidence of impaired memory in depression

Memory impairment is the most frequently reported cognitive symptom in people with depression (Airaksinen, Larsson et al. 2004). However, research in this area has presented mixed findings in terms of the type, severity and specificity of memory deficits. One finding that has been well established is the impairment in declarative memory, particularly episodic memory (memory for a specific past experience in one's life) with a sparing of semantic memory (present knowledge of universal truths such as "the sky is blue"), and short-term memory (Burt, Zembar et al. 1995, Ilsley, Moffoot et al. 1995, Tulving and Markowitsch 1998, Zakzanis, Leach et al. 1998a, Sweeney, Kmeic et al. 2000).

Episodic memory has been defined as "the conscious recollection of previous experiences of events, happenings, and situations" (Tulving and Markowitsch 1998) that involves the binding of information about what, where and when it occurred. Research has shown that the largest deficits in episodic memory processes is the inability to bind or encode features of an event in MDD populations (Zakzanis, Leach et al. 1998a). The

most widely used test to evaluate episodic memory in MDD populations is the Autobiographic Memory Test (Williams and Broadbent 1986), in which participants are asked to retrieve specific personal memories when given an emotional cue-word. Impairments in autobiographic memory have been consistently reported (Brittlebank, Scott et al. 1993, Peeters, Wessel et al. 2002, Söderlund, Moscovitch et al. 2014), in which patients have difficulty retrieving a single remembered event and instead overgeneralize by summarizing categories of events (Williams, Barnhofer et al. 2007). More recently, episodic memory impairments in MDD have been further supported by evidence from functional neuroimaging techniques that will be later discussed.

Behavioural evidence of impaired executive function in depression

The concept of executive function is a broad term that has been defined as a “complex cognitive process requiring the co-ordination of several sub processes to achieve a particular goal” (Elliott 2003). Studies investigating executive function have mainly used tasks that assess cognitive control, inhibition, flexibility, planning, and working memory (Funahashi 2001). There is a general consensus that neural processes involved in cognitive control (the ability to coordinate thought and action in harmony with internal goals; Miller & Cohen, 2001), and cognitive flexibility (the ability to change goal states; Ravizza & Carter, 2008) underlie the impairment in executive function observed in MDD populations (Fossati, Ergis et al. 2002, Beck 2008, Lee, Hermens et al. 2012). Cognitive control is an important component of executive function as it enables focussed attention to relevant stimuli while also inhibiting interfering and irrelevant stimuli to achieve a task goal (Hasher and Zacks 1988, Gotlib and Joormann 2010). Inhibition is considered the deliberate, controlled suppression of an automatic or

prepotent response, that can interfere with the correct response (Miyake, Friedman et al. 2000). Inhibition deficiencies have been reported in those suffering with MDD (Snyder 2013). For instance, deficits in attentional control have been demonstrated in depressed patients by their difficulties with inhibiting emotionally distracting negative information (Goeleven, De Raedt et al. 2006, Joormann 2006). Inhibition deficits have also been demonstrated using emotionally neutral stimuli during reading tasks that involve ignoring semantically distracting words, in which depressed patients read more slowly and produce more errors than healthy controls. (Gohier, Ferracci et al. 2009). The Stroop task is another test that requires inhibitory control processes and is commonly used in the MDD literature. In this test participants must inhibit the inclination to produce a more automatic and incorrect response (i.e., name the colour of the word RED that is displayed in blue). Several studies have reported that depressed patients produce significantly more errors (i.e. reading the word) and are significantly slower to name the colour of incongruent colour words than healthy controls. A long-term perspective study examined inhibition in MDD patients during the symptomatic period and at six months following antidepressant therapy. Findings revealed no improvement in Stroop performance at six months despite significant improvement depressive symptoms (Hammar, SØRensen et al. 2010). These results provide further evidence that deficits in cognitive function are independent of depressive severity and persist as a residual symptom of MDD.

The Wisconsin Card Sorting Test (Heaton, Chelune et al. 1993) is set-shifting test that is widely used to examine cognitive flexibility in depressed populations. Initially, participants are required to sort cards based on dimensions of colour, shape and number of shapes on each card. After learning a dimension, negative feedback is provided

requiring participants to then to learn the new rule and switch to a different dimension. A number of studies have shown that depressed individuals make more perseverative responses and errors and show longer times to reach the first category, fewer categories, fewer conceptual-level responses and lower learning-to-learn scores than healthy controls (Channon 1996, Merriam, Thase et al. 1999, Ilonen, Leinonen et al. 2000, Must, Szabó et al. 2006). Set-shifting deficits in MDD have also been demonstrated with the Intradimensional/Extradimensional Shift task (Robbins, James et al. 1998). Like the Wisconsin Card Sorting Task, the Intradimensional/Extradimensional Shift task requires learning from negative feedback to select a visual stimulus based on one dimension, switching back to the previous stimulus (intradimensional shift), and then switching to a third stimulus dimension (extradimensional shift). Studies have shown that depressed individuals take more trials to reach the criteria for the intradimensional stage of the task and are more likely to fail the task at the extradimensional shift stage versus healthy controls (Purcell, Maruff et al. 1997, Clark, Sarna et al. 2005, Michopoulos, Zervas et al. 2006, Reppermund, Ising et al. 2009). However, it has also been argued that negative feedback provided by the Intradimensional/Extradimensional Shift task may elicit thoughts about failure that consequently disrupt performance in MDD patients (Elliott, Sahakian et al. 1996, Murphy, Michael et al. 2003).

1.2.4 Neural correlates of episodic memory

The hippocampus

In humans, the hippocampal formation is located in the medial temporal lobe (MTL) and protrudes into the temporal horn of the lateral ventricle laying along the posterior-to-anterior axis forming an arch around the mesencephalon (see Figure 1.1). Resembling the shape of a seahorse, the hippocampal formation is a bilaminar structure consisting of the hippocampal proper, the dentate gyrus (DG), the subicular complex, and the entorhinal cortex. The HF is comprised of six layers based on neuronal function: the alveus, stratum oriens, stratum pyramidale, stratum radiatum, stratum lacunosum, and stratum moleculare.. The hippocampal proper is mainly comprised of layer II, the stratum pyramidale, and is further divided into subfields of the cornu ammonis (CA1-CA3) based on different aspects of its pyramidal neurons. The DG is separated from CA1–CA3 by the hippocampal sulcus and is structurally composed of three layers: the granule cell layer (stratum granulosum), molecular layer, and the polymorphic layer (hilus). The general anatomical arrangement of the hippocampal formation can be divided into three segments; a body when sagittally oriented, an anterior (head) and a posterior (tail) region when transversely oriented, see Figure 1.2 (Duvernoy 2005, Deshmukh and Knierim 2012, Adler, Pluta et al. 2014).

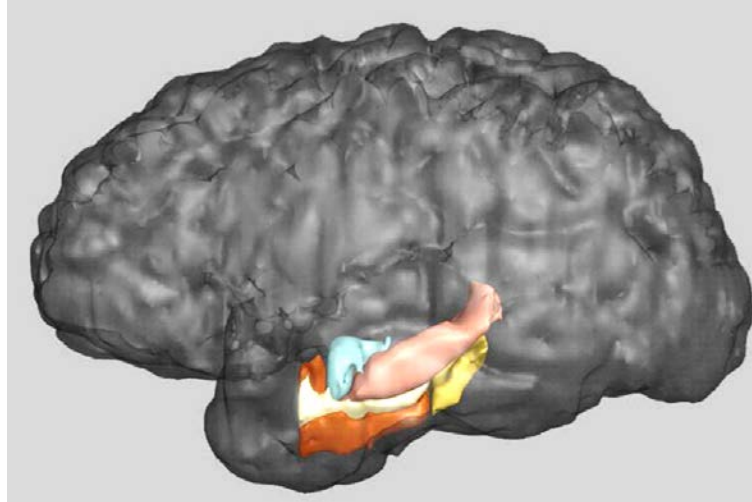


Figure 1. 1 - Anatomy of the medial temporal lobe (MTL): This represents a sagittal segmented MTL: amygdala (blue), hippocampus (brown), anterior parahippocampus (dark brown), posterior parahippocampus (gold), perforant path (white) Adapted from: (Seidman, Rosso et al. 2014).

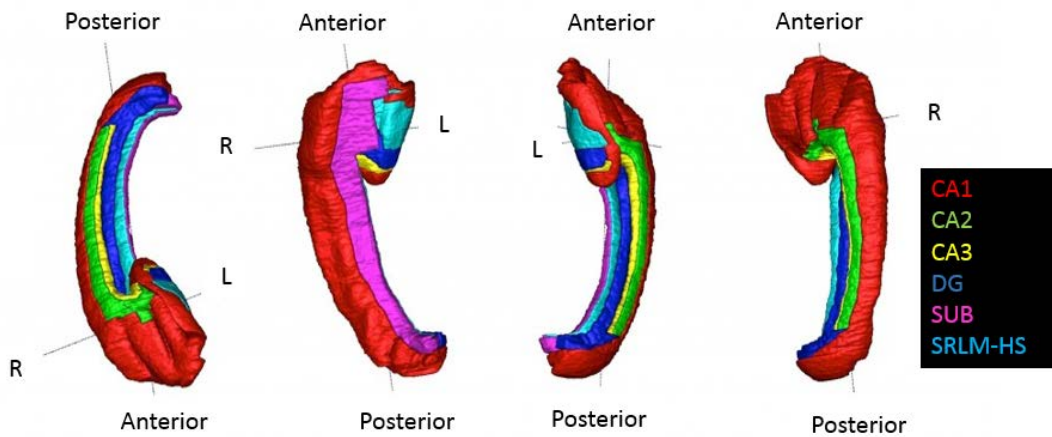


Figure 1. 2 - Histology-derived volumetric annotation of the human hippocampal subfields in postmortem MRI. Abbreviations: CA=cornu ammonis; DG=dentate gyrus; SUB=subiculum; SRLM-HS=stratum radiatum, lacunosum-moleculare, and hippocampal sulcus (Adler, Pluta et al. 2014)

Information processing within the MTL

Several lines of evidence from brain lesion studies (Mayes, Holdstock et al. 2004), electrophysiology (Shapiro and Eichenbaum 1999) and functional neuroimaging studies (Kapur, Friston et al. 1995, Henke, Buck et al. 1997, Grady, McIntosh et al. 1998) have identified the hippocampus and neighbouring cortices (perirhinal, entorhinal, and parahippocampal) to be involved in episodic memory processing. The MTL facilitates the flow of information between the neocortex, notably the prefrontal and retrosplenial cortices, and the hippocampus (see Figure 1.3).

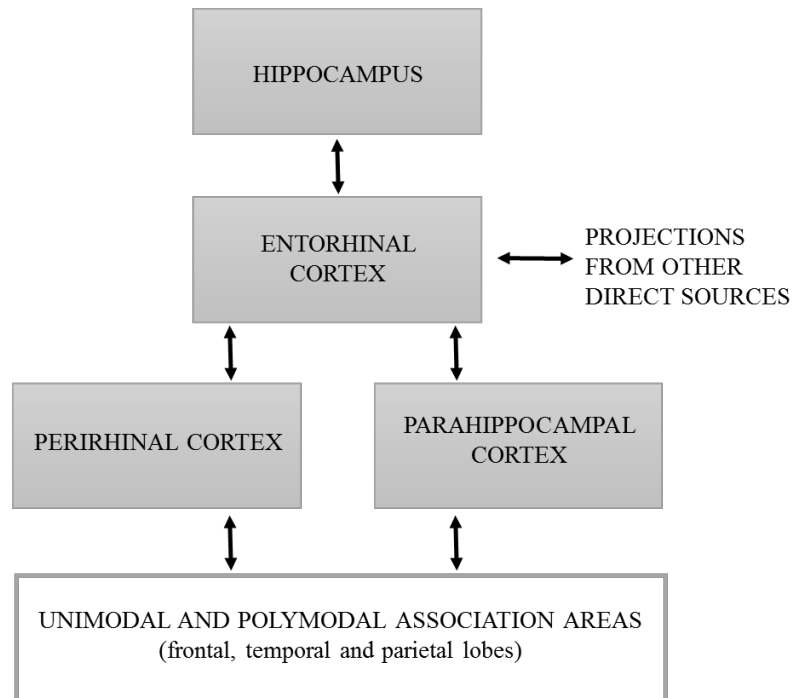


Figure 1. 3 - Schematic illustration of the medial temporal lobe memory system. The perirhinal and parahippocampal cortices receive projections from unimodal and polymodal regions in the frontal, temporal, and parietal lobes. Two-thirds of the cortical input to the entorhinal cortex is received from the perirhinal and parahippocampal cortices which are the main source of cortical input to the hippocampal formation. The entorhinal cortex also receives other direct inputs from orbital frontal cortex, cingulate

cortex, insular cortex and superior temporal gyrus (Adapted from Zola-Morgan, Squire & Ramus, 1994).

The trisynaptic pathway is the primary neural circuit involved in the feed-forward flow of information processing by the hippocampus. The entorhinal cortex is a major source of cortical sensory information that the hippocampus uses to perform its functions. In sequence, the entorhinal cortex is the main excitatory neuron output to the hippocampus, with the strongest projections passing through the perforant path to the DG. The DG is the major termination of projections from the entorhinal cortex and therefore considered the first step in the processing of information into episodic memory (Amaral, Scharfman et al. 2007). The DG projects a powerful excitatory output to the CA3 region via the mossy fiber pathway and the CA3 projects excitatory output to the CA1 region via the Schaffer Collateral pathway with the CA1 projecting back to the entorhinal cortex (See Figures 1.4). Subsequently passing through the hippocampus, the information to be remembered is stored in the association cortex (Yeckel and Berger 1990, Squire and Zola-Morgan 1991, Rolls and Kesner 2006, Knierim 2015).

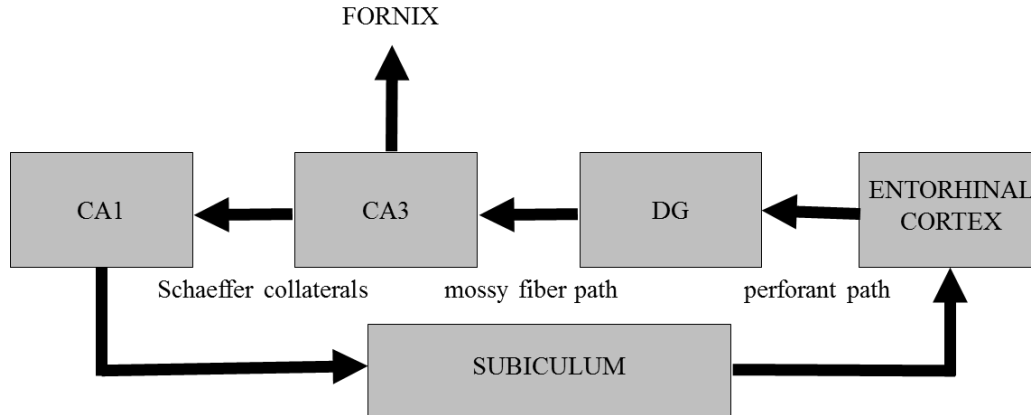


Figure 1. 4 - Schematic illustration of the unidirectional trisynaptic neural circuitry involved for the processing of information processing by the hippocampus. The main input to the hippocampus is from the entorhinal cortex that projects to the DG and CA3 pyramidal neurons via the perforant path. CA3 neurons receive input from the DG via the mossy fibres. The CA3 projects to the CA1 pyramidal cells via the Schaeffer collateral pathway. CA1 neurons receive input from the perforant path and project back to the entorhinal cortex forming a loop.

The DG granule cell system is considered a competitive learning network that removes redundant information to produce a more orthogonal, sparse, and categorised set of neural outputs to the CA3 neurons. Consequently, the DG facilitates an effective autoassociation process in the pyramidal cells of the CA3 where the learning of non-related associations are binded as one event (Norman and O'reilly 2003, Gruart, Muñoz et al. 2006, Rolls and Kesner 2006). Pattern separation is another key component of the DG, where the transformation of relatively similar input patterns into significantly different output patterns occur (Bakker, Kirwan et al. 2008). The main inhibitory control of granule cell output is provided by gamma-aminobutyric acid (GABA)ergic interneurons, that act to balance excitatory and inhibitory neural activity to enable the coordination,

separation and accurate transmission of information to the CA3 subregion (Hasselmo, Wyble et al. 1996, Duvernoy 2005, Rolls and Kesner 2006, Knierim 2015).

Although the exact function of the hippocampus in creating successful memories is not fully understood, converging evidence from animal models of amnesia (Zola, Squire et al. 2000) and neuroimaging studies in humans (Köhler, Moscovitch et al. 2000, Heckers, Weiss et al. 2002, Sperling, Chua et al. 2003, Kirwan and Stark 2004, Bray 2014) have found the hippocampus to play an essential role in the encoding and retrieval process of episodic memories. During memory encoding, the hippocampus plays an important role in creating new associations between previously unrelated items of information into an integrated memory trace that can be subsequently retrieved (Squire 1992, Eichenbaum, Schoenbaum et al. 1996, Davachi and Wagner 2002, Konkkel, Warren et al. 2008). The subsequent memory paradigm is an event-related functional magnetic resonance imaging (fMRI) method and a powerful tool to identify neural correlates of memory that identifies brain activity elicited during episodic memory encoding that is associated with successful subsequent memory retrieval. Specifically, the subsequent memory effect is a measure of neural activity during memory encoding that is correlated with later remembered items. Studies using this approach have provided evidence that the hippocampus mediates the relational binding of items into a cohesive memory trace so that the event can be later retrieved (Wagner 1998, Davachi and Wagner 2002, Paller and Wagner 2002). Furthermore, fMRI investigations have reported robust subsequent memory effects in the anterior hippocampal region that include the CA2, CA3 and the DG region during encoding of face-name pairs (Sperling, Chua et al. 2003, Zeineh, Engel et al. 2003, Fairhall, Sharma et al. 2010)

The prefrontal cortex (PFC)

Episodic memory is associated with a widespread network of brain regions such as the MTL and PFC (Cabeza and Nyberg 2006, Eichenbaum, Yonelinas et al. 2007, Dickerson and Eichenbaum 2010, Dietsche, Backes et al. 2014). The PFC is strongly connected with MTL structures and thought to govern the basic processes of the MTL (Spaniol, Davidson et al. 2009). Subregions within the PFC activate cognitive control processes that augment memory processes such as the selection and organization of information at encoding, directing search at retrieval, and the appraisal of memories to ensure they align with task goals (Moscovitch and Winocur 2002, Blumenfeld and Ranganath 2007). A meta-analysis investigation demonstrated that both episodic encoding, as measured in the subsequent-memory paradigm and retrieval success were associated with activation in the parietal, medial-temporal, and prefrontal regions. Notably, the ventrolateral PFC and medial-temporal regions were strongly involved during memory encoding, whereas the superior parietal and dorsolateral and anterior PFC regions were strongly involved in memory retrieval (Spaniol, Davidson et al. 2009).

1.2.5 Alterations in brain structure and function in MDD

Structural brain changes in depression

Alterations in brain structure have been implicated in the pathophysiology of MDD (Drevets, Price et al. 2008, Fitzgerald, Laird et al. 2008). Among the MDD literature, reduced volume of the PFC and hippocampus are the most consistently reported findings (Videbech and Ravnkilde 2004, Hickie, Naismith et al. 2005, McKinnon, Yucel et al. 2009, Savitz and Drevets 2009). Volumetric reductions in these brain regions have been

negatively correlated to both number of depressive episodes and illness duration (Sheline, Wang et al. 1996, Sheline, Sanghavi et al. 1999, MacQueen, Campbell et al. 2003, Treadway, Waskom et al. 2015). Meta analyses have reported hippocampal volumes to be approximately 4-8% smaller in patients with MDD compared to healthy controls (Campbell, Marriott et al. 2004, Videbech and Ravnkilde 2004, McKinnon, Yucel et al. 2009, Cole, Costafreda et al. 2011). Animal models of depression and post-mortem studies investigating brain tissue from clinically depressed subjects, have also revealed alterations at the neural level, such as dendritic atrophy, reduction in glial numbers, and glial densities in both the PFC and the hippocampus (Öngür, Drevets et al. 1998, Rajkowska, Miguel-Hidalgo et al. 1999, Sousa, Lukoyanov et al. 2000, Cotter, Mackay et al. 2002, Chana, Landau et al. 2003, Stockmeier, Mahajan et al. 2004, Banasr, Dwyer et al. 2011).

Functional alterations in depression

Considering the large number of studies investigating the structure of the hippocampus in MDD, very few neuroimaging studies have investigated the functional integrity of the hippocampus in this group during a hippocampal-dependant task. Considering also that MDD is associated with attentional bias toward negative emotional stimuli and enhanced memory for negative events (Leppänen 2006), there is a shortage of studies using emotionally neutral stimuli. As such, it remains unclear as to whether the neural dysfunction observed in MDD is one of hippocampal hyperreactivity or hyporeactivity. To investigate hippocampal function during the encoding and retrieval processes in MDD patients, Werner et al. (2009) used an event-related fMRI subsequent memory paradigm of emotionally neutral stimuli. During the encoding phase, participants

were instructed to learn several face-occupation associated pairs. During the retrieval phase, only the faces from the encoding trials were presented and participants were instructed to indicate the occupation that was paired with each face during the learning phase. Results showed that MDD patients and healthy controls did not differ in either performance or hippocampal activity during the encoding or retrieval of remembered or forgotten trials (Werner, Meindl et al. 2009). A similar fMRI subsequent memory paradigm examined hippocampal integrity exclusively during the encoding of a neutral face-name associative memory task (Fairhall, Sharma et al. 2010). Although groups did not differ in performance and there was no main effect of group in the hippocampus, researchers observed a distinct activation pattern in the anterior hippocampal region during the encoding of successfully remembered items in the healthy controls that was absent in those with MDD. Researchers interpreted these findings as a breakdown in memory-related hippocampal function (dysregulation) rather than hypo- or hyperactivation of the hippocampus. This study also revealed greater activity in the intraparietal cortex during successful encoding in MDD patients compared to the healthy controls, suggesting MDD patients used compensatory mechanisms to complete the task (Fairhall, Sharma et al. 2010). In agreement with the Fairhall et al. study, Dietsche et al. (2014) used an fMRI subsequent memory paradigm of emotionally neutral face-sex pairs. Findings revealed both poorer performance and lower levels of hippocampal activity in MDD patients during the encoding of remembered items compared to healthy controls. Also, the healthy controls showed a strong association between hippocampal and parahippocampal activation during memory encoding and subsequent memory performance that was absent in the MDD patients. However, MDD was associated with

increased activity in the right inferior frontal gyrus during retrieval, suggesting compensatory brain regions were recruited to perform the cognitive task (Dietsche, Backes et al. 2014). Compensatory brain mechanisms counteract age-related neural decline in which there is a reorganization of neurocognitive networks so that additional brain resources are activated to ‘compensate’ for the deficit (Cabeza, Anderson et al. 2002, Ward 2006, Park and Reuter-Lorenz 2009). Further support for compensatory brain mechanisms in MDD are characterized by increased activity in the lateral PFC during the *n*-back working memory task (Harvey, Fossati et al. 2005, Matsuo, Glahn et al. 2007), Stroop task (Banich, Milham et al. 2000, Wagner, Sinsel et al. 2006), delayed match-to-sample working memory task (Walter, Wolf et al. 2007) and Tower of London planning task (Fitzgerald, Srithiran et al. 2008).

Altogether, MDD is associated with a dysregulation of cognitive neural networks, particularly those involved with episodic memory and executive function. However, the relationship between MDD and cognitive function remains unclear partly due to the heterogeneity across patient samples and study designs. Since many studies fail to assess or control for variables such as age, comorbidity, depressive subtype, symptom severity, illness duration and medication, and the effects of increased sedentary lifestyles in depression, more research is needed to differentiate the effects of each of these variables (Snyder 2013).

1.2.6 Mechanisms associated with depression

Given the extensive range of symptoms and comorbidities associated with MDD, there have been significant challenges for both the diagnosis and development of

efficacious therapies. Further, we do not yet understand the pathophysiology of this disorder due to the heterogeneous nature and multimodal biological mechanisms shown to be associated with the disorder.

1.2.6.1 Neuroplasticity

The relationship between the cognitive deficits and structural and functional alteration in the hippocampus in MDD remains elusive (Werner, Meindl et al. 2009). The animal literature has provided insight to our understanding of both the neuroplastic changes that occur within the brain when exposed to stressful environments and the biological mechanisms that underlie these changes. The hippocampus is an extremely adaptive brain structure that undergoes rapid plasticity at the molecular, cellular, structural and functional levels in response to stimuli (DeCarolis and Eisch 2010). A remarkable feature of the hippocampus is the ability of the subgranular zone in the DG to generate new neurons throughout the lifespan (Gould, Beylin et al. 1999, Ming and Song 2005, Leuner, Gould et al. 2006). The rodent literature has shown that these newly generated cells correlate with hippocampal-dependent memory performance (Drapeau, Mayo et al. 2003) and when neurogenesis is experimentally interrupted hippocampal-dependent memory becomes impaired (Winocur, Wojtowicz et al. 2006). Animal studies have also demonstrated the capacity of hippocampal neurogenesis in altered environments. For example, environmental enrichment including increased living space, social interaction, and physical activity increase cell proliferation and cell survival time for newly generated hippocampal neurons (Gould, Beylin et al. 1999, van Praag, Kempermann et al. 1999, Deng, Aimone et al. 2010). On the other hand, rodents that are exposed to chronic stress exhibit volumetric reductions of the hippocampus similar to that

seen in MDD (Sapolsky 2000, Czéh, Michaelis et al. 2001). At the cellular level, chronic stress is associated with a reduction in neurons, neuronal atrophy, dendritic retraction and decreased capillary density within the DG (Watanabe, Gould et al. 1992, Czéh, Abumaria et al. 2010). Physiologically, chronic stress has also been shown to alter the synaptic transmission in the hippocampus while also improving spatial learning and memory (Sousa, Lukoyanov et al. 2000). Synaptic plasticity is displayed by long-term potentiation (LTP) that occurs predominately in the hippocampus, and considered to be a critical mechanism that facilitates the formation of learning and memory (Bliss and Collingridge 1993). Evidence from animals has shown that chronic stress induces a site-specific suppression of LTP in the medial perforant input to the DG altering the flow of information through the trisynaptic circuit of the hippocampus. (Pavlidis, Nivón et al. 2002).

Dysregulation of hippocampal function and the ability for neuroplasticity partly underlie the cognitive impairments observed in MDD. Playing a central role in episodic memory, the hippocampus is also a key regulator of PFC function that work cooperatively together to regulate explicit memory (Pittenger and Duman 2007). As such, disruption of hippocampal function likely contributes to the deficits in executive function as previously described. Several cellular and molecular mechanisms that regulate different aspects neuroplasticity have also been implicated in pathophysiology of MDD and will be further discussed.

1.2.6.2 The hypothalamic pituitary adrenal (HPA) axis in MDD

Chronic stress is known to be a strong causal factor in the onset of depression (Kendler, Karkowski et al. 1999). Too much stress and increased cortisol is a major risk

factor for mental illness such as depression and other psychotic disorders (Brown, Varghese et al. 2004, Phillips, McGorry et al. 2006). It has been well established that a history of prolonged stressful events predict subsequent depression (Kessler 1997) and stressful events are often associated with the onset of MDD (Kendler, Thornton et al. 2000).

The stress response is a biochemical cascade of neurochemical reactions triggered by the HPA axis that can affect several brain structures and physiological processes (Kim and Diamond 2002). In short, the HPA axis is controlled by the hypothalamic paraventricular nucleus (PVN). The PVN synthesizes and releases corticotropin-releasing hormone (CTH) and vasopressin (AVP) which triggers the synthesis and release of corticotropin hormone (ACTH) from the pituitary which then stimulates the release of the glucocorticoids (cortisol in humans and corticosterone in rodents) from the adrenal cortex. Under normal conditions, the release of glucocorticoids to their receptors located at multiple target sites, initiate an inhibitory response for further release via a negative feedback mechanism. The hippocampus has been found to have the highest levels of glucocorticoid receptors of any brain structure and lesions on this structure are associated with excessive glucocorticoid release (Sapolsky, Krey et al. 1984). Both the hippocampus and PFC play an important inhibitory role on the regulation of the HPA axis through projections to the hypothalamus (Herman, Ostrander et al. 2005).

Cortisol is a lipophilic steroid hormone synthesized by the adrenal cortex in response to stress. Approximately 80% of cortisol is inactive and bound to cortisol-binding globulin (CBG) while the remaining 20% is free and biologically active (Le Roux, Sivakumaran et al. 2002). Free cortisol enters the saliva through passive diffusion

and active transport mechanisms (Vining, McGinley et al. 1983). Research has shown that salivary measures of cortisol tend to be more accurate and sensitive to subtle changes versus plasma or serum and considered to be a more convenient method in clinical populations (Guechot, Fiet et al. 1982, Vining, McGinley et al. 1983, Gozansky, Lynn et al. 2005).

The main function of cortisol is the stimulation of gluconeogenesis in the liver. Cortisol is also an inhibitor of the HPA and pituitary–gonadal axis and known to suppress acute inflammatory reactions of the immune system (Kleine and Rossmann 2016). Cortisol secretion follows a distinct circadian rhythm with levels peaking in the early morning and lowest in the evening. Within 30 minutes upon awakening, there is a dramatic 50-75% increase in cortisol secretion that is referred to as the cortisol awakening response (CAR; Wust et al., 2000b). The CAR represents a transition from sleep to full alertness that is a reciprocal switching between activation in cortical and sub-cortical brain regions (Pruessner, Wolf et al. 1997, Balkin, Braun et al. 2002, Clow, Thorn et al. 2004).

The CAR is considered a reliable marker of HPA axis activity as it measures the reactivity of the HPA axis in response to the natural challenge of awakening (Clow, Thorn et al. 2004). Dysfunction of the HPA axis is characterized by an abnormal CAR in often observed in MDD (Stetler and Miller 2005, Adam, Hawkley et al. 2006, Huber, Issa et al. 2006). However, the nature of CAR abnormalities observed in MDD have been inconsistent with patients showing both an exaggerated CAR (Bhagwagar, Hafizi et al. 2005, Vreeburg, Hoogendijk et al. 2009) and blunted CAR (Huber, Issa et al. 2006,

Hsiao, Yang et al. 2010, Mondelli, Dazzan et al. 2010) when compared to healthy controls.

In healthy individuals, periods of elevated cortisol are beneficial as it redistributes energy, to increase ones focus, alertness, and memory to cope with a stressful event (Krugers & Hoogenraad, 2009; McEwen & Sapolsky, 1995). However, chronically elevated levels of cortisol have deleterious effects on neuroanatomy and cognitive function. Chronic elevations of cortisol are a hallmark finding in people with MDD and also considered to be a risk factor risk for the onset of MDD (Davis, Greenblatt et al. 1987, Newcomer, Selke et al. 1999, Harris, Borsanyi et al. 2000, Sapolsky 2000, Young, Carlson et al. 2001, Brown, Varghese et al. 2004, Kim, Song et al. 2006, Krishnan and Nestler 2008). Chronically high levels of cortisol have been shown to impair memory (Bemelmans, Goekoop et al. 1996, Vythilingam, Vermetten et al. 2004, Hinkelmann, Muhtz et al. 2013), attention (Hinkelmann, Moritz et al. 2009), inhibitory control (Bora, Harrison et al. 2013), new learning and executive function (O'Brien, Lloyd et al. 2004).

The animal literature has provided evidence that chronic elevations in glucocorticoid concentrations lead to hippocampal degeneration such as, reduced cell survival, impaired neurogenesis, neuronal atrophy and impaired neural function (McEwen 2000, Sapolsky 2000, Kim and Diamond 2002). Electrophysiological studies have revealed that stress-induced elevations in corticosterone suppress synaptic plasticity which likely disrupts the flow of information through the trisynaptic circuit. Specifically, chronic elevations in corticosterone inhibits LTP in the CA1, CA3 and DG subfields and also in the medial performant input to the DG and in the commissural/associational input

to the CA3 (Pavlidis, Watanabe et al. 1993, McEwen and Sapolsky 1995, Pavlidis, Nivón et al. 2002).

The neurotoxic effects of glucocorticoids are linked to impaired glutamate clearance via glial resulting in an accumulation of glutamate at the synapse. As a result, increases in calcium produce aberrant overactivity of calcium-dependent enzymes and the generation of toxic oxygen radicals that eventually lead to neuron death (Sapolsky 2000, Lee, Ogle et al. 2002). Additionally, chronic exposure to high doses of corticosterone has been shown to down-regulate BDNF gene expression and protein concentrations in all subfields of the hippocampus (Chao and McEwen 1994, Smith, Makino et al. 1995). Consequentially, the neuroprotective effects of BDNF on cell metabolism and glutamate neurotoxicity becomes diminished, making hippocampal neurons more vulnerable to insult. Together these data suggest that chronically elevated cortisol levels have deleterious effects on neurogenesis and neural integrity and is a candidate mechanism underlying the pathophysiology of MDD (MacQueen, Campbell et al. 2003, Belmaker and Agam 2008, Dedovic, Engert et al. 2010, Mondelli, Pariante et al. 2010).

1.2.6.3 Cytokines

Early research on depression, neurodegeneration and cognitive function mainly focused on the neurotoxic effects of elevated glucocorticoids. More recently, MDD has been linked to a dysregulated immune system that is characterized by a chronic inflammatory state (Schiepers, Wichers et al. 2005). The ‘inflammatory response system’ model of major depression (Maes 1999), the ‘macrophage theory of depression’ (Smith 1991) and the ‘cytokine hypothesis of depression’ (Yirmiya, Weidenfeld et al. 1999) all imply that MDD is a psychoneuroimmunological condition in which peripheral immune

activation, via the release of proinflammatory cytokines, underlies the various behavioural and neurophysiological alterations that are associated with this disorder (Schiepers, Wichers et al. 2005).

As a component of the innate immune response, cytokines are a large and heterogeneous group of pleiotropic proteins that are the body's first line defence mechanism against tissue injury, pathogen invasion or antigenic stimulation. Released by macrophages and lymphocytes, especially helper T cells, and a variety of non-immune tissues, cytokines function as intercellular signalling mechanisms that regulate immune response. Cytokines can produce an autocrine action by affecting the cells that releases them, a paracrine action by affecting nearby cells or an endocrine action by affecting distant cells. Through receptor binding, cytokines can produce an array of responses, depending on the cytokine and target cell. Cytokines are grouped into two broad classes based on their effects on the immune response, although some can be considered both pro- and anti-inflammatory such as interleukin (IL)-6. Pro-inflammatory cytokines are released at the site of injury or infection and trigger a cytotoxic inflammatory response by attracting a host of other immune cells such as monocytes, neutrophils, and also acute-phase proteins. Anti-inflammatory cytokines attenuate inflammatory processes by inhibiting that activity of immune cells, such as replication, activation, and synthesis of other cytokines (Robles, Glaser et al. 2005, Schiepers, Wichers et al. 2005, Duque and Descoteaux 2014).

Peripheral cytokines are reasonably large hydrophilic molecules that do not freely pass through the blood-brain barrier (BBB). The animal research has demonstrated that cytokines in the circulation can enter the brain parenchyma via several pathways such as

activation of the vagus nerve, a leaky BBB, active transport, or binding to the surface of endothelial cells (Dantzer, O'Connor et al. 2008, Miller, Maletic et al. 2009, Raison, Borisov et al. 2009, Loftis, Huckans et al. 2010). Once entering the brain parenchyma, peripheral cytokines are able to bind to cytokine receptors on the surface of various cells, including microglia, astrocytes and neurons. In addition to entry from the periphery, cytokines including IL-1 β , IL-6 and tumor necrosis factor alpha (TNF- α), and their receptors, are constitutively released in the CNS, primarily by astrocytes and microglia and sometimes neurons (Maier and Watkins 1998, Schiepers, Wichers et al. 2005). Brain regions that produce and release cytokines include the circumventricular regions, hypothalamus, hippocampus, cerebellum, forebrain regions, basal ganglia, and the brainstem nuclei (Anisman and Merali 2002). Pro-inflammatory cytokines have complex and contrasting functional roles in the CNS (Miller, Maletic et al. 2009). Under normal conditions, IL-1 β , IL-6, and TNF- α are important for providing trophic support to neurons, promoting neurogenesis and synaptic plasticity (Maier and Watkins 1998, Miller, Maletic et al. 2009). However, when there is excessive and/or prolonged activation, cytokine networks within the CNS disrupt the brain parenchyma (Miller, Maletic et al. 2009). Within the CNS, microglial cells play a similar role as macrophages do in peripheral tissue being the brain's first line defense mechanism against pathogens or injury (Tilleux and Hermans 2007). Animal experiments that use direct exposure to the bacterial endotoxin lipopolysaccharide (LPS) to induce neuroinflammation have shown a robust microglial activation and release of TNF- α , IL-1 β , and interferon gamma (IFN- γ). Elevations of hippocampal TNF- α and IL-1 β , are associated with a down-regulation of BDNF expression and its receptor tyrosine kinase-B (TrkB), as well as reduced

hippocampal neurogenesis (Wu, Chen et al. 2007). Additionally pro-inflammatory cytokines, notably TNF- α and IL-1 β , potentiate glutamate excitotoxicity through inhibition of glutamate uptake by astrocytes (Tilleux and Hermans 2007). However, blocking glutamate receptors with a *N*-methyl-*D*-aspartate (NMDA) receptor antagonist has been shown to protect neurons against neuroinflammatory insult (Willard, Hauss-Wegrzyniak et al. 2000).

MDD is highly prevalent in patients suffering from neurodegenerative, autoimmune, and infectious diseases (Pollak and Yirmiya 2002, Rook and Lowry 2008). Evidence from experimental models that assess the acute immune response to infection in humans via administration of the endotoxin LPS, have shown increases in pro-inflammatory cytokines produce behavioural symptoms similar to those found in MDD (Reichenberg, Yirmiya et al. 2001, Dantzer, O'Connor et al. 2008, Harrison, Brydon et al. 2009, Eisenberger, Inagaki et al. 2010, Loftis, Huckans et al. 2010, Haroon, Raison et al. 2011). A dose-response effect has also been observed, in which higher pro-inflammatory concentrations produce greater depression severity (Miller, Maletic et al. 2009, Janssen, Caniato et al. 2010). Exogenous cytokine administration in patients undergoing long-term cytokine therapy have shown to produce depression-like symptoms. For instance, up to 50% of patients receiving chronic IFN- α therapy for the treatment of infectious diseases or cancer subsequently develop clinical case of depression (Musselman, Lawson et al. 2001, Capuron, Raison et al. 2003, Asnis and De La Garza 2006).

Psychological stressors can activate immune cells in both the periphery and CNS that lead to neurochemical and behavioural changes (Maier and Watkins 1998). The depression-cytokine literature has identified IL-1 β , IL-6, IFN- γ and TNF- α to be the most

reliable peripheral pro-inflammatory biomarkers in MDD (Mössner, Mikova et al. 2007). A meta-analysis that examined pro-inflammatory cytokines in MDD patients revealed that peripheral TNF- α , IL-6, and IL-1 β concentrations were all significantly elevated during the initial diagnosis phase (Howren, Lamkin et al. 2009, Dowlati, Herrmann et al. 2010). Post-mortem studies in depressed individuals who committed suicide have revealed increased IL-6 concentration in cerebrospinal fluid compared to non-depressed individuals (Lindqvist, Janelidze et al. 2009). Studies have also shown the ratio of pro- to anti-inflammatory cytokines also to be altered in MDD (Dhabhar, Burke et al. 2009). Decreased concentrations of the immunomodulatory/anti-inflammatory IL-10 cytokine and a higher IL-6/IL-10 ratio prevent the counterbalancing role of IL-10 in response to increasing IL-6 concentrations. Consequently, lower IL-10 concentrations are not able to dampen the pro-inflammatory cytokine actions of IL-6 and resolve inflammation (Dhabhar, Burke et al. 2009).

Poor sleep quality is a frequently reported symptom of MDD and has been suggested to be a strong inducer of neuroinflammation (Bryant, Trinder et al. 2004). Sleep disturbance in non-depressed individuals is associated with increased peripheral concentration of IL-6, and TNF- α , when compared to periods of uninterrupted sleep (Vgontzas, Zoumakis et al. 2004, Irwin, Wang et al. 2006, Irwin, Olmstead et al. 2016). Although there has been no study that has systematically evaluated whether elevated levels of pro-inflammatory cytokines mediate the relationship between poor sleep quality and MDD, these findings suggest that poor sleep may be a risk factor for the onset of MDD.

The pro-inflammatory signalling network is intricately connected with the HPA axis. Under normal conditions, glucocorticoids exert anti-inflammatory actions by increasing anti-inflammatory cytokine concentrations and decreasing pro-inflammatory cytokine concentrations. However, during episodes of chronic stress, pro-inflammatory cytokines disrupt glucocorticoid signalling and the negative feedback regulation of the HPA axis, which in turn exacerbates pro-inflammatory cytokine activity increasing the risk for depression (Kim, Na et al. 2016). Particularly, IL-1 β , IL-6, TNF- α and IFN- γ increase HPA axis activity and the release of glucocorticoids (Song 2002, O'Brien, Scott et al. 2004, Hayley, Poulter et al. 2005, Schiepers, Wichers et al. 2005, Dantzer, O'Connor et al. 2008). Moreover, chronic administration of IFN- α in humans has been associated with an increase in cortisol concentrations and flattening of the diurnal cortisol slope that was also associated with depressive behaviours (Raison, Borisov et al. 2008).

Normally, pro-inflammatory cytokines play an important role in providing neurotrophic support to neurons, augmenting neuroplasticity and contributing to hippocampal-dependent memory processes (Goshen, Kreisel et al. 2007b, Bernardino, Agasse et al. 2008). However, the literature has shown that during episodes of excessive and/or prolonged activation, cytokine networks within the CNS can induce an interconnected cascade of neuroplastic abnormalities underlying the pathophysiology of MDD, such as decreased neurotrophic support, decreased neurogenesis, cellular apoptosis and impaired cognitive function (Hayley, Poulter et al. 2005, Miller, Maletic et al. 2009, Dowlati, Herrmann et al. 2010). The animal literature has shown that both exogenous and endogenous (chronic stress models) increases in hippocampal IL-1 β in the DG and CA subfields result in impaired hippocampal-dependent memory, impaired LTP, reductions

in cell proliferation and increased cell atrophy (Vereker, Campbell et al. 2000, Song 2002, Avital, Goshen et al. 2003, Barrientos, Higgins et al. 2006, Goshen, Kreisel et al. 2007a, Hennigan, Trotter et al. 2007, Pickering and O'Connor 2007, Chen, Buchanan et al. 2008). Studies using *in vivo* and *in vitro* methodologies have provided evidence that depressive-like behaviours and decreases in cell proliferation through activation of IL-1 β signalling in the hippocampus are mediated via activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signalling pathway. Researchers have also demonstrated that administration of the IL-1 β receptor antagonist (ra), IL-1ra, decreases NF- κ B signalling and blocks the antineurogenic and antiproliferative actions of chronic stress (Koo and Duman 2008, Koo, Russo et al. 2010).

1.2.6.4 Brain-derived neurotrophic factor (BDNF)

BDNF is a polypeptide that is a member of the neurotrophin family of growth factors. It is broadly expressed in the mammalian brain, with high concentrations in the hippocampus (Poo 2001). BDNF is also produced in peripheral tissues including skeletal muscle and adipose tissue and is able to cross the blood-brain barrier (BBB) by a high-capacity, saturable transport system (Pan, Banks et al. 1998, Poo 2001, Klein, Williamson et al. 2011b). Known for its neuroprotective effects, BDNF promotes growth and development of dopaminergic, GABAergic, cholinergic, and serotonergic neurons and plays a critical role in a variety of neural processes including cell proliferation, neuronal survival, neurogenesis and synaptic plasticity (Poo 2001, Monteggia, Barrot et al. 2004, Autry and Monteggia 2012). BDNF also exerts excitoprotective effects that suppress glutamate-induced neurotoxicity via the activation of signalling pathways that induce the expression of antioxidant enzymes, anti-apoptotic proteins, and apoptosis inhibitor

proteins (Mattson 2008). The BDNF protein is synthesized as a pre-pro BDNF precursor that is cleaved into pro-BDNF, and subsequently cleaved into its mature form (Lessmann, Gottmann et al. 2003). The conversion of pro-BDNF to mature BDNF is not an effective process leaving a large portion of intracellular pro-BDNF uncleaved and active in the CNS (Lessmann, Gottmann et al. 2003). Activating different signalling pathways that induce opposing effects, pro-BDNF binds to its low-affinity neurotrophin receptor p75^{NTR} that promotes cell death whereas mature BDNF binds to its high-affinity TrkB receptor that promotes neural growth and survival (Roux and Barker 2002, Lu, Pang et al. 2005). Being an activity-dependent protein, BDNF expression is sensitive to electrical activity and regulated by neuronal activity via non-NMDA glutamate receptors (Zafra, Hengerer et al. 1990, Poo 2001). BDNF acts at both excitatory and inhibitory synapses and is known to facilitate LTP through the conversion of early LTP to late LTP and by enhancing subthreshold neural activity to elicit LTP (Autry and Monteggia 2012). The BDNF gene and its protein have been extensively studied and BDNF activity is considered a strong candidate mechanism underlying neurodegenerative and psychiatric disorders such as MDD.

Several studies have shown reduced peripheral BDNF concentrations in people with MDD (Shimizu, Hashimoto et al. 2003, Karege, Vaudan et al. 2005a, Lee, Kim et al. 2007, Brunoni, Lopes et al. 2008, Bocchio-Chiavetto, Bagnardi et al. 2010) with greater reductions in those who are more severely depressed (Shimizu, Hashimoto et al. 2003). Findings from post-mortem tissue studies in depressed suicide victims have revealed reduced levels of BDNF and its main receptor TrkB in regions of the hippocampus and PFC when compared to tissues from non-suicide controls (Karege, Vaudan et al. 2005a,

Ray, Weickert et al. 2011). Several studies have shown reduced BDNF concentrations in MDD patients that can be normalized by successful ADM treatment (Karege, Vaudan et al. 2005b, Piccinni, Marazziti et al. 2008). The relationship between circulating BDNF concentrations and brain structure and function has also been investigated in non-depressed populations. In elderly adults, lower BDNF concentrations are associated with reductions in hippocampal and white matter volume (Erickson, Prakash et al. 2009, Driscoll, Martin et al. 2012), poorer memory (Li, Peskind et al. 2009), poorer neuropsychological function (Gunstad, Benitez et al. 2008) and faster age-related cognitive decline (Laske, Stellos et al. 2011). Compared to healthy controls, lower BDNF concentrations correlate with cognitive deficits in schizophrenic patients (Carlino, Leone et al. 2011, Zhang, Liang et al. 2012) and in patients with type 2 diabetes (Zhen, Zhang et al. 2013).

The pro-neurogenic effects of BDNF have been consistently demonstrated in the animal literature. A single, unilateral infusion of BDNF in the rat DG, induces LTP of the medial perforant path, upregulates bilateral hippocampal neurogenesis and produces rapid antidepressant effects similar in magnitude with repeated systemic administration of antidepressant agents (Shirayama, Chen et al. 2002, Scharfman, Goodman et al. 2005, Kuipers, Trentani et al. 2016). In contrast, blockade of hippocampal BDNF signalling, has been shown to inhibit LTP, decrease neurogenesis, increase depressive behaviour and impair learning and memory (Korte, Carroll et al. 1995, Shirayama, Chen et al. 2002, Heldt, Stanek et al. 2007).

Several lines of evidence suggest there to be a more complex association for BDNF-driven neuroplasticity that is based on the imbalance between mature BDNF-TrkB

receptor signalling and pro-BDNF- p75^{NTR} receptor signalling (Castrén and Rantamäki 2010). For instance, activation of the pro-BDNF - p75^{NTR} receptor signalling pathway has been shown to induce neuronal atrophy, dendritic pruning, apoptosis and the induction of LTD. As such, excessive pro-BDNF- p75^{NTR} receptor signalling has been suggested to underlie several neurodegenerative and psychiatric conditions such as MDD (Lu, Pang et al. 2005, Martinowich, Manji et al. 2007, Yang, Je et al. 2009). In support of this hypothesis, post-mortem evidence has revealed increased levels of p75^{NTR} in the brain tissue of depressed suicide subjects versus non-suicide controls (Dwivedi, Rizavi et al. 2009). Research has indicated that reduced BDNF-TrkB signalling pathway activity is associated with MDD may be partly mediated by sequence variations within the BDNF gene. A single nucleotide polymorphism (SNP) has been identified in the BDNF prodomain region that leads to a nucleotide change from a guanine to adenine producing a valine (Val) to methionine (Met) substitution at codon 66 (val66met) that dramatically alters the intracellular trafficking and packaging of BDNF (Egan, Kojima et al. 2003). The *in vitro* data has shown that the val66met substitution affects the activity-dependent secretion of BDNF and the met BDNF protein cannot be secreted at synapses that may impede local and synapse-specific regulation by BDNF leading to impairments in hippocampal function (Egan, Kojima et al. 2003). Thus, the Met allele has been associated with impaired episodic memory, reduced hippocampal volume and abnormal hippocampal activation (Bueller, Aftab et al. 2006, Hajek, Kopecek et al. 2012, Kambeitz, Bhattacharyya et al. 2012). However, the relationship between the val66met genotype and MDD remains unclear as some studies have reported a relationship (Frodl, Schüle et al. 2007, Colle, Trabado et al. 2017) whereas others have not found a

relationship (Lang, Hellweg et al. 2005, Domschke, Lawford et al. 2010, Verhagen, Van Der Meij et al. 2010).

Taken together, the literature has consistently reported that BDNF expression is attenuated in MDD and shown to increase in response to ADM (Shimizu, Hashimoto et al. 2003). As such, many researchers have focused on BDNF as a “biomarker” in MDD and as a candidate mechanism underlying treatment response.

1.2.7 Current therapies for depression

To determine whether an antidepressant treatment has been effective, a set of criteria defining specific change points during the course of depressive illness has been established. Achieving a state of remission is the desired outcome for all antidepressant treatments. Remission is determined once a patient reaches a specific cut-off score as indicated by the depression rating scale and is characterized by the absence of depressive symptoms (Frank, Prien et al. 1991, Rush, Kraemer et al. 2006, Shelton 2006). A therapeutic response is a useful indicator that determines whether a patient is responding to treatment. Response is defined as a $\geq 50\%$ improvement from the baseline score on a recognized rating scale for depression, however, the patient is still experiencing depressive symptoms (Rush, Kraemer et al. 2006, Shelton 2006). These universal definitions also allow researchers to make cross-study comparisons enabling the ability to evaluate the efficacy of antidepressant therapies.

The first-line treatment recommendations for MDD include antidepressant monotherapy, psychotherapy, and the combination of both (Davidson 2010). In very severe cases, or in treatment-resistant MDD, the use of electroconvulsive therapy (ECT)

may be recommended. Despite high remission rates, ECT is associated with significant cognitive impairments and up to 50% of patients have a subsequent MDE relapse within 6 months following treatment (Fava and Kendler 2000, Davidson 2010, Prudic, Haskett et al. 2013). As such, ECT is considered a last-resort treatment option. Even with the availability of many pharmacological agents and psychological interventions, there are wide variations in the efficacy and tolerability of treatments that leaves many individuals undertreated (Shelton 2006).

Selective serotonin uptake inhibitors (SSRIs) are the most frequently prescribed therapeutic class of antidepressant agents. SSRIs target the monoamine neurotransmitter systems to increase signalling at the synapse through increased levels of extracellular serotonin, 5-Hydroxytryptophan (5-HT) in the synaptic cleft via the blockade of the serotonin transporter (5-HTT) on the presynaptic nerve terminals (Vaswani, Linda et al. 2003). Fundamentally, SSRIs affect the potentiation of 5-HT by the inhibition of its neuronal uptake pump. Although SSRIs have rapid immediate synaptic effects they are associated with delayed onset of clinical efficacy (Autry and Monteggia 2012) suggesting the primary mechanism of action is not antagonism of 5-HT reuptake but likely the substrates, receptors and pathways for 5-HT that underlie its therapeutic actions (Vaswani, Linda et al. 2003). The onset of action time for SSRI therapy is approximately 2 to 3 weeks (Blier and De Montigny 1994). Therefore, any immediate therapeutic effects have been ascribed to a placebo effect (Quitkin, Rabkin et al. 1987). However many patients undergoing SSRI therapy experience immediate unwanted side effects such as movement disorders, sexual dysfunction, headache, poor sleep, anorexia and nausea causing them to prematurely discontinue treatment (Vaswani, Linda et al. 2003).

CBT is also a first-line treatment for MDD that is often prescribed in combination with ADM or when ADM is contraindicated (Alexopoulos 2005, Shelton 2006). CBT focuses on identifying and changing maladaptive, dysfunctional thoughts and behaviours while engaging in enjoyable social activities. Cognitive and behavioural strategies teach the patient to monitor negative thoughts; recognize the links between cognition, mood and behaviour; assess previous experience for and against distorted automatic thoughts; substitute rational interpretations for biased cognitions and gather data to disprove dysfunctional beliefs (Beck 1979). Initially, a functional analysis is conducted to establish the features of the abnormal behaviours, emotions, and cognitions, as well as their functional relationships with each other (Arch and Craske 2009). The contribution of environmental and cultural factors to these relationships is also evaluated in order to elucidate the variables that underlie a specific problem (Arch and Craske 2009). This functional analysis then guides the therapist to develop an appropriate treatment approach. CBT interventions often consist of self-monitoring, psychoeducation, muscle relaxation, cognitive restructuring, activity scheduling, self-control techniques, social skills training, stress management and problem solving (Jarrett and John Rush 1994, Arch and Craske 2009). CBT as an add-on treatment to ADM has been shown to increase the rates of remission compared to ADM alone, with the greatest effects in those with more severe MDD (Hollon, DeRubeis et al. 2014). A meta-analysis of randomized trials examined the effects of treatment with ADM combined with CBT and ADM monotherapy in with MDD and comorbid anxiety. Researchers found a moderately large effect, Hedges' $g = 0.43$, that favoured a combined treatment approach for MDD. (Cuijpers, Sijbrandij et al. 2014).

The efficacy of CBT and SSRI therapy are comparable, with less than 50% of MDD patients who achieve remission (Thase, Entsuah et al. 2001, DeRubeis, Hollon et al. 2005, Thase, Haight et al. 2005). Consequently, more than 50% of patients continue to experience symptoms and are functionally impaired (Fava and Davidson 1996). This large portion of nonresponders imposes a significant challenge to healthcare practitioners, who must seek out additional therapeutic options in over half of their patients to achieve a therapeutic response (Rush and Trivedi 1995).

1.2.8 Effects of exercise

Exercise for the treatment of depression is a common research theme. Many studies have reported higher levels of cardiorespiratory fitness and increased habitual physical activity being associated with lower depressive symptomatology and greater emotional well-being (Martinsen 1990, Galper, Trivedi et al. 2006, Boettger, Wetzig et al. 2009, Kelley and Kelley 2012), whereas low levels of cardiorespiratory fitness being linked with an increased risk of developing MDD (Åberg, Waern et al. 2012). Exercise alone or in combination with other conventional treatments, such as pharmacotherapy or cognitive behavioural therapy have all been effective in alleviating depressive symptoms with response and remission rates for exercise being comparable to these first-line therapies (Martinsen, Medhus et al. 1985, Blumenthal, Babyak et al. 1999, Babyak, Blumenthal et al. 2000, Stathopoulou, Powers et al. 2006, Blumenthal, Babyak et al. 2007, Perraton, Kumar et al. 2010). Exercise has also been shown to improve cognitive function (Khatri et al., 2001) and sleep quality (Rethorst, Sunderajan et al. 2013) which are the two of the most frequently reported residual symptoms among patients with MDD who achieve remission (Conradi, Ormel, & de Jonge, 2011).

The beneficial effects of exercise on overall brain health have also been observed in non-depressed populations. In elderly adults with dementia, exercise has been shown to slow disease progression (Stevens and Killeen 2006) and improve overall cognitive function (Heyn, Abreu et al. 2004, Ahlskog, Geda et al. 2011). In non-demented elderly populations, aerobic exercise protects against the development of neurodegenerative diseases (Ahlskog, Geda et al. 2011), improves memory performance (Erickson et al., 2011; Voss et al., 2013) and executive function (Voss et al., 2010). Neuroimaging studies have also demonstrated the effects of exercise on brain structure and function. In schizophrenics, a three month aerobic exercise intervention increased hippocampal volume by 12% that was positively correlated with fitness, and also improved short-term memory that was positively correlated with change in hippocampal volume (Pajonk, Wobrock et al. 2010). In aging populations, an aerobic exercise intervention reverses age associated brain volume loss (Colcombe et al., 2006; Erickson et al., 2009) and increases task-related activity in attentional control regions such as the superior frontal gyrus, middle frontal gyrus and the superior parietal lobe (Colcombe, Kramer et al. 2004). More recently, an fMRI study showed that a six month aerobic exercise intervention increased neural specificity, the degree to which neural representations of different stimuli can be distinguished, and that changes in neural plasticity were positively correlated with changes in fitness (Kleemeyer, Polk et al. 2017). Another recent fMRI study showed that a six month aerobic exercise intervention decreased neural activity in the left lateral occipital cortex and right superior temporal gyrus that was associated with improved executive function during a flanker task (Hsu, Best et al. 2017).

The effects of exercise on neural structure and function have been demonstrated in the animal literature. In rodents, long-term exercise increases cell proliferation and neurogenesis in the DG (van Praag, Kempermann et al. 1999, Pereira, Huddleston et al. 2007), increases dendritic spine synapses in granule cells of the DG and the stratum radiatum of the CA1 region (Dietrich, Andrews et al. 2008), induces the formation of new blood vessels (Lopez-Lopez, LeRoith et al. 2004), and improves dendritic morphology in the hippocampus (Redila and Christie 2006, Yau, Lau et al. 2011). Exercise has also been shown to enhance learning and memory on tasks mediated by the hippocampus including the Morris Water maze task (Adlard, Perreau et al. 2004, Vaynman, Ying et al. 2004, Van Praag, Shubert et al. 2005) and reduce depressive-like symptoms when exposed to chronic stress (Solberg, Horton et al. 1999, Sigwalt, Budde et al. 2011, Patki, Li et al. 2014).

The neurogenic effects of exercise are partly mediated by an increase in cerebral blood volume in the DG that facilitates an interactive cascade of growth factor signalling essential for neuroplasticity (Cotman, Berchtold et al. 2007, Pereira, Huddleston et al. 2007, Hillman, Erickson et al. 2008, Davenport, Hogan et al. 2012). Increased levels of BDNF, insulin-like growth factor-I (IGF-I) and vascular endothelial growth factor (VEGF) have all been associated with long-term exercise and suggested to underlie the neurogenic effects of exercise (Fabel, Fabel et al. 2003, Lopez-Lopez, LeRoith et al. 2004, Hillman, Erickson et al. 2008). Rodent studies have shown that blockade of BDNF, IGF-1 and VEGF abrogates the exercise-induced increase in newborn granule cells, angiogenic and anti-depressant effects in exercised animals (Fabel, Fabel et al. 2003, Lopez-Lopez, LeRoith et al. 2004, Rossi, Angelucci et al. 2006, Kiuchi, Lee et al. 2012).

In humans, the effects of exercise on growth factors is less clear and far less investigated. Part of the reason is the ambiguity over whether peripheral growth factor concentrations represent those in brain-tissue. Of the growth factors that have been linked to neuroplasticity, BDNF has received the most attention. An eloquent study conducted in pigs, has recently shown that measures of blood and plasma BDNF concentrations reflect BDNF concentrations in the hippocampus (Klein, Williamson et al. 2011a). Human studies have consistently shown increased peripheral BDNF concentrations following a single bout of acute aerobic exercise in both healthy individuals (Ferris, Williams et al. 2007, Dinoff, Herrmann et al. 2017, Håkansson, Ledreux et al. 2017) and individuals with MDD. However, the long-term effects of exercise on resting BDNF concentrations have been mixed and remain unclear (Huang, Larsen et al. 2014). For instance, a study investigated the effects of a five-week aerobic activity on resting serum BDNF concentrations in young and healthy adults. Researchers also compared resting serum BDNF concentrations in trained athletes and untrained adults. Trained athletes showed significantly higher BDNF concentrations than their untrained counterparts, and exercise significantly increased resting BDNF concentrations in the untrained participants (Zoladz, Pilc et al. 2008). A recent study investigated effects of a four-week exercise intervention in patients suffering from MDD. All participants were medicated with SSRI agents at study enrolment. Patients performed aerobic exercise on a treadmill for 45 minutes, three times per week. Result showed a significant decrease in depression severity and a significant increase in plasma BDNF concentrations at four weeks (Salehi, Hosseini et al. 2016). In contrast, the Treatment with Exercise Augmentation for Depression (TREAD) study investigated a dosed aerobic exercise intervention in partial

responders to antidepressant medication. Depressed participants were randomized to either a high (16 kcal/kg/week) or low (4 kcal/kg/week) energy expenditure exercise for a duration of 12 weeks. Resting serum BDNF concentrations were quantified at baseline and at 12 weeks. Findings revealed no change in serum BDNF concentrations at 12 weeks for either group. The authors concluded that participants entered the study with resting BDNF levels that may have been already normalized by SSRI treatment (Toups, Greer et al. 2011a). Similar results have been recently reported from a study that investigated the effects of a 12-week supervised exercise intervention on non-medicated individuals with mild to moderate depression. Participants performed three 45-minute aerobic sessions per week at an intensity of 80% of their maximal HR. Despite a significant increase in fitness, no change in serum BDNF, IGF-1 or VEGF concentrations were observed at 12 weeks (Krogh, Rostrup et al. 2014). Taken together, it remains difficult to understand the relationship between exercise, BDNF and depression. One possible explanation may be the methodology difference in measuring plasma versus serum BDNF concentrations across studies. Animal research has shown that plasma BDNF concentrations reflects hippocampal BDNF concentrations while there is no relationship with serum BDNF (Karege, Schwald et al. 2002, Klein, Williamson et al. 2011a). Although the origin of BDNF in blood is not entirely clear, research has demonstrated that the brain is the main contributor to peripheral BDNF concentrations during exercise and therefore plasma measures may be more accurate (Rasmussen, Brassard et al. 2009).

Regular exercise has also been shown to reduce systemic inflammation in other pathological conditions such as cardiovascular disease and Type 2 diabetes mellitus

(Balducci et al., 2010; Meirelles et al., 2014; Pedersen, 2006). Such studies have reported a simultaneous increase in the systemic levels of cytokines with anti-inflammatory properties including IL-10, IL-1ra and a decrease in the pro-inflammatory cytokines IL-6 and TNF- α (Júnior, Lopes, Seelaender, & Lopes, 2009; Petersen & Pedersen, 2007).

The anti-inflammatory effects of long-term exercise may be partly mediated by muscle-derived IL-6. The immune response to exercise contrasts the response that is produced by severe infections. IL-6 is considered both a pro- and anti-inflammatory cytokine that is released in the circulation by contracting skeletal muscle during exercise. During acute exercise, circulatory levels of IL-6 increase up to 100-fold and then decline in the postexercise period (Pedersen, Steensberg et al. 2001, Suzuki, Nakaji et al. 2002, Petersen and Pedersen 2007). Once released in the circulation, IL-6 is linked to increased production of anti-inflammatory cytokines IL-1ra and IL-10 and decreased production of the proinflammatory cytokine TNF- α (Mizuhara, O'Neill et al. 1994, Petersen and Pedersen 2005). Unlike IL-6 signalling in monocytes or macrophages, which trigger the activation of NF κ B signalling pathways, intramuscular IL-6 expression induces a cascade of signalling networks including the nuclear factor of activated T-cells (NFAT) and mitogen activated protein kinase (MAPK) pathways creating an anti-inflammatory response (Brandt and Pedersen 2010). Nonetheless, the literature examining the relationship between exercise and inflammatory markers in MDD populations is limited.

More recently, Moon et al., (2016) identified a novel protein that may play a key role in the beneficial effects of exercise on neural function. Cathepsin B (CTHB), a cysteine proteinase produced by contracting skeletal muscle, is capable of penetrating the blood-brain barrier and upregulating both BDNF expression and hippocampal

neurogenesis in wild-type mice (Moon et al., 2016). Following long-term running, researchers observed an increase in plasma CTHB concentrations associated with improved memory performance in mice, Rhesus monkeys and humans. CTHB is an autophagy-related protein also shown to prevent memory deficits in Alzheimer's disease by upregulating autophagic-lysosomal processes and reducing accumulations of amyloid- β peptides in the brain (Mueller-Steiner et al., 2006; Yang et al., 2011). However, the role of CTHB in neuroplastic processes requires further investigation.

Finally, the inconsistent findings among studies may be a result of the heterogeneous nature of the exercise interventions. For instance, not all studies define exercise prescription variables such as the type, frequency, intensity and duration of the exercise (Lee 2007). There is also a wide range of methods that report the quantity and intensity of exercise in various ways making it difficult to interpret findings. Although many studies provide a general description of the exercise intervention such as the type, frequency, and duration of the exercise, the majority of studies do not provide information as to whether intensity was maintained throughout the exercise session. For instance, many exercise interventions are based on self-reported feedback from participants to ensure they fulfilled the exercise prescription while others are supervised by an exercise professional.

1.3 Conclusions

The literature has shown MDD to be a severely undertreated disorder in the primary care setting. Current treatments for MDD are far from satisfactory warranting the need for more efficacious treatment options. MDD is a heterogeneous disorder both clinically and biologically. In addition to low mood, MDD is associated with cognitive impairments that persist beyond the remissive and recovery period. Structural and functional neuroimaging studies have implicated abnormalities in the hippocampal region to underlie the memory impairments observed in MDD. Studies have shown that MDD is associated with abnormal HPA axis functioning, lower levels of BDNF and increased levels of inflammation, which have been shown to attenuate neuroplasticity within the hippocampus.

Converging evidence from animals and non-depressed human studies have shown that exercise targets mechanisms suggested to underlie MDD. The animal literature has consistently shown exercise to enhance neuroplasticity in the hippocampus. These findings suggest that the underlying mechanism involved in the etiology and pathogenesis of MDD may be confounded by physical activity and fitness variables that are often not reported in the MDD literature.

In humans, the effects of exercise on cognitive performance and mechanisms underlying cognitive function are mixed. The inconsistent findings among studies may be a result of the heterogeneous nature of the exercise interventions. Not all studies define exercise prescription variables and there is a wide range of methods that report the

quantity and intensity of exercise. Many exercise interventions are based on self-reported feedback and very few are supervised by an exercise professional.

The vast majority of findings from the exercise-cognition literature comes from elderly adults or those with age-associated neurodegenerative diseases. As such, there is a gap in the literature demonstrating the effects of exercise on brain function in young and healthy adults. This makes it difficult to determine the magnitude of effect of exercise on cognitive function and mechanisms associated with cognitive function before the onset on any age-related neurodegeneration or psychiatric illness.

Exercise is an effective treatment option in MDD, but its mechanism of action remains unknown. The ‘typical’ MDD patient seen in the primary care setting is treated with ADM and/or psychotherapy. To date, there are no studies that have used a multi-disciplinary approach to investigate the effects of exercise in combination with ADM and CBT, on clinical symptoms, cognitive symptoms, neural function and biochemical marker associated with MDD. The following PhD thesis will address these gaps in the literature.

1.4 Research objectives: research questions and hypotheses

1.4.1 Study 1: Research objectives, questions and hypotheses

Research objectives

Memory impairment is the most frequently reported cognitive symptom in MDD (Airaksinen, Larsson et al. 2004) and often persists as a residual symptom following antidepressant therapy (Shilyansky, Williams et al. 2016). Research suggests that the hippocampus, which plays a critical role in the formation of new memories, also plays a role in the pathogenesis of MDD (Campbell and MacQueen 2004). Functional neuroimaging evidence has identified hippocampal dysregulation during the encoding of episodic memory (Fairhall, Sharma et al. 2010). In animals, exercise has been shown to enhance neuroplasticity within the hippocampus and improve performance on hippocampal-dependent tasks (Van Praag, Shubert et al. 2005). In humans, exercise has been shown to delay age-related neurodegeneration and cognitive decline (Colcombe, Kramer et al. 2004, Chang, Jonsson et al. 2010). However, it remains unknown the effects of exercise on brain function in young and healthy adults. Also, exercise has been shown to be an effective treatment for MDD but there are no studies that have investigated the effects of exercise on hippocampal function during a memory task.

The main objectives of study one were to investigate the effects of a well-defined, supervised exercise prescription on depressive symptoms, cognitive function, neural function and fitness in a group of MDD patients. I also included a sample of young and healthy adults to determine if the effects of exercise on brain function can be generalized to those without psychiatric illness or any age-related cognitive decline. I used an fMRI

subsequent memory paradigm to examine memory encoding within the hippocampus during an associative memory task.

Research question

Does a structured, moderate-intensity supervised eight-week exercise intervention improve depressive symptoms in medicated patients with MDD? In addition, will exercise improve fitness, episodic memory and change hippocampal activity during memory encoding in untrained MDD patients and untrained young and healthy adults?

Hypotheses

At baseline, the healthy controls will perform significantly better on the associative face-name memory task compared to the MDD group. fMRI results will show a significant difference in hippocampal activation during the successful encoding of face-name pairs between the healthy controls and MDD patients. Following the eight-week intervention, both the MDD and healthy control groups will show improvements in fitness. The MDD group will show significant improvements in depressive symptoms. The MDD group will also perform better on the episodic memory task and will show a more normalized hippocampal activation pattern during the encoding of successfully remembered items similar to the healthy control group. There will be no change in memory performance or hippocampal fMRI measures for the healthy control group.

1.4.2 Study 2: Research objectives, question and hypotheses

Research objectives

More than half of the MDD population fail to receive effective treatment for their disorder warranting the need for additional treatment options (Shelton 2006). Exercise has been shown to be effective in treating depressive symptoms, however its mechanism of action is unknown. In non-depressed populations, exercise has been shown to increase circulating BDNF concentrations, normalize cortisol secretion and reduce inflammation by balancing the ratio of pro- and anti-inflammatory cytokines (Cotman and Berchtold 2002, Cotman, Berchtold et al. 2007). Recently, exercise was shown to concomitantly increase CTHB and improve memory performance in both animals and healthy adults (Moon, Becke et al. 2016).

The main objectives of study two was to investigate the additional effects of exercise in combination with ADM and CBGT in low active patients with MDD. Depressive symptoms, cognitive function, sleep quality, cardiorespiratory fitness and biochemical markers shown to be altered in MDD were measured. The results were compared to those of low active MDD patients who received ADM and CBGT only. A group of non-depressed, young and healthy adults who were considered low active were recruited to provide normal healthy values for comparison.

Research questions

Does a structured, moderate-intensity, supervised eight-week exercise intervention in addition to ADM and CBGT improve depressive symptoms, anxiety, sleep quality and cognitive function in patients with MDD more so than for a group who

received only ADM and CBGT? In addition, will exercise normalize cortisol, BDNF, CTHB and cytokine concentrations known to be altered in MDD? Will changes in depression, sleep quality and cognitive function be associated with changes in biochemical markers? At baseline, will sleep quality, cognitive performance and biochemical markers in the MDD groups be significantly different from healthy control values?

Hypotheses

At baseline, the MDD groups will show significantly higher depression, anxiety and sleep quality scores compared to the healthy controls. The MDD group will perform more poorly on the cognitive tasks and will have altered biochemical marker profiles compared to the healthy controls. Following the eight-week exercise intervention, the MDD exercise group will show greater improvements in depression, anxiety, sleep quality and cognitive performance compared to the non-exercise MDD group. The MDD exercise group will also show improved fitness and a more normalized biochemical marker profile whereas the non-exercise MDD group will show no change.

1.4.3 Study 3: Research objectives, questions and hypotheses

Research objectives

Regular exercise has been linked to better cognitive function during various periods throughout the lifespan. Higher levels of cardiorespiratory fitness are associated with better cognitive function in children (Hillman, Castelli et al. 2005) adolescents (Stroth, Kubesch et al. 2009) and in elderly adults (Colcombe and Kramer 2003). However, the effects of exercise on cognitive function in younger adults is unclear and under-researched. Researchers have postulated that cognitive performance peaks during early adulthood leaving little room for improvement (Hillman, Erickson et al. 2008). However, the animal literature provides evidence that exercise enhances neuroplasticity and improves cognitive performance in younger animals and these effects are mediated by increases in BDNF expression (Kobilo, Liu et al. 2011). In humans, acute exercise increases circulatory BDNF concentrations, however the long-term effects of exercise on BDNF concentrations have presented mixed findings. A novel protein CTHB was recently found to be increased following long-term exercise and associated with enhanced neurogenesis in animals and better cognitive functioning in healthy humans (Moon, Becke et al. 2016). However, further research is needed to confirm these results.

Research question

Does a structured, moderate-intensity supervised eight-week exercise program improve fitness and cognitive function in low active, young and healthy adults? In addition, will exercise change plasma BDNF and CTHB concentrations in young and healthy adults? Will changes in plasma BDNF and CTHB concentrations be related to changes in cognitive performance?

Hypotheses

Following the eight-week exercise program, the exercise group will show improvements in fitness and cognitive performance. The exercise group will also show an increase in plasma BDNF and CTHB concentrations that will be associated with improvements in cognitive performance. The non-exercise group will show no change in fitness, cognitive function or plasma BDNF and CTHB concentrations.

Chapter 2: Exercise Promotes Neuroplasticity in Both Healthy and Depressed Brains: An fMRI Pilot Study

Adapted from: Gourgouvelis, J., Yilder, P., & Murphy, B. (2017). Exercise Promotes Neuroplasticity in Both Healthy and Depressed Brains: An fMRI Pilot Study. *Neural Plasticity*, 2017, 1–13.

2.1 Abstract

Memory impairments are a frequently reported cognitive symptom in people suffering from major depressive disorder (MDD) and often persist despite antidepressant therapy. Neuroimaging studies have identified abnormal hippocampal activity during memory processes in MDD. Exercise as an ad-on treatment for MDD is a promising therapeutic strategy shown to improve mood, cognitive function, and neural structure and function. To advance our understanding of how exercise impacts neural function in MDD, we must also understand how exercise impacts healthy individuals without MDD. This pilot study used a subsequent memory paradigm to investigate the effects of an eight-week exercise intervention on hippocampal function in low active healthy ($n=8$) and low active MDD ($n=8$) individuals. Results showed a marked improvement in depression scores for the MDD group ($p < .0001$) and no change in memory performance for either group ($p > .05$). Functional imaging results showed a marginally significant decrease in hippocampal activity in both groups following the exercise intervention. Our whole brain analysis collapsed across groups revealed a similar deactivation pattern across several memory-associated regions. These results suggest that exercise may enhance neural efficiency in low-fit individuals while still resulting in a substantially

greater mood effect for those suffering from MDD.

This trial is registered with clinical trials.gov NCT03191994.

2.2 Introduction

Memory impairment is the most frequently reported cognitive symptom in people suffering from major depressive disorder (MDD) and often persists as a residual symptom following antidepressant therapy [1, 2]. Although the neural underpinnings of impaired memory in MDD remain unclear, research suggests that the hippocampus, which plays a critical role in the formation of new memories, also plays a role in the pathogenesis of MDD. To date, cognitive literature has presented mixed findings in terms of the type, severity, and specificity of memory deficits in people with MDD, although the plurality of data has suggested an impairment in episodic (autobiographical) memory with a sparing of semantic (general knowledge) memory and short-term memory [3–8]. The hippocampus has been shown to play an essential role in the encoding of episodic memories [5, 9–13], and pathologies associated with this neural structure may underlie the episodic memory impairments observed in MDD populations. The relationship between MDD, memory impairments, and hippocampal structure and function is based on converging lines of research from animal studies, neuroimaging, neuropsychology, and postmortem investigations which have all shown hippocampal abnormalities at the structural, functional, and cellular level. Structural brain imaging studies have shown robust hippocampal volume reductions particularly in persistent and early onset MDD [14–16]. Functional neuroimaging studies have found that both the memory encoding and retrieval processes within the hippocampus are to be impaired in MDD [4, 6, 17–19].

Neuropathological evidence from animal models of depression and postmortem studies in depressed humans have revealed cellular abnormalities in the hippocampus such as dendritic atrophy and reduced neuron and glial densities [20–24].

Despite many efforts to develop effective antidepressant therapies, MDD remains a severely undertreated disorder in the primary care setting leaving more than half of individuals plagued with symptoms [25–28]. Exercise as an add-on to conventional antidepressant therapies is a promising treatment strategy for MDD. It is well established that exercise is efficacious in treating mild to moderate depression with response rates comparable to mainstream therapies such as antidepressant medication and cognitive behavioral therapy [29–34]. However, there is a lack of understanding of the neurobiological mechanisms that underlie or mediate the antidepressant effects of exercise. It is well established that exercise facilitates neuroplasticity [35–37]. To date, much of our understanding of how exercise facilitates neural and cognitive plasticity has come from the extensive animal literature. For instance, rodent studies have shown that exercise increases new cells in the dentate gyrus of the hippocampus, and this is associated with improved learning and spatial memory [36, 38–40]. Further evidence has shown that exercise increases synaptogenesis [41] and angiogenesis [42] and improves dendritic morphology in the hippocampus [43, 44]. However, the effects of exercise on brain structure and function in humans have been more equivocal. In elderly populations, aerobics exercise training has been shown to improve spatial memory [45], executive function [46, 47], and short-term memory [48]; however, others observed no benefits [49–52]. Neuroimaging studies have found that aerobics exercise reverses age-associated brain volume loss in the prefrontal and temporal cortices [53, 54], improves functional

connectivity in the default mode and frontal executive networks [47], and increases hippocampal volume in schizophrenics [55]. To date, the literature examining the effects of chronic exercise on neural function in both healthy and MDD populations remains scant. To capitalize on the full treatment potential of exercise in MDD populations, we must also understand the relationship between cardiovascular fitness, neural function, and cognitive performance in healthy individuals in order to identify neural mechanisms specific to MDD.

To our knowledge, this is the first study using a subsequent memory paradigm to determine the effects of an eight-week exercise prescription on the functional integrity of the hippocampus in low active patients with MDD and low active healthy individuals. The aim of this pilot study was twofold: (1) using fMRI to examine changes in hippocampal function following an exercise intervention, and (2) to conduct an exploratory whole brain analysis to determine how exercise affects overall brain activity.

2.3 Materials and Methods

2.3.1 Participants

Eight patients (mean age = 37.25, SD = 8.00; 7 females) with comorbid MDD and anxiety were recruited from an outpatient Mental Health Day Treatment Program at a local hospital in Oshawa, Ontario Canada. Eight healthy participants (mean age = 20.63, SD = 1.19; 4 females) with no history of mental health illness or neurological disease were recruited from a local university in Oshawa, Ontario Canada. Depressed patients had a diagnosis of MDD according to an unstructured clinical interview by hospital psychiatrists based on Diagnostic and Statistical Manual of Mental Disorders—Fourth

Edition (DSM-IV-TR) [56] criteria, no coexisting DSM-V Axis I disorders apart from anxiety, and a score ≥ 20 on the Beck Depression Inventory—Second Edition (BDI-II) [57], and their pharmacological treatment was stabilized a minimum of six weeks prior to study enrolment. In order to be considered eligible for the study, participants needed to indicate that they exercised less than 20 minutes, three times per week. Both groups were also safety screened for MRI and screened with the Physical Activity Readiness Questionnaire (PAR-Q) to ensure they had no medical contraindications to exercise. All participants provided written consent.

2.3.2. Psychometric Evaluation

Participants completed the Montreal Cognitive Assessment (MoCA) which is a brief neurocognitive tool with high sensitivity for screening patients with mild cognitive impairment. This cognitive assessment was performed to identify participants who may have difficulty performing the associative memory task. The internal consistency of the MoCA is good, with a coefficient alpha of 0.83 [58]. Depression was measured using the Beck Depression Inventory (BDI-II) [57] which is one of the most widely used self-reported instrument capable of measuring depression severity ranging from not depressed to severely depressed. The BDI-II demonstrated excellent internal consistency, with a coefficient alpha of 0.91 [59]. All measures were performed before and after the eight-week exercise intervention.

2.3.3 Fitness Assessment

Cardiorespiratory fitness was measured before and after the exercise intervention using the YMCA cycle ergometer protocol recommended by the American College of

Sports Medicine [60–62]. The YMCA cycle ergometer protocol is an indirect submaximal exercise test used to estimate maximal oxygen consumption (VO₂max) from heart rate (HR) measurements. The protocol consists of two or more consecutive 3-minute stages at a given workload. The objective was to elevate the participant's HR to a target zone to approximately 85% of the age-predicted maximum HR for two consecutive stages. The initial workload consisted of a 25-watt workload at a cadence of 50 revolutions per minute. HR was measured and recorded using the radial pulse method during the final 15 seconds of each minute, which determined the workload of subsequent stages indicated by the YMCA protocol. Once a steady state HR (two successive measures that differ from <5 bpm) was within 10 bpm of the 85% age-predicted maximum HR, the test was complete. VO₂max was estimated using an equation that includes workload, body mass, and derived constants.

2.3.4 Exercise Intervention

Participants performed an individualized eight-week exercise program consisting of three weekly sessions (described below). Exercise sessions were performed alone, on nonconsecutive days, and each session was supervised by a qualified exercise professional to increase compliance [34]. Attendance was recorded and all participants completed >80% of the exercise sessions.

The exercise prescription was based on international recommendation to obtain at least 150 minutes per week of moderate to vigorous intensity aerobics exercise and to perform strengthening activities twice per week, for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in healthy adults [63, 64].

This minimum-effective dose of exercise was prescribed to encourage better compliance since people with depression, and are , tend to be less motivated [65]. Research has also shown that combining aerobics with strength training improves depression and cognitive function such as attention, processing speed, executive function, and memory performance more than aerobics exercise alone [51, 66].

2.3.4.1 Resistance Sessions

Resistance sessions were completed twice per week and incorporated a whole-body exercise prescription using larger muscle groups. Each session included eight resistance exercises using both resistance training machines and free weights. Initial workloads were approximately 95% of the 10 repetition maximum to ensure proper form. Exercises were performed in two or three supersets (one set of each exercise with no rest between sets) with an 8–12 repetition range in order to decrease rest times and to maintain target HR. Workload was increased approximately 5% once participants were able to complete three sets of 12 repetitions with proper form. Specific exercises were changed every four weeks; however, they targeted the same muscle groups. Resistance exercises included variations of the chest press, pull downs, triceps extension, biceps curl, shoulder press, leg press, leg extensions, leg curls, squats, split squats, calf raises, and abdominal exercises. During each session, HR was monitored to ensure that the participant maintained a HR of between 60–80% of their age-predicted maximum HR. Each session began with a 5-minute aerobics warmup and ended with 15 minutes of aerobics activity that was performed on either the treadmill, stationary bike, or elliptical trainer.

2.3.4.1 Aerobics Session

Participants completed an aerobics-only session once per week. They were given the choice to perform their aerobics activity on either the treadmill, stationary bike, or elliptical trainer. The aerobics session workloads were determined by HR response and increased by five-minute increments over the eight weeks reaching a maximum of 60 minutes per session. HR was monitored throughout the session to ensure the participant was in the target HR range.

2.3.5 Statistical Analysis

Statistical analyses were performed using GraphPad Prism software, version 6.0 data. Data are presented as mean (standard deviation (SD)). *P* values less than 0.05 were considered significant. Differences in baseline variables between groups were tested using a two-tailed Student's *t*-test and chi-square test for gender distribution. Within group differences for pre-post-BDI, MoCA, BMI, and VO₂max were tested using a paired *t*-test. A two-way repeated measures analysis of variance (ANOVA) was used to determine any group × time of interactions and to compare the changes between the two treatment groups. Cohen's *d* was used to represent the effect size within each group. For between group effect sizes, we used d_{ppc2} [67] which uses the difference between Hedge's *g* of two different treatment groups in pre-post research designs.

2.3.6 Associative Memory Task

To evaluate the encoding and retrieval processes of memory, fMRI studies frequently use a recognition memory paradigm that consists of an “encoding” and “recall” phase [5, 68]. Associative memory refers to memory for the relationships

between memoranda rather than memory for objects themselves [69–71]. The role of the hippocampus in memory formation has also been specifically linked to associative memory [72]. A specific version of an associative paradigm [17] using face-name pairing known to reliably activate the hippocampus during the successful encoding event and sensitive enough to detect hippocampal dysregulation in a MDD sample [16] was used to investigate activation patterns of the hippocampus during the encoding process inside the MRI scanner (see Figure 2.1). During the encoding phase inside the MRI, participants were presented with face-name pairs and used a response box provided to indicate if the name suited the face. The retrieval phase was performed after the MRI scan. Participants were presented with a face and two names and instructed to indicate which name was paired with that face during the encoding phase. Participants also rated the confidence of their responses. Trials during the encoding phase were then reclassified based on the responses during the retrieval phase into correct (the participant selected the correct name for the face and indicated a high confidence in their response, suggesting that the face-name association was successfully encoded), guesses (a correct selection with low confidence), or incorrect (the wrong name was selected).

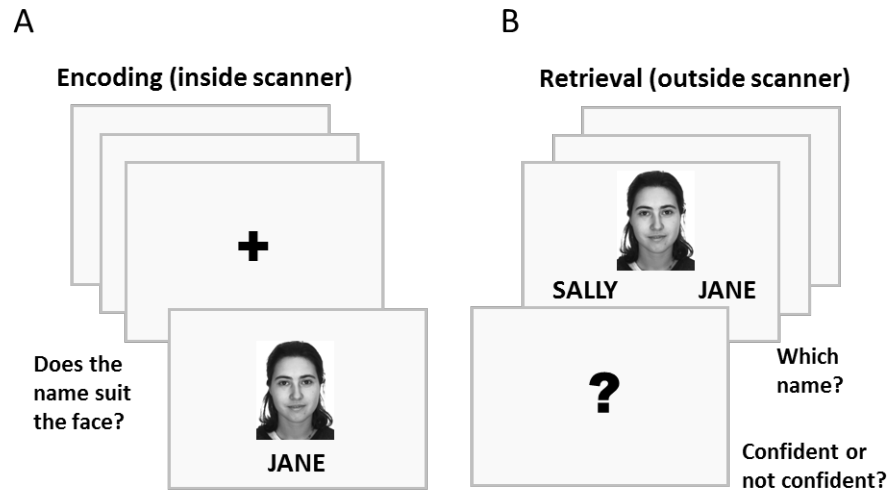


Figure 2. 1 - (A) During the encoding task, participants viewed 240 face name pairs over two nine minute fMRI runs. Participants were asked if they thought the name suited the face and responded using a response box. Each run included 120 face name pairs presented for a duration of 3000 ms, jittered with 34 fixation crosses ranging from 3000-9000 ms in increments of 3000 ms. (B) The retrieval task was then performed on a laptop computer outside the MR scanner. Participants were instructed to choose which of the two names was originally paired with the face shown and then asked if they were confident with their choice. This was used to identify the correct successful encoding trials as remembered (correct) vs lucky guesses.

2.3.7 fMRI Scanning Parameters

Participants were scanned on a 3-Tesla Tim trio MRI scanner equipped with a 32-channel phased array head coil. E-prime software version 2.0 (Psychology Software Tools) was used to present stimuli on a rear-projection system (Avotec, Inc., Stuart, FL) in two separate nine-minute functional runs. To obtain optimal hippocampal resolution, all scans were acquired in the oblique coronal plane perpendicular to the long axis of the hippocampus to maximize the anatomic delineation. A total of 416 functional scans were acquired with a T2-weighted gradient echo planar imaging sequence (TR =2500 ms, TE = 27 ms, FOV = 192 mm, 3 mm × 3 mm × 3 mm, and flip angle = 70°; in-plane

resolution = 3 mm × 3 mm; and 50 slices with 3.5 mm slice thickness). The first 4 volumes of each run were discarded to allow for T1 equilibration. The anatomical scan lasted six minutes and was acquired with a T1 MPRAGE imaging sequence (TR = 2000 ms, TE = 2.63 ms, FOV 256 mm, 1 mm × 1 mm × 1 mm voxels, and flip angle = 9°).

2.3.8 fMRI Analysis

Image preprocessing was performed using SPM12 methods (Statistical Parametric Mapping, Wellcome Department of Cognitive Neurology, London, UK: <http://www.fil.ion.ucl.ac.uk/spm>) within MatLab 8.3 (The MathWorks Inc., MA). Individual functional images were slice time corrected and realigned to the first image in the series to correct for motion. The EPI images were coregistered to the T1, and segmentation was applied to the T1 anatomical images to extract grey matter, white matter, and CSF masks and calculate a deformation field to transform the data into MNI space. All EPI images were then spatially normalized to the ICBM template using the deformation field, resampled to 3 × 3 × 3, and smoothed using a 6 mm full-width-half maximum isotropic Gaussian filter. General linear model (GLM) was performed at the single-subject level and statistical contrasts were created modeling the hemodynamic response function (HRF) of remembered items with high confidence (correct), remembered items with low confidence (lucky guess), and incorrect trials (incorrect). Six head motion parameters (three rigid body translations and three rotations) were included in the model to reduce the potential effects of motion. Second-level random effects analysis was performed using the contrast of t-test of correct > incorrect. Correct retrieval requires well encoding of the items. As such, this contrast which differentiates between

poorly and well-encoded trials, known as the subsequent memory effects, is a powerful tool for examining successful memory encoding in the brain [73, 74]. As our primary hypothesis was related to activity in the hippocampus, a hippocampal mask was defined using the automated anatomical labeling (AAL) atlas. Significant clusters from an independent sample t-test within the hippocampus ($p < .01$ uncorrected, 10 voxels, for this a priori ROI-defining analysis only) for correct > incorrect at baseline were used as an ROI to extract contrast beta values for correct > incorrect in pre- and postscans for each participant. The average beta values from each ROI were imported into SPSS version 20, and a 2×2 repeated measures ANOVA (group \times time) was run. We then conducted an exploratory whole brain analysis to determine if other brain regions showed task-related effects. For our whole brain analysis, significant clusters were defined as 20 contiguous voxels (180 mm³) with $p < .005$ uncorrected. A 2×2 repeated measures ANOVA (group \times time) was run on β values for the correct > incorrect contrast in order to identify regions in which there was a difference in pre-post changes across groups. Additionally, an exploratory analysis was run examining a group \times time interaction across the whole brain.

2.4 Results

2.4.1 Baseline Characteristics

At baseline, there were no significant differences between groups for BMI, VO₂max, and MoCA scores (all $p < .05$). BDI scores for the MDD group scores indicated severe depression while the healthy group BDI scores indicated no depression

($p < .0001$). The depressed group was also older than the healthy group ($p < .0001$). See Table 2.1.

Table 2. 1 - Baseline characteristics of participants

Variables	MDD	<i>n</i>	Healthy	<i>N</i>	<i>df</i>	<i>p</i>
Sex: (male/female)	1/7	8	4/4	8	1	.106 ^a
Age (years)	37.25 (8.00)	8	20.63 (1.19)	8	14	<.0001 ^b
Body mass index (kg/m ²)	28.33 (5.12)	8	28.29 (7.91)	8	14	.993 ^b
VO ₂ max (ml.kg ⁻¹ .min ⁻¹)	24.82 (8.00)	7	20.81 (6.48)	8	12	.326 ^b
BDI	41.75 (3.50)	8	5.88 (5.03)	8	14	<.0001 ^b
MoCA	24.63 (1.41)	8	26.13 (3.23)	8	14	.248 ^b

^aPearson's chi-square

^bStudent's t-test

VO₂max = maximum oxygen consumption; BDI = Beck Depression Inventory;

MoCA=Montreal Cognitive Assessment

Data are expressed as the mean with the standard deviation in parentheses.

2.4.2 Psychometric, memory and fitness results

A 2 x 2 repeated measures ANOVA revealed a group x time interaction for BDI scores ($f(1,14) = 30.42, p < 0.0001$) indicating the MDD group had a greater decrease in depression scores pre-post. There were no significant changes in BMI, MoCA scores, or performance on the associative memory task ($p > .05$) for either group pre-post. Although baseline memory scores between groups was not significantly different ($p = .477$), our results showed that the MDD group performed more poorly on the associative memory task compared to the Healthy group (71.48% vs 75.32%) indicating likely memory impairments in the MDD group. One MDD ($n=1$) participant discontinued baseline VO₂max testing due to exhaustion and was excluded from VO₂max analysis. Baseline VO₂max scores revealed that one MDD participant ($n=1$) was in the Good Health Benefit Rating Zone and the remaining participants ($n=14$) were in the Poor Health Benefit

Rating Zone based on the Canadian Society for Exercise Physiology guidelines [63]. The Healthy group showed a 47% increase in VO_2max that was significant ($p=.014$) while the MDD group showed a marginally significant increase of 31% ($p=.073$). There was no significant difference in VO_2max between groups ($p=.661$). These improvements in VO_2max suggest that the exercise intervention was successful at improving cardiorespiratory fitness (see Table 2.2).

2.4.3 fMRI results

Using a main effects contrast of correct > incorrect, collapsing across groups, at baseline, we identified active voxels in the hippocampus, and created ROIs for right and left hippocampus (see Fig. 2.2a). A repeated measures ANOVA examining group x time using β values for the correct > incorrect contrasts for pre and post revealed a marginal main effect of time ($f(1,14) = 3.3, p = 0.09$), no main effect of group ($f(1,14) = 0.005, p = 0.957$) or group x time interaction ($f(1,14) = 0.165, p = 0.69$). This marginal main effect of time is driven by a decrease in the correct > incorrect contrast in the hippocampus indicating that there was a decrease in hippocampal activity during successful encoding in both groups following the exercise intervention (see Fig. 2.2b).

The exploratory whole brain analysis did not reveal any clusters in which there were group differences in the pre-post changes following exercise, or a main effect of group differences. Given the lack of interaction of main effects of group or group x time interaction, a post-hoc whole brain analysis was run in which both groups were collapsed. Given the relatively small sample size, this analysis maximizes the power to detect changes in brain activity following the exercise intervention that are common to both

Healthy and MDD, using the more powerful paired samples *t*-test. Changes in neural activity in the correct > incorrect contrast were compared from the pre-treatment to post-treatment MRI scans. Decreases in activity following exercise were noted in several regions (see Fig. 2.3 and Table 2.3). Regions included a larger cluster in the left posterior insula, and smaller clusters in the medial superior frontal/mid cingulate and post-central superior parietal gyrus.

In order to examine regions in which changes in neural activity were related to changes in BDI score an additional contrast was run, regressing change in BDI against the paired *t*-test described above. Again, in order to maximize power the Healthy and MDD cases were both included in this analysis. The justification for including both groups are as follows: firstly, although the Healthy group was not clinically depressed there was some pre-post reduction in BDI scores for the Healthy group, and secondly, since cases with depression tended to have a larger decrease in BDI this analysis may be more sensitive to group x time effects, reflected as BDI changes, while also better reflecting areas in which the pre-post differences were behaviorally meaningful. The regression against BDI for pre-post changes found a negative relationship between changes in depression scores and activation in the right occipital, left occipital/fusiform and left precentral gyrus (see Fig. 2.4 and Table 2.4).

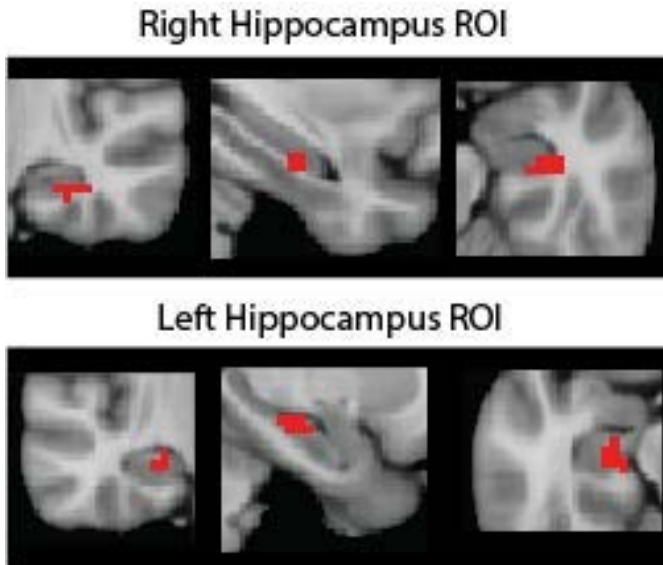
Table 2. 2 - Results of pre-post changes for depression scores, cognitive assessment, memory performance, body mass index and fitness

Measure	MDD					Healthy					Between Group Analysis		
	<i>n</i>	Pre Mean (SD)	Post Mean (SD)	<i>p</i>	<i>d</i>	<i>n</i>	Pre Mean (SD)	Post Mean (SD)	<i>p</i>	<i>d</i>	F	<i>p</i>	<i>d_{ppc2}</i>
BDI	8	41.75 (3.50)	15.50 (10.43)	.0004	2.89	8	5.88 (5.03)	3.25 (4.53)	.072	.545	30.42	<.0001	5.34
MOCA	8	24.63 (1.41)	25.75 (2.38)	.229	.564	8	26.13 (3.23)	27.13 (1.81)	.286	.338	.011	.920	.047
Memory task (high confidence correct %)	8	71.48 (9.50)	69.08 (12.03)	.359	.210	8	75.32 (9.29)	75.13 (9.07)	.942	.020	.418	.529	.230
BMI (kg/m ²)	8	28.33 (5.12)	28.29 (4.48)	.934	.007	8	28.29 (7.91)	27.95 (6.61)	.530	.023	.205	.657	.044
VO ₂ max (ml.kg ⁻¹ .min ⁻¹)	7	24.82 (8.00)	32.52 (10.12)	.073	.834	8	20.81 (6.48)	30.57 (8.66)	.014	1.26	7.96	.661	.279

Note: BDI = Beck Depression Inventory; MoCA = Montreal Cognitive Assessment; BMI = body mass index; VO₂max = maximum oxygen consumption; *d* = Cohen's D

Data are expressed as mean with standard deviation in parentheses.

A



B

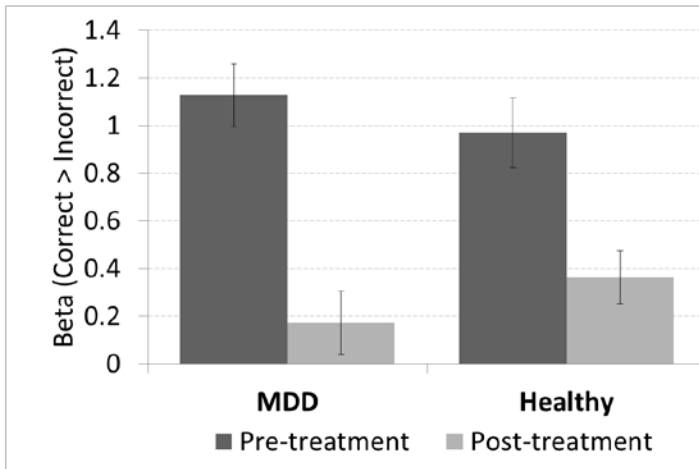


Figure 2. 2 - (A) Regions within the hippocampus found to be active in the correct > incorrect contrast for both Healthy and MDD at baseline, used as an ROI to extract Beta values for an analysis of activity in the hippocampus. (B) Beta values for correct > incorrect from both groups at pre-treatment and post-treatment. Both groups showed a

reduction in hippocampal activity within the bilateral ROI following exercise. Error bars represent standard error.

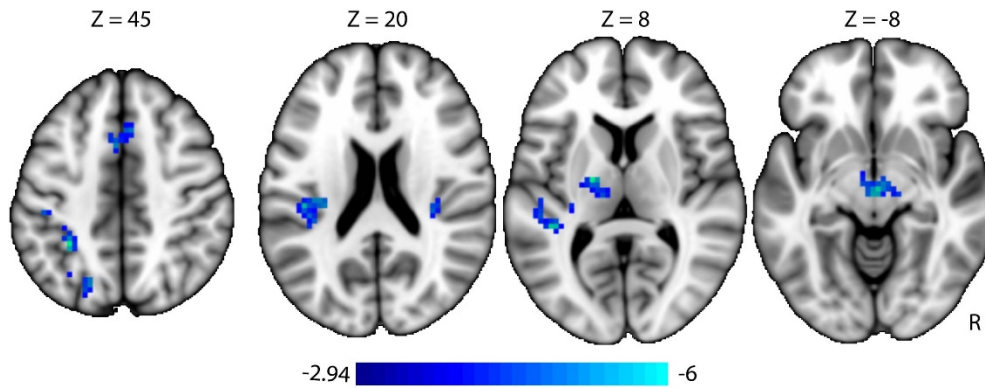


Figure 2. 3 - Pre to post changes in neural activity in the correct > incorrect contrast (paired-samples t-test). Decreases in activity following exercise were noted in several regions, irrespective of group.

Table 2. 3 - Brain regions showing pre-post changes in activity for the correct > incorrect, irrespective of group

Voxels	Peak T	MNI Coordinates			BA	Location
		X	Y	Z		
37	-6.27	-6	17	41	32	Medial Superior Frontal/Mid Cingulate
35	-5.85	-18	-10	8		Left Putamen
35	-5.79	-30	-46	44	40	Left Supramarginal/Intraparietal Sulcus
45	-5.61	-42	-28	35	3	Post-central, superior parietal gyrus
50	-5.34	3	-16	-7		Thalamus/midbrain
139	-5.3	-42	-37	8	41	Left posterior insula
30	-5.22	-18	-70	47	7	Left superior parietal
36	-5.17	30	-28	14		Right Posterior Insula
20	-4.75	54	-43	-4	21	Right Posterior mid temporal
25	-3.82	12	-82	-7	18	Right Occipital Gyrus

Note: MNI=Montreal Neurological Institute, BA=Broadman's Area

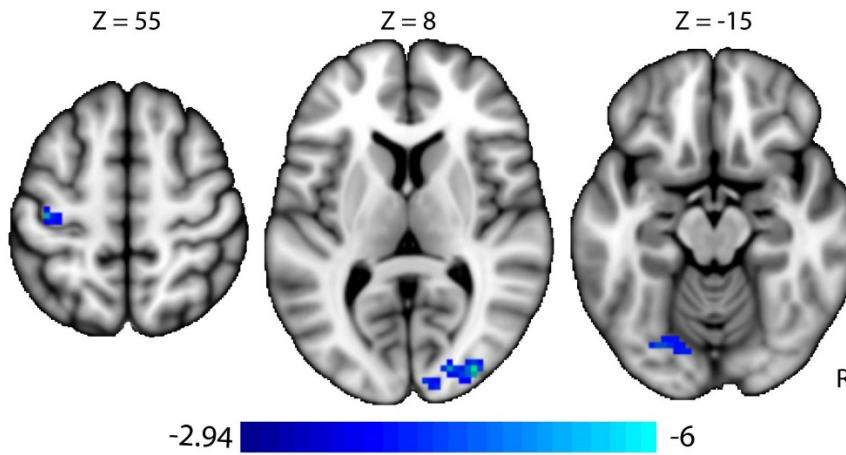


Figure 2. 4 - Pre-post changes found a negative relationship between changes in depression scores and activation in the right occipital, left occipital/fusiform and left precentral gyrus, irrespective of group.

Table 2. 4 - Regions showing decreased activation associated with depression, irrespective of group

Voxels	Peak T	MNI Coordinates			BA	Location
		X	Y	Z		
58	-6.41	36	-88	11	19	Right Occipital
27	-4.92	-39	-22	56	4	Left Precentral Gyrus
29	-4.1	-24	-73	-13	18	Left Occipital/Fusiform

Note: MNI=Montreal Neurological Institute, BA=Broadman's Area

4. Discussion

This small fMRI pilot study used a subsequent memory paradigm to investigate the effects of an eight-week structured, supervised exercise intervention on hippocampal

function and overall brain activity in low active patients with MDD and low active healthy individuals. The current study yielded two main findings. First, our ROI analysis of the hippocampus showed a marginal decrease in activation for both groups pre-post exercise. Although this decrease in hippocampal activation was only marginally significant, a deactivation pattern was present in both groups and was consistent across other memory-related brain regions noted in the whole brain analysis. These data provide the first evidence that improved cardiovascular fitness, following eight weeks of the minimum recommended dose of exercise, affects neural function alike in healthy and MDD brains. The overall deactivation pattern that we observed in the hippocampus and several other brain regions despite similar memory performance pre-post suggests increased cortical inhibition that attenuated neural activity in a subset of brain regions known to inhibit memory encoding and/or an increase in neural network efficiency during the memory encoding process. Second, our study showed that exercise had a robust antidepressant effect on the MDD group who went from the severe to mild depression range, providing additional support to the growing body of literature that exercise is an effective adjunctive therapy for MDD [75].

A common theme in the neurocognitive literature is that brain activity for remembered items is greater than brain activity for forgotten items, as this suggests successful memory encoding [17, 76–79]. However, neuroimaging studies employing a subsequent memory design have identified a negative relationship between remembered items and neural activity in brain regions such as the insula and the supramarginal gyrus,

and hyperactivity in these regions may be detrimental to new memory formation [76, 80–82]. A candidate mechanism for the decrease in neural activity that we observed following the exercise intervention may be a modulation in the main inhibitory neurotransmitter γ -aminobutyric acid (GABA). Cortical inhibition, mediated by GABA via cortical interneurons, is an essential mechanism that eliminates task-irrelevant distractors that increase neural noise, which negatively affects attention for task demands. Inhibitory pathways consisting of GABAergic projections between the thalamus and cortex provide a mechanism that may eliminate task-irrelevant distractors by suppressing irrelevant sensory inputs early in sensory processing [83, 84]. A plethora of evidence has identified GABA deficits in MDD, and it has been postulated that GABAergic dysregulation may play a significant role in the pathogenesis of the disorder [85–88]. For example, neuroimaging studies have identified GABA deficits in the dorsolateral prefrontal and occipital cortex in depressed individuals [89–91]. Histopathological studies of postmortem tissue from MDD brains have revealed a reduction in both the density and size of GABAergic neurons in the prefrontal and occipital cortex that conceivably underlie the low levels of GABA seen in neuroimaging studies [92, 93]. Research has shown that exercise may facilitate cortical inhibition by regulating the interplay between glutamatergic excitatory neurons and GABAergic inhibitory interneurons. In mice, running engaged inhibitory mechanisms in the hippocampus through an increased expression of vesicular GABA transporter and extracellular GABA release that was also associated with improved anxiety regulation [94]. In humans with

early Parkinson's disease, a neurophysiological study used transcranial magnetic stimulation (TMS) to examine cortical inhibition of the primary motor cortex (M1) following an eight-week, high-intensity aerobics exercise intervention. In addition to improving clinical symptoms, the exercise intervention normalized corticomotor excitability through an increase in GABA-mediated cortical inhibition [95]. Nonetheless, literature supporting the role of exercise in normalizing cortical inhibition via the GABAergic system remains sparse.

Our observed decrease in brain activity during successful memory encoding pre-post the exercise intervention also suggests lowered demands on neural networks and increased neural processing efficiency. Our results provide additional support to a recent body of literature, which postulates that exercise increases neural efficiency. In children, an eight-month aerobics exercise program was associated with decreased activity in several brain regions during an antisaccade task alongside improvements in performance [96]. In elderly adults, a 12-week aerobics exercise program was associated with decreased prefrontal activation despite improvements in visual short-term memory [97]. A similar study conducted in elderly adults with mild cognitive impairment found that 12 weeks of aerobics exercise decreased brain activity in 11 brain regions during memory retrieval despite improvements in memory performance [98]. In adolescence, high-fit individuals showed a pattern of decreased activation in the hippocampus and right superior frontal gyrus combined with a deactivation in the default mode network (DMN) during the encoding of subsequently remembered items, that was absent in low-fit

individuals [99]. To determine if aerobics exercise influences learning and memory-associated neural circuitry, a group of researchers examined the brain activity in high-fit and low-fit adolescents during an SME paradigm. Despite comparable memory performance between the two groups, there were notable differences in memory-related and default mode (DMN) brain regions during encoding of successfully remembered word pairs versus forgotten word pairs. Results showed that high-fit individuals displayed a robust deactivation pattern in the DMN areas, such as the ventral medial prefrontal cortex and posterior cingulate cortex, which was absent in the low-fit group. The low-fit group also showed a greater bilateral hippocampal and right superior frontal gyrus activation during encoding of later remembered versus forgotten word pairs. Our results taken together with previous research suggest that improvements in aerobics fitness from the exercise intervention can promote neural processing efficiency during memory encoding processes.

Finally, the neurocognitive benefits associated with exercise may be attributed to increases in cerebral blood flow and neural growth factors, particularly brain-derived neurotrophic factor (BDNF), a key mediator of neuroplasticity in the brain [36, 37]. BDNF, a member of the neurotrophin family, upregulates neurogenesis, promotes neural survival, improves neural structure, and increases synaptic efficacy [100–103]. BDNF also modulates the formation and plasticity of GABAergic synapses and promotes maturation of GABAergic inhibitory networks [104–106]. Reduced BDNF levels are a consistent finding in animal models of depression [107], and administration of exogenous

BDNF into the hippocampus is able to produce antidepressant behavioral responses comparable to antidepressant medications [108]. Exercise is known to elevate BDNF production in the hippocampus [35, 109] and has been postulated as a leading candidate mechanism underlying the antidepressant effects of exercise [110, 111].

5. Limitations

This pilot study has some limitations. First, the sample size used is rather small and therefore statistically underpowered. We did not age match our groups, which resulted in the MDD group being significantly older than the healthy group. Intrinsically, we wanted to compare MDD brains to young healthy brains with no history of mental health illness or other confounding comorbidities that increase with age and determine if exercise affects neural function in healthy populations who are . Also, we did not measure sedentary behavior time which has been shown to have deleterious health consequences independent of daily physical activity levels [112]; as a result, future work must consider sedentary behavior independent of physical activity levels and cardiorespiratory fitness. Another limitation is that our MDD samples were all medicated which may have also affected results. However, this is the typical patient seen in clinical practice, and in any real-world clinical intervention using exercise, the participants would likewise be similarly medicated. Next, even though our analysis collapsing across groups mediates some of the power issues for a transdiagnostic analysis of the effects of exercise

on neural activity, the analysis was still underpowered to detect group \times time interaction effects.

While we did not closely replicate the results of Fairhall et al., it should be noted that they used a contrast comparing correct trials to fixation, while we made use of a more standard subsequent memory contrast (correct > incorrect). Nevertheless, we did observe a decrease in the correct > incorrect contrast in the hippocampus indicating that there was a decrease in hippocampal activity during successful encoding in both groups following the exercise intervention. We did not however observe any group effects. Given the small sample size, we were likely underpowered to detect any subtle group effects, though it remains possible that the decreases in activity observed following the intervention are common across low active individuals regardless of diagnostic status. In fact, it should also be noted there was even a small decrease in BDI scores amongst the healthy group. The physiological effects of exercise on the brain may be common amongst both healthy and MDD while still resulting in a substantially greater mood effect for those suffering from depression.

6. Future Research

This small pilot study demonstrates that eight weeks of the minimum recommended dose of exercise improved cardiorespiratory and significantly reduced depression severity in the MDD group. Importantly, we were able to demonstrate that combining the minimum recommended dose of exercise with conventional treatments

was effective in treating the typical patient seen in the primary care setting who continues to experience severe depressive symptoms despite being treated with antidepressant medication. On the other hand, prescribing exercise to MDD patients presents many challenges to the practitioner since many patients lack motivation to initiate and maintain an exercise routine. Introducing patients to the minimum recommended dose of exercise as an add-on therapy may offer a practical approach for practitioners to help patients initiate and maintain a routine of daily exercise [113, 114].

An interesting finding from this pilot study was that eight weeks of exercise affected healthy and MDD brains similarly. The deactivation pattern we observed in several brain regions warrants further investigation with a larger sample size to allow a more robust statistical analysis. Future work must also include an MDD control group, as this will help us understand the magnitude of the effect of exercise, in combination with other therapies, on depressive symptomology and neural function. Moreover, there is a shortage of reporting sedentary behavior, physical activity levels, and cardiovascular fitness parameters in the MDD literature. As such, some of the differences observed in studies comparing MDD to controls might be confounded by a low active lifestyle, which may be more prevalent in MDD. To address this gap, future research should compare “fit” and “low-fit” MDD groups to identify markers independent of cardiorespiratory fitness and unique to MDD. Furthermore, the exercise and cognitive literature have not established whether the psychological effects from engaging in exercise, independent of changes in fitness, are still beneficial to mental health and brain function. Future research

must indicate whether the effects seen following an exercise intervention are associated with improved cardiovascular fitness or from the psychological benefits from engaging in exercise.

Lastly, MDD is a heterogeneous disorder, and it is likely to be a multifaceted interaction of psychological and neurobiological mechanisms that underlie or mediate the effects of exercise. Future research must consider using a combination approach of multimodal imaging techniques, behavioral assessments, and biochemical analysis to delineate the biological and clinical signatures of fit and unfit MDD populations. Once we are able to elucidate these key biomarkers unique to MDD, novel intervention strategies can then be designed to prevent or reverse neuropsychological pathologies such as MDD.

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Connecting statement I

Study one showed that eight weeks of exercise, based on the minimal recommended guidelines, improved fitness in both MDD and young and healthy adults and significantly improved depressive symptoms in those with MDD. Results also showed that the MDD group performed significantly more poorer on the associative memory task when compared to young and healthy adults, indicating impaired episodic memory. Although no pre-post change in memory performance was observed for either group, fMRI results showed a marginally significant decrease in hippocampal activity in both groups following the exercise intervention. The exploratory whole brain analysis collapsed across groups revealed a similar deactivation pattern across several memory associated regions. These results indicate that the effects of exercise on neural function is not specific to those with MDD but may be a generalized effect in people who are considered low active and low-fit.

The following study examined the effects of an eight-week exercise intervention in MDD patients who were undergoing ADM treatment and cognitive behavioural group therapy (CBGT) versus ADM plus CBGT only. A power calculation yielded six participants based on a previous meta-analysis that examined the effects of exercise on depressive symptoms revealing an overall effect size of -0.80 (Rethorst, Wipfli et al. 2009). The purpose of recruiting MDD patients undergoing CBGT was twofold; 1) to control for the confounding variable of increased social contact that the exercise group

would receive from the exercise professional, 2) to compare the additional effects of exercise in those undergoing ADM treatment and CBGT. Since we did not observe any change in memory performance from the first study, I chose a battery of cognitive tests from CANTAB that have previously shown to be sensitive to MTL impairments and detect small changes in cognitive function. Sleep quality was also measured since sleep disturbance is the most frequently reported residual symptom in remissive patients. To determine whether behavioural changes were linked to physiological changes, salivary cortisol, plasma BDNF, plasma CTHB and plasma pro-inflammatory IL-1 β , IL-6, TNF- α , and anti-inflammatory IL-1ra and IL-10 cytokines were quantified.

Chapter 3: Exercise leads better clinical outcomes in those receiving medication plus cognitive behavioural therapy for major depressive disorder

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3. 1 Abstract

Objective

To investigate the effects of exercise as an add-on therapy with antidepressant medication and cognitive behavioural group therapy (CBGT) on treatment outcomes in MDD patients. We explored whether exercise reduces the residual symptoms of depression, notably cognition and sleep quality, and to identify putative biochemical markers related to treatment response.

Methods

Sixteen MDD patients were recruited from a mental health day treatment program at a local hospital. Eight medicated patients performed an eight-week exercise intervention in addition to CBGT, and eight medicated patients attended the CBGT only. Twenty-two , healthy participants with no history of mental health illness were also recruited to provide normal healthy values for comparison.

Results

Results showed exercise resulted in greater reduction in depression symptoms ($p=0.007$, $d=2.06$), with 75% of the patients showing either a therapeutic response or complete remission of symptoms versus 25% of those who didn't exercise. In addition, exercise was associated with greater improvements in sleep quality ($p=0.046$, $d=1.28$) and cognitive function ($p=0.046$, $d=1.08$). The exercise group also had a significant increase in plasma brain-derived neurotrophic factor (BDNF), $p=0.003$, $d=6.46$ that was associated with improvements in depression scores ($p=0.002$, $R^2 = 0.50$) and sleep quality ($p=0.011$, $R^2 = 0.38$).

Conclusion

We provide evidence that exercise as an add-on to conventional antidepressant therapies improved the efficacy of standard treatment interventions. Our result emphasize the clinical importance of measuring peripheral BDNF concentrations and sleep quality in MDD patients, to monitor markers most significant in clinical recovery.

Key words

Major Depressive Disorder (MDD), exercise, brain-derived neurotrophic factor (BDNF), sleep quality, cognition

3.2 Introduction

Major depressive disorder (MDD) is a global public-health problem being the second leading cause of disability worldwide (Ferrari, Charlson, & Norman, 2013) and projected to be the leading cause by 2030 (WHO, 2008). Despite many efforts to develop effective antidepressant therapies, depression remains a severely undertreated and under recognized disorder in the primary care setting. It has been estimated that merely half of depressed individuals seek medical treatment and among those who do seek help, just over 30% receive an efficacious treatment (Andrews, Sanderson, Corry, & Lapsley, 2000; Diverty & Beaudet, 1997; Fava & Ruini, 2002; Insel & Charney, 2003; Rush et al., 2008). Furthermore, over 40% of MDD patients who are considered in partial or full remission continue to experience residual symptoms and are at greater risk for relapse, highlighting the need for more efficacious antidepressant therapies (Fava et al., 2006; Paykel et al., 1995).

MDD is a clinically and biologically heterogeneous disorder that frequently coexists with other medical illnesses (Moussavi et al., 2007). Consequently, the etiology and pathogenesis of MDD is thought to be multifaceted, making it very challenging for researchers to develop novel efficacious antidepressant therapies. Converging evidence from brain imaging and neuropathological studies in humans and animals have linked MDD to structural, functional and cellular changes within the hippocampal formation. People with MDD have consistently been found to have reduced hippocampal volumes (McKinnon, Yucel, Nazarov, & MacQueen, 2009; Schmaal et al., 2016; Videbech &

Ravnkilde, 2004) and impaired hippocampal function during memory encoding and retrieval processes (Fairhall, Sharma, Magnusson, & Murphy, 2010; Milne, MacQueen, & Hall, 2012; Sweeney, Kmeic, & Kupfer, 2000; Toki et al., 2014; Zakzanis, Leach, & Kaplan, 1998).

Compelling evidence has shown that reductions in neurotrophins and growth factors, particularly brain-derived neurotrophic factor (BDNF), to be a central player for both the onset of MDD and recovery once levels are normalized (Bocchio-Chiavetto et al., 2010; Brunoni, Lopes, & Fregni, 2008; Calabrese, Molteni, Racagni, & Riva, 2009; Ronald S Duman & Monteggia, 2006; Ronald S Duman, Malberg, Nakagawa, & D'Sa, 2000; Karege, Vaudan, Schwald, Perroud, & La Harpe, 2005). BDNF is necessary for the birth, survival and function of neurons in the adult brain (Allen & Dawbarn, 2006; Autry & Monteggia, 2012; Kubo, Nonomura, Enokido, & Hatanaka, 1995; Li & Liu, 2010). Furthermore, BDNF is an activity-dependent secreted protein that plays a critical role in synaptic plasticity processes underlying learning and memory (Cunha, Brambilla, & Thomas, 2010). Consequently, therapeutic interventions that augment neuroplasticity, via increases in BDNF, have been shown to reverse the pathological effects of depression (Jacobs, Van Praag, & Gage, 2000; Serafini, 2012; Wainwright & Galea, 2013).

A growing body of research is now suggesting that a chronic inflammatory response may also play a role in the pathogenesis of MDD (Krishnadas & Cavanagh, 2012; Raison & Miller, 2011). The inflammatory hypothesis of depression was founded on the common comorbidity of depression-like behaviors with systemic infection, cancer

and autoimmune diseases (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008). Increased levels of pro-inflammatory interleukin (IL)-1 beta, IL-6, and tumor necrosis factor (TNF) alpha, and decreased levels of anti-inflammatory IL-1 receptor antagonist (ra) and IL-10 are the most commonly reported cytokines in the depression literature (Dowlati et al., 2010; Hiles, Baker, de Malmanche, & Attia, 2012; Howren, Lamkin, & Suls, 2009; Liu, Ho, & Mak, 2012; Miller & Raison, 2016; Schiepers, Wichers, & Maes, 2005; Zorrilla et al., 2001). Chronic inflammation has been shown to have a detrimental impact on neuroplasticity, such as reductions in BDNF expression, neurogenesis, and neuronal survival (Calabrese et al., 2009; Goshen et al., 2008; Guan & Fang, 2006)..

Several studies have reported that exercise alone or in combination with other therapies to be as efficacious in treating mild to moderate depression with response rates similar to antidepressant medication and cognitive behavioural therapy (Babyak et al., 2000; J. A. Blumenthal et al., 2007; J. a Blumenthal et al., 1999; Hallgren et al., 2015; Martinsen, Medhus, & Sandvik, 1985; Stathopoulou, Powers, Berry, Smits, & Otto, 2006). Furthermore, exercise for depression has been shown to improve cognitive function (Khatri et al., 2001) and sleep quality (Rethorst et al., 2013) which are the two of the most frequently reported residual symptoms among patients with MDD who achieve remission (Conradi, Ormel, & de Jonge, 2011). The beneficial effects of exercise on overall brain health has also been observed in other populations. In elderly adults, exercise has been shown to protect against the development of neurodegenerative diseases (Cotman, Berchtold, & Christie, 2007), reverse age associated brain volume loss

(Colcombe et al., 2006; Erickson et al., 2009), improve memory performance (Erickson et al., 2011; Voss et al., 2013) and improve executive function (Voss et al., 2010).

Exercise has also been shown to facilitate neurocognitive recovery from traumatic brain injury (Devine & Zafonte, 2009; Mossberg, Amonette, & Masel, 2010) and increase hippocampal volume in schizophrenics (Pajonk et al., 2010). In rodents, exercise increases adult neurogenesis (Pereira et al., 2007; H van Praag, Kempermann, & Gage, 1999), synaptogenesis (Dietrich, Andrews, & Horvath, 2008), angiogenesis (Lopez-Lopez, LeRoith, & Torres-Aleman, 2004), improves dendritic morphology (Redila & Christie, 2006; Yau et al., 2011) and enhances learning and memory (Henriette van Praag, Shubert, Zhao, & Gage, 2005).

The mechanism which exercise improves depression and overall brain health remains unclear. However, the molecular link may be partly mediated by increases in neurotrophic growth factors that promote neuroplasticity, particularly BDNF. Robust evidence from the animal literature has shown that exercise improves memory and increases hippocampal BDNF (Cotman & Berchtold, 2002; Marlatt, Potter, Lucassen, & van Praag, 2012). However, in humans, the link between exercise and BDNF is less clear. Acute exercise has consistently been shown to increase peripheral BDNF levels in healthy (Dinoff, Herrmann, Swardfager, & Lanctôt, 2017; Ferris, Williams, & Shen, 2007; Heyman et al., 2012) MDD (Gustafsson et al., 2009; Laske et al., 2010), and elderly (Håkansson et al., 2016) individuals, whereas, the long-term effects of exercise on resting BDNF concentrations have been mixed (Köhler et al., 2014; Toups et al., 2011;

Zoladz et al., 2008). Exercise has also been shown to reduce systemic inflammation in other pathological conditions such as cardiovascular disease and Type 2 diabetes mellitus (Balducci et al., 2010; Meirelles et al., 2014; Pedersen, 2006). Studies have reported a simultaneous increase in the systemic levels of cytokines with anti-inflammatory properties including IL-10, IL-1ra and a decrease in the pro-inflammatory cytokines IL-6, TNF- α , (Júnior, Lopes, Seelaender, & Lopes, 2009; Petersen & Pedersen, 2007). Nonetheless, the literature examining the relationship between exercise and inflammatory markers in MDD populations remains scant. More recently, Moon et al., (2016) identified the cysteine proteinases cathepsin B (CTHB), to be a novel protein that may play a key role in the beneficial effects of exercise on neural function .

The main objective of this exploratory feasibility study was to explore the effects of combining exercise as an add-on therapy with antidepressant medication and cognitive behavioural group therapy (CBGT) treatment outcomes in individuals. Sedentary time has been shown to be positively associated with low grade chronic inflammation in non depressed populations (Henson et al., 2013) while BDNF levels are higher in cardiorespiratory fit individuals versus unfit individuals (Zoladz et al., 2008). As such, the research investigating the underlying mechanism involved in the etiology and pathogenesis of MDD may be confounded by physical activity variables that are often not reported. For this reason, we specifically recruited MDD patients and controls to control for variations in baseline fitness level. In addition to reduction in depressive symptoms, we were interested in exploring if exercise reduces the residual symptoms of depression,

notably cognition and sleep quality, and identifying putative biochemical biomarkers (such as BDNF, cytokines, and CTHB) related to treatment response. These findings provide preliminary evidence which can be used to focus future research aimed at understanding of the etiology and pathophysiology of MDD as well as indicators associated with treatment response in exercise.

3.3 Methods

All procedures were approved by the University and Hospital Institutional Review Boards and all participants provided written informed consent. The study was registered with Clinicaltrials.gov (#NCT03191994)

3.3.1 Participants

Sixteen patients (mean age=39.31 years, SD=7.02; 12 females) with comorbid MDD and anxiety were recruited from an outpatient cognitive behavioural group therapy (CBGT) program at a local hospital in Oshawa, Ontario, Canada. Twenty-two , healthy participants (mean age=20.63, SD=1.19; 11 females) with no history of mental health illness or neurological disease were also recruited from a local university in Oshawa, Ontario Canada to provide normal healthy values for comparison. Depressed participants (n = 16) had a confirmed diagnosis of MDD according to an unstructured clinical interview by hospital psychiatrists based on criteria from the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV-TR: American Psychiatric Association, 1994) and a score ≥ 20 on the Beck Depression Inventory – Second Edition

(BDI-II: Beck, Steer, & Brown, 1996). Eligible MDD participants had no co-existing DSM-IV-TR Axis I disorders apart from anxiety. MDD participants were eligible if their pharmacological medication was stabilized a minimum of six weeks prior to study enrolment, experienced depression symptoms for a minimum of six months and screened negative on the Global Appraisal of Individual Needs (GAIN) for substance abuse (Dennis, Chan, & Funk, 2006). MDD and healthy participants were considered if they exercise less than 20 minutes, three times per week. All participants were screened with the Physical Activity Readiness Questionnaire (PAR-Q) to ensure they had no medical contraindications to physical activity.

3.3.2 Psychometric measures: anxiety, depression, sleep quality

The BDI-II (Beck et al., 1996) was used to measure depression severity. The BDI-II is the most commonly used self-reported instrument that measures depression severity ranging from mild to severe. The Hospital Anxiety and Depression Scale (HADS) was used to measure both depression and anxiety (Zigmond & Snaith, 1983). The HADS is also a reliable and widely used self-reporting instrument that consists of two 7 item subscales, one measuring anxiety (HADS-A) and one measuring depression (HADS-D) that assesses feelings of anxiety and depression. Poor sleep quality is one of the two most frequently reported residual symptom among patients with MDD who achieve remission (Conradi et al., 2011). The Pittsburgh Sleep Quality Index (PSQI) was used to measure sleep quality during the previous month (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The PSQI is a 19-item questionnaire that measures seven components of sleep

quality including, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. The maximum PSQI score is 21 points and an overall PSQI score > 5 points indicates that the individual has poor sleep quality.

3.3.3 Cognitive measures

Cognitive impairment is one of the two most frequently reported residual symptom among patients with MDD who achieve remission (Conradi et al., 2011). To assess cognitive performance within selected domains we used a computerized cognitive battery, the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Cambridge Cognition, Cambridge, UK; <http://www.cambridgecognition.com/cantab/cognitive-tests/>). The CANTAB is a fast and accurate method to assess cognitive functioning (Fray & Robbins, 1996) and shown to possess acceptable to high levels of concurrent validity and test–retest reliability (Fowler, Saling, Conway, Semple, & Louis, 1995). Each test is presented on a computer touch screen and uses non-verbalizable patterns presented in a game-like format that provides immediate feedback to maintain interest and reduce boredom (Levaux et al., 2007)(Levaux, Potvin et al. 2007)(Levaux, Potvin et al. 2007)(Levaux, Potvin et al. 2007). Three CANTAB tests were included in our assessment battery that have been previously used to identify impaired cognitive function in MDD and shown to be sensitive to changes in the hippocampus and frontal lobes (de Rover et al., 2011; Heinzl, Northoff, Boeker, Boesiger, & Grimm, 2010; Porter, Gallagher, Thompson, & Young,

2003). The Paired Associates Learning (PAL) assesses visual learning and memory. The Delayed Matching to Sample (DMS) assesses recognition memory for patterns. The Intra-Extra Dimensional Set Shift (IED) is a measure of rule acquisition and reversal, often considered a test of cognitive flexibility. In addition, the Montreal Cognitive Assessment (MoCA), a brief neurocognitive tool with high sensitivity for screening patients with mild cognitive impairment, was used to assess global function. The maximum MoCA score is 30 and an overall score ≤ 25 is indicative of mild cognitive dysfunction (Nasreddine et al., 2005).

3.3.4 Plasma collection

Non-fasting peripheral venous blood was collected mid-day from each participant at baseline and eight weeks by venipuncture into ethylenediaminetetraacetic acid (ECBGTA) tubes. Blood samples were prepared within 30 minutes by centrifugation and the plasma was stored at -85°C until assayed. Plasma proteins IL-1 β , IL-1Ra, IL-6, IL-10, TNF- α , BDNF and total CTHB were quantified using enzyme-linked immunosorbent assays (ELISA) following manufacturer's protocols (R&D Systems, MN, USA; BioLegend, CA, USA). ELISA plates were read at a wavelength of 450nm using a Synergy HTTR microplate reader (Bio-Tek Instrumentation, VT, USA).

3.3.5 Fitness assessment

The YMCA cycle ergometer test recommended by the American College of Sports Medicine was used to measure cardiorespiratory fitness at baseline and eight

weeks (Beekley, Brechue, and Dehoyos 2004; Golding, Myers, and Sinning 1989; Pescatello and American College of Sports Medicine. 2014). The YMCA protocol is an indirect submaximal exercise test that uses heart rate (HR) measurements to estimate maximal oxygen consumption ($VO_2\text{max}$). The test consists of two or more consecutive 3-minute stages at a given workload. The objective was to elevate the participant's HR between 110 bpm and 85% of age-predicted maximal HR for two consecutive stages. The first stage of the test was a 25 Watt workload at 50 revolutions per minute. Radial pulse was used to measure HR during the final 15 seconds of each minute to determine the workload of the following stages. After a steady state HR (two successive measures that differ < 5 bpm) was within 10 bpm of the 85% age-predicted maximum HR the test was complete. $VO_2\text{max}$ was predicted using the YMCA formula that includes workload, body mass and predetermined constants.

3.3.6 Exercise intervention

The eight week exercise prescription was based on the international recommendation to perform a minimum of 150 minutes per week of moderate to vigorous intensity aerobic exercise in addition to resistance activities two times per week, for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in healthy adults (Canadian Society for Exercise Physiology 1998; Garber et al. 2011). This minimum recommended dose of exercise was prescribed to increase participant adoption and adherence since people with depression generally lack motivation to begin an exercise program (Stanton & Reaburn, 2014). The research has

also found that a combining aerobic with resistance training is more effective than aerobic exercise alone in improving depressive symptoms and cognitive function (Cooney, 2013; Smith et al., 2010). The CBGT + exercise (exercise) group performed one aerobic only and two resistance (with a shorter bout of aerobic activity) weekly sessions for a duration of eight weeks. All exercise sessions were performed alone, on non-consecutive days and each session was supervised by a qualified exercise professional to increase participant compliance and to ensure all participants fulfilled the exercise prescription (Felipe B. Schuch et al., 2016). The exercise intensity for aerobic and resistance sessions was based on a target HR between 60-80% of their age-predicted maximum HR. The aerobic workloads were determined by HR response and increased by five-minute increments over the course of the eight weeks, reaching a maximum of 60 minutes per session. Resistance sessions incorporated a whole-body exercise prescription using the larger muscle groups and workloads were approximately 95% of the 10 repetition maximum to ensure proper form. Resistance exercises were performed in two or three supersets (one set of each exercise with no rest between sets) with an 8-12 repetition range to decrease rest times and to maintain target HR. Radial pulse was measured throughout each exercise session to ensure that participants maintained their target HR. Attendance was recorded and only those participants who completed >80% of the exercise sessions were included in the analysis. For a full description of the exercise intervention, please see Gourgouvelis et al., 2017.

3.3.7 Statistical analysis

All statistical analyses were conducted using GraphPad Prism, v6 (La Jolla, CA, USA). Continuous data are presented as means and standard deviations (SD). Categorical data are presented as frequencies. Baseline group differences were compared using a two-tailed Student's *t*-test and Fisher's exact test. Paired *t*-tests were used to compare the pre-post change for each group and a two-way repeated measures analysis of variance (ANOVA) was used to determine group-by-time interactions. P values less than 0.05 were considered statistically significant. Effects sizes were determined using a modified version of Cohen's D (d_{ppc2}) method which divides the difference in mean pre-post change between groups by the baseline pooled standard deviation to account for any baseline differences (Morris, 2007). The criterion used to determine remission and response rates were BDI cut off scores ≤ 11 and $\geq 47\%$ respectively (Riedel et al., 2010). Simple linear regression analyses were performed to examine the relationship between pre-post changes in plasma BDNF levels and BDI scores, sleep quality and correct response latency.

3.4 Results

3.4.1 Baseline characteristics between MDD and healthy groups

Analysis revealed no significant difference in gender distribution between groups ($p = 0.182$). As expected, the MDD group was significantly older than the healthy group, $t(36) = 12.31, p < 0.0001$, given that we intentionally recruited younger individuals to

provide normative data for comparison from healthy individuals with no history of mental health illness or other confounding pathologies that increase with age. Results showed that patients with MDD had a significantly elevated BDI score, $t(36)=12.90, p < 0.0001$, HADS-A score, $t(36)=13.07, p < 0.0001$ and PSQI score, $t(36)=9.94, p < 0.0001$, compared to the healthy controls. The MDD group had a significantly greater body mass index (BMI) compared to the healthy group, $t(36)=2.08, p = 0.045$. A single participant from the exercise group discontinued baseline VO₂max testing due to exhaustion and was excluded from VO₂max analysis. There were no significant differences between the groups for VO₂max, BDNF, and CTHB. Cytokine data for IL-1 β , IL-1ra, IL-6, and TNF- α were not included in the parametric analysis since greater than 50 percent of the values were below the level of detection. Therefore, we compared the frequencies of detectable cytokine concentrations between the groups using Fisher's exact test. Results showed no differences between groups in frequency of individuals with detectable circulating concentrations of IL-1 β , IL-1ra, IL-6, IL-10 and TNF- α ($p > 0.05$), suggesting that depressed subjects were not displaying classical signs of systemic inflammation at the study baseline. Cognitive tests revealed that the MDD group performed significantly poorer on the MoCA, $t(36)=2.32, p = 0.026$, had significantly more errors for the PAL test, $t(35)=3.90, p = 0.0004$, and had a significantly longer correct response latency for the DMS test $t(35)=2.44, p = 0.020$, suggesting cognitive impairment. Performance did not differ between groups for the DMS and IED cognitive tests ($p > 0.05$). See Table 3.1.

3.4.2 Baseline characteristics between MDD groups

At baseline, the exercise group had a significantly higher BDI score compared to the CBGT only (non-exercise) group, $t(14)=2.38, p=0.032$, indicating greater depression severity. The non-exercise group had significantly higher plasma BDNF concentrations compared to the exercise group, $t(14)=2.40, p=0.031$. There were no other baseline differences between groups (see Table 3.2). More than 50 percent of the patients did not have detectable plasma cytokine concentrations and were not included in the parametric analysis. We therefore conducted a Fisher's exact test on the frequencies of detectable plasma cytokine concentrations and found no group differences at baseline ($p > 0.05$).

3.4.3 Pre-post measures for MDD groups

Depressive Symptoms: Both MDD groups showed a statistically significant decrease in BDI and HADS-D scores following treatment. A two way repeated measures ANOVA revealed a group-by-time interaction, $f(1,14)=10.18, p=0.007$, and a large effect size of $d=2.06$ indicating that the exercise group had a greater reduction in BDI scores compared to the non-exercise group at eight week (see Figure 3.1a; 63% vs. 27%). Moreover, 75% of the patients in the exercise group showed either a therapeutic response or complete remission of symptoms versus 25% of the non-exercise group (see Figure 3.2).

Sleep quality: The exercise group showed a significant decrease in PSQI scores ($p=0.010$) while the non-exercise group showed no significant change ($p=0.09$). There was also a significant group-by-time interaction, $f(1,14)=4.81, p=0.046$, and an effect

size of $d=1.28$ indicating that exercise was effective in improving sleep quality (see Figure 3.1b).

Biological markers: There was no group-by-time interaction for $VO_2\text{max}$ pre-post. However, the exercise group showed a 31% increase in $VO_2\text{max}$ that was marginally significant $t(6)=2.17, p=0.073$, suggesting that the exercise intervention was successful at improving cardiorespiratory fitness (see Table 3.3). Biochemical marker analyses revealed a significant increase in plasma BDNF levels for the exercise group at eight weeks with a group-by-time interaction ($f(1,14)=12.47, p=0.003$) and a large effect size of $d=6.46$ (see Figure 3.1c). There were no pre-post changes in CTHB or cytokines in either group. A simple linear regression revealed that changes in BDNF were significantly associated with changes in BDI and PSQI scores indicating that those who experienced a greater increase in BDNF also experienced greater improvement in depression and sleep quality (see Figure 3). No significant relationship for changes in BDNF and correct response latency was found ($p=0.190$).

Cognition: There were no changes in performance for the MoCA, DMS, PAL, or IED tasks for either group at eight weeks. A two way repeated measures ANOVA revealed a group-by-time interaction for the DMS correct response latency ($f(1,13)=4.85, p=0.046$) and a large effect size of $d=1.08$ indicating that the exercise group was significantly faster in making a correct decision post intervention (see Table 3.3).

Table 3. 1 - Baseline characteristics of depressed patients and healthy controls

Variables	MDD (n=16)	Healthy (n=22)	<i>p</i>
Demographic			
Sex: (male/female)	4/12	11/11	.452
Age (years)	39.31 (7.02)	20.95 (1.25)	<.0001
Psychometric			
BDI (depression)	37.50 (8.18)	7.55 (6.15)	<.0001
HADS-Anxiety	15.13 (2.73)	4.77 (3.24)	<.0001
PSQI (sleep)	13.81 (3.47)	4.36 (2.40)	<.0001
Biological			
Body mass index (kg/m ²)	28.79 (5.17)	24.89 (5.17)	.045
VO _{2max} (ml.kg ⁻¹ .min ⁻¹)	23.40 (6.05) ^a	21.79 (7.77)	.510
BDNF (pg/ml)	8,237 (2163)	8,935 (2837)	.415
CTHB (pg/ml)	29,253 (9066)	37,551 (14,867)	.348
Cognitive			
MoCA	24.56 (1.67)	26.18 (2.40)	.026
DMS % correct	85.78 (13.06) ^a	90.30 (10.02) ^a	.241
DMS latency (ms)	4817 (1770) ^a	3640 (1176) ^a	.020
PAL (errors)	24.27 (19.33) ^a	7.50 (5.03) ^a	.0004
IED (errors)	19.07 (12.41) ^a	22.80 (17.93) ^a	.495

Note: MDD; Major Depressive Disorder; BDI = Beck Depression Inventory; HADS=Hospital Anxiety and Depression Scale; MoCO = Montreal Cognitive Assessment; PSQI=Pittsburgh Sleep Quality Inventory; BMI = body mass index; VO_{2max} = maximum oxygen; BDNF=brain-derived neurotrophic factor; CTHB=cathepsin B; DMS=Delayed Matching to Sample; PAL=Paired Associates Learning; IED=Intra/Extra Dimensional Shift

Data are expressed as mean with SD in parentheses.

^a One missing value

Table 3. 2 - Baseline characteristics of depressed groups

Variables	CBGT + Exercise (n=8)	CBGT (n=8)	<i>p</i>
Demographic			
Sex: (male/female)	1/7	3/5	.248
Age (years)	37.25 (8.00)	41.38 (5.66)	.253
Education (years)	13.25 (2.19)	13.50 (1.41)	.790
Cumulative illness duration (years)	3.57 (3.21)	3.00 (3.02)	.432
Psychometric			
BDI (depression score)	41.75 (3.50)	33.25 (9.48)	.032
HADS-Anxiety	15.63 (1.77)	14.63 (3.50)	.483
PSQI (sleep score)	14.38 (3.46)	13.25 (3.62)	.535
Biological			
Body mass index (kg/m ²)	28.33 (5.12)	29.25 (5.52)	.734
VO _{2max} (ml.kg ⁻¹ .min ⁻¹)	24.82(8.00) ^a	22.16(3.80)	.416
BDNF (pg/ml)	7,108.48(596.51)	9,363.74(730.75)	.031
CTHB (pg/ml)	37,580 (10,284)	48,102 (25,327)	.295
Cognitive			
MoCA	24.63 (1.41)	24.50 (2.00)	.887
DMS % correct	90.48 (6.50) ^a	81.67 (16.23) ^a	.203
DMS latency (ms)	4,857 (1,648) ^a	4,781 (1,983) ^a	.938
PAL (errors)	22.14 (20.93) ^a	26.13 (19.05) ^a	.706
IED (errors)	20.57 (16.09) ^a	17.75 (9.04) ^a	.677

Note: CBGT = cognitive behavioural group therapy; BDI = Beck Depression Inventory; HADS=Hospital Anxiety and Depression Scale; MoCA = Montreal Cognitive Assessment; PSQI=Pittsburgh Sleep Quality Inventory; BMI = body mass index; VO_{2max} = maximum oxygen consumption; BDNF=brain-derived neurotrophic factor; CTHB=cathepsin B; DMS=Delayed Matching to Sample; PAL=Paired Associates Learning; IED=Intra/Extra Dimensional Shift

Data are expressed as mean with SD in parentheses.

^a One missing value

Table 3. 3 - Pre-post changes for depressed groups

Measure	CBGT + Exercise (n=8)				CBGT (n=8)				Between Group Analysis		
	Pre Mean (SD)	Post Mean (SD)	<i>p</i>	<i>d</i>	Pre Mean (SD)	Post Mean (SD)	<i>p</i>	<i>d</i>	F	<i>p</i>	<i>d_{ppc2}</i>
Psychometric											
BDI	41.75 (3.50)	15.50 (10.43)	.0004	2.89	33.25 (9.48)	24.38 (10.01)	.042	0.91	10.80	.007	2.38
HADS-Depression	13.63 (2.97)	5.88 (2.23)	<.0001	2.86	12.00 (3.59)	9.75 (3.73)	.034	0.61	20.91	.0004	1.63
HADS-Anxiety	15.63 (1.77)	11.38 (4.53)	.010	0.90	14.63 (3.50)	11.25 (2.38)	.030	1.11	0.253	.623	0.31
PSQI (sleep)	14.38 (3.46)	7.75 (4.20)	.011	1.68	13.25 (3.62)	11.38 (3.30)	.090	0.54	4.81	.046	1.32
Biological											
BMI (kg/m ²)	28.33 (5.12)	28.29 (4.48)	.934	0.01	29.25 (5.52)	29.95 (5.36)	.068	0.13	1.84	.196	0.14
VO _{2max} (ml.kg ⁻¹ .min ⁻¹)	24.82 (8.00) ^a	32.52 (10.12) ^a	.073	0.83	22.16 (3.80)	26.42 (8.17)	.130	0.60	0.659	.432	0.54
BDNF (pg/ml)	7107 (596.51)	10,642 (957.45)	.008	1.54	9363 (730.75)	8497 (943.75)	.304	0.36	12.47	.003	6.46
CTHB (pg/ml)	37,580 (10,284)	39,293 (14,278)	.697	0.13	48,102 (25,327)	55,477 (22,450)	.109	0.30	0.947	.347	0.28
Cognitive											
MoCA	24.63 (1.41)	25.75 (2.38)	.229	0.56	24.50 (2.00)	25.75 (2.71)	.380	0.40	0.006	.938	0.07
DMS % correct	90.48 (6.50) ^a	89.48 (3.50) ^a	.721	0.19	81.67 (16.23)	80.00 (21.97)	.844	0.09	0.005	.943	0.05
DMS latency (ms)	4857 (1,648) ^a	2650 (510.50) ^a	.010	1.68	4781 (1,983)	4601 (3785)	.800	0.02	4.85	.046	1.08
PAL (errors)	22.14 (20.93) ^a	19.86 (11.44) ^a	.772	0.13	25.13 (19.05)	19.63 (21.14)	.056	0.33	0.304	.591	0.16
IED (errors)	20.57 (16.09) ^a	18.57 (7.59) ^a	.774	0.16	17.75 (9.04)	19.50 (7.62)	.666	0.21	0.252	.624	0.28

Note: CBGT = cognitive behavioural group therapy; BDI = Beck Depression Inventory; HADS = Hospital Anxiety and Depression Scale; PSQI = Pittsburgh Sleep Quality Inventory; BMI = body mass index; VO_{2max} = maximum oxygen consumption; MoCA = Montreal Cognitive Assessment; DMS = Delayed Matching to Sample; PAL = Paired Associates Learning; IED = Intra/Extra Dimensional Shift; *d* = Cohen's D; *d_{ppc2}* = Cohen's D; Data are expressed as mean with SD in parentheses ^a One missing value

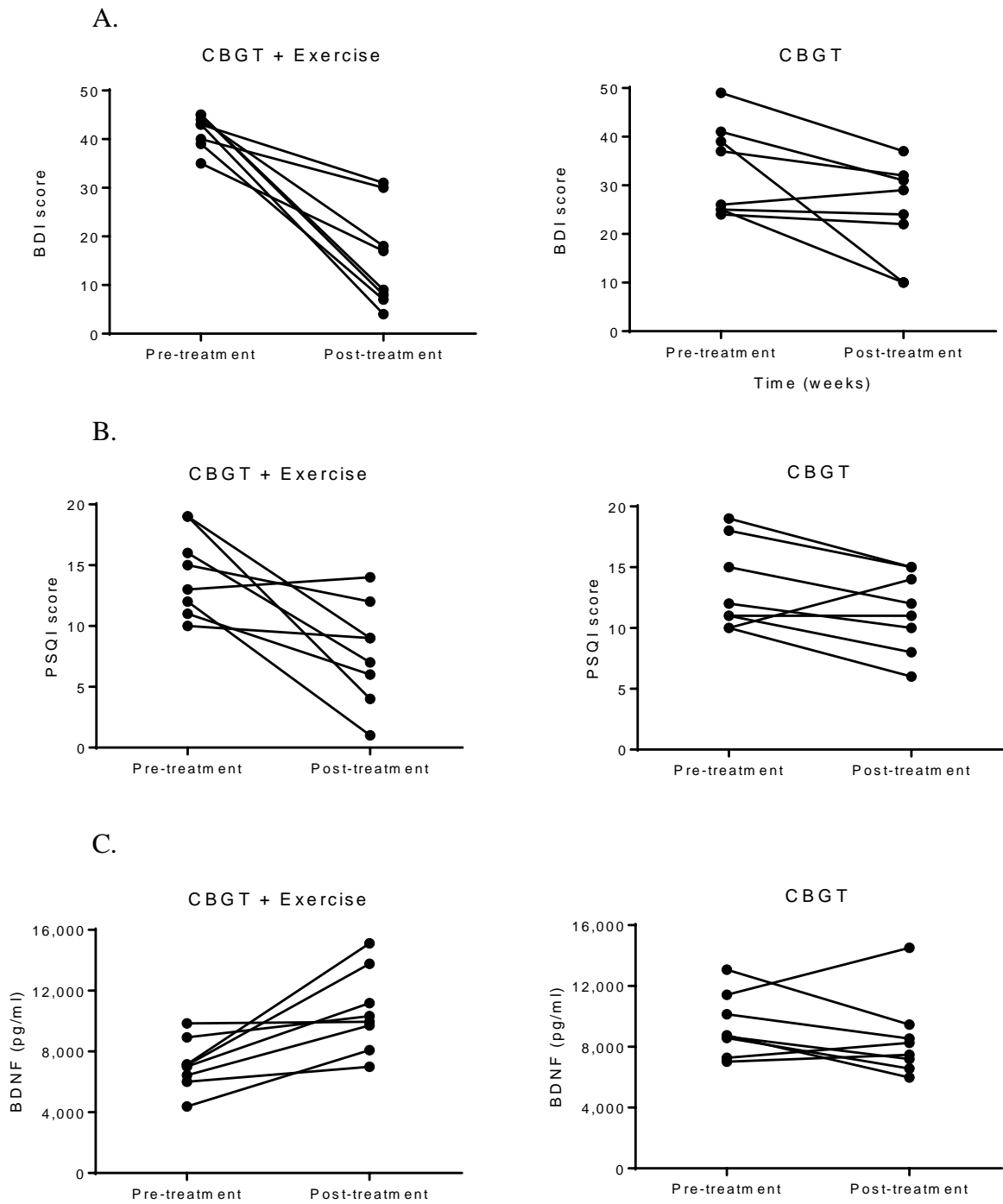


Figure 3. 1 - Individual group plots illustrating pre-post changes for (A) BDI depression scores, (B) PSQI scores and (C) BDNF levels. Abbreviations: CBGT=cognitive

behavioural group therapy; BDI=Beck Depression Inventory; PSQI=Pittsburgh Sleep Quality Inventory; BDNF=brain-derived neurotropic factor

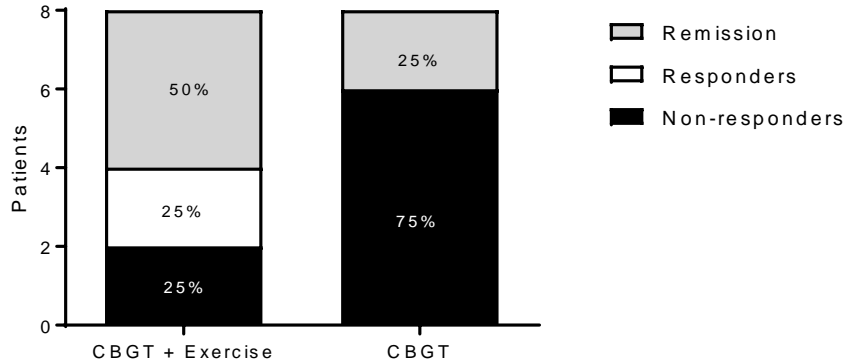


Figure 3. 2 Responders, non-responders and remissive MDD patients at 8 weeks for each group. Benefit of exercise was greater as defined by treatment response and remission (N=6) compared to (N=2) in the non-exercise group. Responders represent patients with a greater than or equal to a 47% reduction BDI score at 8 weeks compared to baseline and remission represents patients with a BDI score less than or equal to 11. Abbreviation: CBGT=cognitive behavioural group therapy

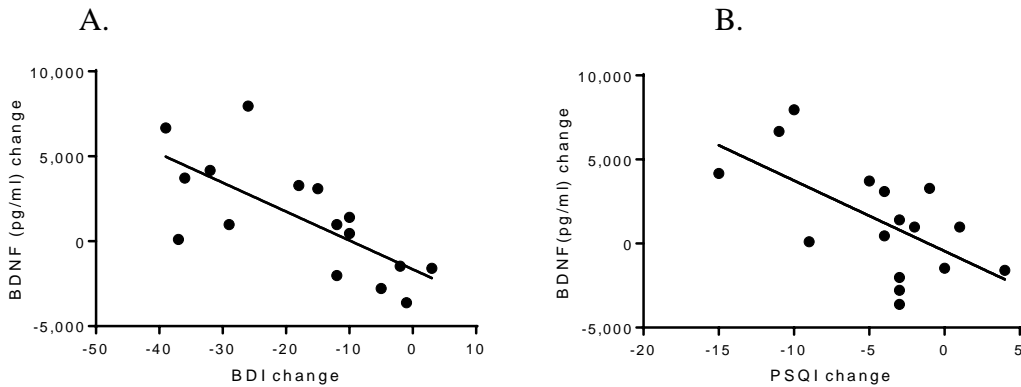


Figure 3. 3 A) Linear regression of pre-post changes for BDI and PSQI scores against BDNF change, irrespective of group. (A) A significant negative correlation was found for (A) BDI scores and BDNF levels ($p=0.002$, $R^2 = 0.50$) and (B) PSQI scores and BDNF levels ($p=0.011$, $R^2 = 0.38$) indicating that improvements in depression and sleep quality scores are associated with an increase in BDNF levels. Abbreviations: BDI, Beck Depression Inventory, BDNF, brain-derived neurotropic factor, PSQI, Pittsburgh Sleep Quality Index

3.5 Discussion

This feasibility study investigated the effects of an eight-week exercise

prescription, based on the minimal recommended dose, on a series of symptom, biochemical, and cognitive measures. Our preliminary study provides evidence that exercise as an add-on therapy led to higher remission/treatment response rates versus more common treatment approaches alone. In addition, we found that exercise improves sleep quality and cognitive function, and BDNF levels increased in the exercise group post-treatment. These changes in BDNF were significantly associated with symptom improvement in depression and sleep quality scores, providing potential biomarkers of treatment response. We also did not observe any significant differences between MDD patients and healthy controls for plasma CTHB, anti-inflammatory and pro-inflammatory cytokines, and no changes pre-post, suggesting BDNF may be a specific marker for the positive changes which come about following an exercise intervention in patients who do not have co-morbid inflammation.

To the best of our knowledge, this is the first study to investigate the effects of exercise in combination with ADM and CBGT specifically in a MDD population. As such, there are limited data to compare our research findings. Our results provide evidence for the therapeutic use of exercise in treating MDD collaborating with previous findings that exercise as an add-on therapy to ADM is more efficacious in alleviating MDD symptoms than ADM alone (Pilu et al., 2007; Schuch, Vasconcelos-Moreno, Borowsky, & Fleck, 2011). While the sample in our study was small, the added benefit of an exercise intervention had a large effect size with respect to the changes in clinical scores. The efficacy of exercise is further substantiated by the fact that 75% of the patients in the exercise group achieving either remission or a therapeutic response versus only 25% in the

non-exercise group. This represents substantive improvement in outcomes with the addition of a relatively low-cost add-on intervention.

The increase in plasma BDNF concentration and the associated decrease in depressive symptoms and improvements in sleep quality observed in the exercise group adds further support to the interplay between depression, sleep quality and BDNF that may underlie the onset and recovery of MDD (Schmitt, Holsboer-Trachsler, & Eckert, 2016). Sleep disturbances are reported by up to 90% of depressed subjects (Mendlewicz, 2009; Palagini, Baglioni, Ciapparelli, Gemignani, & Riemann, 2013) and sleep studies have shown that depression is associated with reductions in slow-wave activity (SWA), a reliable EEG marker of sleep homeostasis (Borbély et al., 1984; Hoffmann, Hendrickse, Rush, & Armitage, 2000). SWA is an essential mechanism for restoring synaptic plasticity processes associated with learning and memory (Gorgoni et al., 2013; Huber, Ghilardi, Massimini, & Tononi, 2004). BDNF, a mediator of activity-dependent synaptic plasticity, has been suggested to be the molecular mechanism that links synaptic plasticity and the homeostatic sleep response (Bachmann et al., 2012; Huber, Tononi, & Cirelli, 2007). Rats administered higher levels of intracortical injections of BDNF during wakefulness show a stronger SWA response during subsequent sleep and stronger synaptic potentiation during waking. However, this effect is reversed when blocking BDNF during wakefulness (Faraguna, Vyazovskiy, Nelson, Tononi, & Cirelli, 2008). As such, one possible mechanism of the improved sleep quality of patients in the exercise group may be the increase in plasma BDNF concentrations brought about via increased physical activity.

Our initial baseline comparison between MDD patients and healthy controls

revealed that the MDD patients performed below the healthy controls on the hippocampal-dependent cognitive tests. These behavioural results complement our previous fMRI findings that explored the effects of an eight week exercise intervention on hippocampal function during a memory encoding task, in low fit MDD and healthy individuals (Gourgouvelis, Yelder, & Murphy, 2017). Despite no pre-post change in memory performance for either group, there was a consistent deactivation pattern in the hippocampus and other memory related brain regions during the memory encoding process. This deactivation pattern was common amongst both the MDD and healthy groups, suggesting that exercise may have a generalized effect on brain function in low fit individuals by enhancing neural network processing efficiency while still resulting in a greater mood effect for those suffering from MDD. Electroencephalographic studies have also found that active individuals showed less PFC activation and significantly faster reaction times compared to individuals indicating that physically active individuals require less cognitive resources and effortful task preparation that results in faster information processing speeds (Berchicci, Lucci, & Di Russo, 2013).

3.6 Limitations

The sample size of this feasibility study is small, thus even though the exercise group experienced a concomitant decrease in depression severity and increase in plasma BDNF, these results must be considered preliminary. Another possible limitation is that our MDD sample were all undergoing ADM which may have affected our baseline comparison with healthy controls. However, given that we wanted to replicate the typical

patient seen in “real-world” clinical practice, to maximize the external validity of our results, including patients already on ADM actually increases the external validity. Furthermore, since our sample was comprised of MDD patients, we cannot be certain if the link between BDNF, depression and sleep quality exists in high-fit/high-active MDD patients. There is a lack of reporting physical activity levels and cardiorespiratory fitness parameters in the MDD literature. Therefore, significant differences observed in studies that compare MDD to healthy individuals may be confounded by a sedentary lifestyle that may be more common in MDD. Future studies must compare ‘fit’ versus ‘low fit’ MDD groups to identify biological markers, independent of cardiorespiratory fitness and specific to MDD.

3.7 Conclusion

The design of this feasibility study allowed for a “real-world” therapeutic approach that addresses effectiveness while also measuring biochemical markers shown to be altered in MDD. We provide evidence that exercise as an add-on to conventional antidepressant therapies is more efficacious in treating MDD than no exercise. We also found that improvements in depression and sleep quality were associated with an increase in plasma BDNF concentration following exercise, providing a potential biological marker for treatment outcome. These results emphasize the clinical importance of measuring peripheral BDNF concentrations and sleep quality in MDD patients, to monitor changes over the course of treatment that may elucidate markers most significant in clinical recovery. Finally, our study demonstrated that a combined aerobic and resistance exercise

prescription, based on the minimum recommended dose, is well tolerated and adhered to throughout the eight weeks by MDD patients, giving health care practitioners guidelines for prescribing exercise to their patients.

3.8 Conflict of interest disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

3.9 Acknowledgments

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Connecting statement II

This study demonstrated that exercise in addition to ADM and CBGT produced significantly better outcomes in people with MDD than ADM plus CBGT with no exercise. Results showed that exercise as an add-on treatment improved depressive symptoms, sleep quality and cognitive function significantly more than no exercise. Results also showed that improvements in depression scores and sleep quality were associated with an increase in plasma BDNF concentrations suggesting that exercise mediates these effects through an upregulation of BDNF secretion. Findings also indicate that the MDD groups were not in an inflamed state at baseline suggesting that chronic low-grade inflammation was either resolved with ADM treatment or that these individuals had normal immune function. Salivary cortisol was not included in the analysis since 19% of the sample tubes did not contain saliva samples. Also, 28% of participants showed an inverse CAR indicating errors in sampling methods.

The purpose of study three was to examine the effects of exercise on cognitive function, plasma BDNF and CTHB concentrations in young and healthy adults. Since study one showed a change in neural activity during the encoding process of the memory task in young and healthy adults, I wanted to determine whether these changes in neural function were paralleled by changes in plasma BDNF and CTHB concentrations that have been shown to increase following long-term exercise.

Chapter 4: You can't fix what isn't broken: Effects of eight weeks of exercise on cognitive function and biochemical markers in young and healthy adults

Adapted from: Gourgouvelis, J., Yields, P., Clarke, S., Behbahani, H. & Murphy, B. (2017). You can't fix what isn't broken: Effects of eight weeks of exercise on cognitive function and biochemical markers in young and healthy adults. *PeerJ* (under review)

4.1 Abstract

Objective

The benefits of exercise on brain health is well known in aging and psychiatric populations. However, the relationship between habitual exercise in young and healthy adults remains unclear. This study explored the effects an eight week exercise prescription on cognitive function, brain-derived neurotrophic factor (BDNF) and cathepsin B (CTHB) in young and healthy adults.

Methods

Twenty-two untrained, young and healthy adults were recruited from a local university. Twelve participants performed an eight-week exercise prescription and twelve participants served as controls. Cognitive assessments, cardiorespiratory fitness and plasma BDNF and CTHB concentrations were measured at baseline and eight weeks.

Results

Results showed exercise improved cardiorespiratory fitness ($p=0.011$, $d=1.48$) with no improvements in cognitive function or no changes in plasma BDNF and CTHB concentrations.

Conclusion

We provide evidence that eight weeks of exercise does not improve cognitive function or change plasma biochemical markers concentrations in young and healthy adults, despite improvements in cardiorespiratory fitness. These results suggest that cognitive health may peak during early adulthood leaving little room for improvement throughout this period of the lifespan.

4.2 Introduction

Research has consistently demonstrated the health benefits of habitual exercise. Not only has exercise been shown to prevent disease, but exercise is considered an effective treatment for several medical conditions (Naci & Ioannidis, 2013; Pedersen & Saltin, 2006). More recently, considerable attention has focused on the positive effects of exercise on brain structure and function. In elderly populations, exercise has been shown to increase brain volume in selective areas such as the hippocampus and prefrontal cortex (Colcombe et al., 2006; Erickson et al., 2009; Erickson, Voss, Prakash, Basak, Szabo, Chaddock, Kim, Heo, Alves, White, et al., 2011). Additionally, exercise improves memory (Erickson, Voss, Prakash, Basak, Szabo, Chaddock, Kim, Heo, Alves, & White, 2011; Voss et al., 2013), executive function (Voss et al., 2010a), attention (Salthouse & Davis,

2006) and decreases cognitive processing speed (Salthouse & Davis, 2006). Exercise has also shown to be effective in treating mental health disorders such as anxiety (Herring, O'Connor, & Dishman, 2010), depression (Blumenthal et al., 1999; Stathopoulou, Powers, Berry, Smits, & Otto, 2006) and schizophrenia (Stathopoulou et al., 2006). Complementing human findings, the rodent literature has shown exercise to upregulate adult neurogenesis (van Praag, Kempermann, & Gage, 1999), increase neuronal survival (Kobilo et al., 2011), enhance dendritic growth (Leggio et al., 2005), increase dendritic spine density (Eadie, Redila, & Christie, 2005), enhance synaptic plasticity (Farmer et al., 2004), induce angiogenesis (Swain et al., 2003), enhance learning (Henriette van Praag, Shubert, Zhao, & Gage, 2005), and improve memory (Marlatt, Potter, Lucassen, & van Praag, 2012).

Exercise activates cascades of molecular and cellular signalling mechanisms within the central nervous system. Although the precise mechanisms underlying the neurogenic effects of exercise remain unclear, a growing body of literature suggests that exercise activates neurotrophic mechanisms known to promote neuroplasticity. Most notably, brain-derived neurotrophic factor (BDNF) is emerging as a key molecule underlying the benefits of exercise on brain function (Cotman, Berchtold, & Christie, 2007). BDNF is an activity-dependent secreted protein essential for neural growth, neural survival (Barde, 1990) and synaptoplastic processes critical for learning and memory (Pang & Lu, 2004; Yamada, Mizuno, & Nabeshima, 2002). The brain contributes to approximately 70–80% of peripheral BDNF concentrations at rest and during exercise (Rasmussen et al., 2009). BDNF is also produced in various peripheral tissues which is stored and released from circulating platelets upon activation (Fujimura et al., 2002; Yamamoto & Gurney, 1990).

In rodents, exercise rapidly increases the BDNF gene expression in brain regions involved with learning and memory formation, particularly in the hippocampus (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005; Cotman & Berchtold, 2002; Cotman et al., 2007; Neeper, Gómez-Pinilla, Choi, & Cotman, 1995). Similar to the increases of central BDNF expression observed in rodents, research has consistently shown that acute exercise increases peripheral BDNF concentrations in humans (Ferris, Williams, & Shen, 2007; Knaepen, Goekint, Heyman, & Meeusen, 2010; Rojas Vega et al., 2006). However, the literature supporting elevations in resting peripheral BDNF concentrations following a long-term exercise intervention have been mixed. In older adults, a one year moderate intensity aerobic intervention significantly increased resting plasma and serum BDNF concentrations (Erickson, Voss, Prakash, Basak, Szabo, Chaddock, Kim, Heo, Alves, White, et al., 2011) that was positively associated with age (Leckie et al., 2014). In patients with Major Depressive Disorder (MDD), an eight week moderate aerobic and resistance intervention significantly increased plasma BDNF concentrations (Gourgouvelis, Murphy, & Yelder, 2017) while no change in serum BDNF concentrations were observed following a three month aerobic exercise intervention (Krogh et al., 2014). In young and healthy adults, a five week moderate aerobic intervention significantly increased resting plasma BDNF concentrations (Zoladz et al., 2008) while no increase in plasma BDNF concentrations were observed following 12 weeks of strength or 12 weeks of moderate endurance training (Schiffer, Schulte, Hollmann, Bloch, & Strüder, 2009) and no change in serum BDNF concentrations following three weeks of moderate aerobic activity (Griffin et al., 2011). Nonetheless, the lack of consistent findings examining the effects of long-term

exercise on BDNF might be attributed to the heterogeneity of exercise interventions between studies and lack of reporting baseline physical activity levels.

It was recently demonstrated that cathepsin B (CTHB), a cysteine proteinases produced by contracting skeletal muscle, is capable of penetrating the blood-brain barrier and upregulating both BDNF expression and hippocampal neurogenesis in wild-type mice (Moon et al., 2016). Following long-term running, researchers also observed an increase in plasma CTHB concentrations that was associated with improved memory performance in mice, Rhesus monkeys and humans. CTHB is an autophagy-related protein also shown to prevent memory deficits in Alzheimer's disease by upregulating autophagic-lysosomal processes and reducing accumulations of amyloid- β peptides in the brain (Mueller-Steiner et al., 2006; Yang et al., 2011).

Deficits in cognitive function and BDNF expression have been mainly observed in several age associated neurodegenerative diseases and psychiatric disorders (Bocchio-Chiavetto et al., 2010; Diniz & Teixeira, 2011; Erickson & Barnes, 2003). As such, research investigating the exercise-cognition relationship has focused on these populations, with few studies examining this relationship in young and healthy adults. The objectives of this study were to investigate the effects of a well characterized eight-week exercise intervention on cognitive function in untrained young and healthy adults. We also investigated whether changes in cognitive function were linked to changes in plasma BDNF and CTHB concentrations.

4.3 Methods

4.3.1 Participants

Twenty-two university students (mean age=21.10, $SD=1.27$; 12 females) were recruited from a local university in Oshawa, Ontario Canada. All participants completed the Physical Activity Readiness Questionnaire (PAR-Q) to screen for contraindications to exercise. Inclusion criteria included: male or female age 18-30, no history of mental health illness, low active (exercise less than 20 minutes, three times weekly) and low cardiorespiratory fitness based on the Canadian Society for Exercise Physiology guidelines (Canadian Society for Exercise Physiology, 1998). Participants were then randomly assigned to an exercise intervention group or a control group to provide baseline and post assessment comparisons. This study was approved by the Ontario Institute of Technology Research Ethics Board. All participants provided written consent.

4.3.2 Neuropsychological measures

Cambridge Neuropsychological Test Automated Battery (CANTAB)

Cognitive performance was evaluated using the Cambridge Neuropsychological Test Automated Battery (CANTAB) software (Cambridge Cognition, Cambridge, UK; <http://www.cambridgecognition.com/cantab/cognitive-tests/>). CANTAB is currently the most widely published automated neuropsychological test battery (Wild, Howieson, Webbe, Seelye, & Kaye, 2008) possessing high levels of concurrent validity and test–retest reliability (Fowler, Saling, Conway, Semple, & Louis, 1995). CANTAB is an accurate, faster and more efficient method to assess cognitive functioning than traditional pen and

paper tools (Fray & Robbins, 1996). All tests use non-verbalisable patterns and are presented on a computer touch screen in a game-like format that provides immediate feedback to reduce boredom (Levaux et al., 2007)(Levaux, Potvin et al. 2007)(Levaux, Potvin et al. 2007)(Levaux, Potvin et al. 2007). The CANTAB tests included in our assessment battery assess executive function, learning and memory which have previously shown to improve following an exercise intervention (Colcombe et al., 2004; Erickson, Voss, Prakash, Basak, Szabo, Chaddock, Kim, Heo, Alves, White, et al., 2011; Ruscheweyh et al., 2011; Voss et al., 2010b) and to be sensitive to changes in the hippocampus and frontal lobes (de Rover et al., 2011; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991; Winocur, Wojtowicz, Sekeres, Snyder, & Wang, 2006). A brief description of each test included in this study is provided below.

Delayed Matching to Sample (DMS): This test assesses recognition memory for patterns. The subject is shown a complex visual pattern and then must choose one of four similar patterns that matches the original pattern. Trials consist of either the original pattern that is obscured before the choices appear, or there is a brief delay of 0, 4 and 12 seconds between these steps. Outcome measures included accuracy and response latency.

The Paired Associates Learning (PAL): This test assesses visual memory and new learning and is sensitive to changes in the temporal and frontal lobes. In this test, boxes are displayed on the screen and are opened in a randomized order with one or more containing a pattern. Each pattern is then displayed one at a time in the middle of the screen and the participant must identify the box where the pattern was located. The participant proceeds to the next stage when all the correct locations are identified. The test has an increasing level

of difficulty that ranges from two to eight patterns to be remembered. The total number of errors was used as the outcome measure for this test.

The Spatial Recognition Memory (SRM): This test is a measure of visual spatial recognition that uses a forced-choice discrimination paradigm in which participants must choose between previously learned and novel stimuli. The percentage of total responses correct was used as the outcome measure.

The Intra–Extra Dimensional Set Shift (IED): This test is a measure of rule acquisition and reversal. This test assesses visual discrimination and attentional set formation, as well as maintenance, shifting, and flexibility of attention. The number of stages completed and total number of errors were used as the outcome measures.

4.3.3 Plasma collection

Non-fasting blood was collected mid-day from each participant at baseline and eight weeks by venipuncture into ECBGTA tubes and centrifuged within 30 minutes. Plasma was aliquotted and stored at -85°C until analysis. Plasma BDNF and total CTHB were quantified using enzyme-linked immunosorbant assays (ELISA) following manufacturer's protocols (R&D Systems, MN, USA; BioLegend, CA, USA). ELISA plates were read at a wavelength of 450nm using a Synergy HTTR microplate reader (Bio-Tek Instrumentation, VT, USA).

4.3.4 Fitness assessment

In order to assess baseline fitness levels to determine eligibility and starting intensity for the exercise intervention baseline cardiovascular fitness was assessed with the YMCA cycle ergometer protocol recommended by the American College of Sports Medicine (Beekley, Brechue, & Dehoyos, 2004; Golding, Myers, & Sinning, 1989; Pescatello & American College of Sports Medicine., 2014). This protocol is a submaximal exercise that estimates maximal oxygen consumption ($VO_2\text{max}$) from heart rate (HR) measurements and perceived exertion. The protocol consisted of two or more consecutive 3-minute stages at a given workload. The objective was to elevate the participant's HR to a target zone between 110 beats per minute and approximately 85% of the age-predicted maximum heart rate for two consecutive stages. The initial workload consisted of a 25 Watt workload at a cadence of 50 revolutions per minute. The workload of the subsequent stages increased by the amount specified by the YMCA protocol based on the average HR during the last 2 min of each stage. When the target HR was achieved for two consecutive stages, the test was considered complete. Participants were also assessed at eight weeks to determine changes in cardiorespiratory fitness.

4.3.5 Exercise prescription

The exercise prescription was based on international guidelines of a minimum of 150 minutes per week of moderate to vigorous intensity aerobic exercise in combination with resistance activities two times per week, for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in healthy adults (Canadian Society for Exercise Physiology, 1998; Garber et al., 2011). All exercise sessions were

supervised by a qualified exercise professional. The exercise group performed one aerobic only and two sessions per week on non-consecutive days for a duration of eight weeks. The exercise intensity for aerobic and resistance sessions were individualized based on each participant's target HR that ranged between 60-80% of their age-predicted maximum HR. Radial pulse was measured throughout each aerobic and resistance exercise session to confirm that participants maintained their target HR range.

Aerobic session

Participants were given the opportunity to choose their aerobic activity on either the treadmill, stationary bike or elliptical machine. Aerobic workloads were based on HR response and were increased by five-minute increments, over the eight weeks, reaching a maximum of 60 minutes per session.

Resistance sessions

Resistance sessions combined a whole-body exercise prescription engaging the larger muscle groups. For each session, participants performed eight resistance exercises using free weights and resistance training machines. Exercises were performed consecutively in two or three supersets (with an 8-12 repetition range) to minimize rest times and to maintain target HR range. Initial workloads were individualized for each participant based on approximately 95% of their 10 repetition maximum. Subsequent workloads were increased approximately 5% once participants were able to complete three sets of 12 repetitions. Exercises were changed every four weeks to avoid adaptation; although still targeting the same muscle groups. Each session incorporated a 5 minute aerobic warmup and concluded with a 15 minute aerobic activity.

4.3.6 Statistical analysis

All data were analyzed using Prism GraphPad software, version 6.0. Continuous data are presented as means and standard deviation (SD) and categorical data are presented as frequencies. Independent samples *t*-tests were used to compare baseline variables across groups for continuous variables and Fisher's exact tests were used to compare categorical variables. Paired *t*-tests were used to determine within-group changes from pre-post testing. A two-way analysis of variance (ANOVA) with repeated measures (Group by Time) was used to determine pre-post changes and between-group differences. Statistical significance was set at $p < 0.05$ (two-tailed). A modified version of Cohen's *D* (d_{ppc2}) specifically designed for pre-post experiments to account for any differences at baseline was used to calculate effects sizes (Morris, 2007).

4.4 Results

4.4.1 Baseline characteristics between groups

Baseline group analyses revealed no significant differences for sex, age, BMI, BDNF and CTHB (see Table 4.1). One ($n=1$) participant from the control group discontinued VO₂max testing due to exhaustion and was excluded from the VO₂max analysis. The control group showed a significantly higher mean VO₂max than the exercise group, $t(19)=3.29$, $p=.004$, however all participants met the Poor Health Benefit Rating Zone for cardiorespiratory fitness criteria based on the Canadian Society for Exercise Physiology guidelines (Canadian Society for Exercise Physiology, 1998).

4.4.2 Pre-post measures

The exercise group showed a significant increase in VO₂max indicating that the exercise intervention was able to improve cardiorespiratory fitness (see Table 4.2). Biochemical marker analysis revealed no significant group-by-time effects for BDNF, $f(1,20)=1.29$, $p=.296$; $d=.39$, or CTHB, $f(1,19)=.812$, $p=.379$; $d=.253$, see Figure 4.1. Cognitive analyses from the CANTAB battery revealed no significant group-by-time effects for the DMS, $f(1,20)=0.022$, $p=.884$; $d=.52$, PAL, $f(1,20)=0.035$, $p=.854$; $d=.077$, SRM, $f(1,20)=2.20$, $p=.154$; $d=.61$, or IED, $f(1,20)=2.41$, $p=0.136$; $d=.68$, tests (see Figure 4.2). There were no significant group-by-time effects found for correct response latencies on the DMS, $f(1,20)=0.838$, $p=.371$; $d=.52$, or SRM, $f(1,20)=0.019$, $p=.891$; $d=.071$, tests.

Table 4. 1 - *Baseline characteristics of participants*

Variables	Exercise Group (n=12)	Controls (n=10)	<i>df</i>	<i>p</i>
Sex: (male/female)	6/12	4/10	1	.639 ^a
Age (years)	21.08 (1.24)	21.16 (1.30)	20	.976 ^b
BMI (kg/m ²)	24.67 (3.68)	22.90 (4.42)	20	.319 ^b
VO ₂ max	17.06 (6.12)	26.17 (6.53) ^c	20	.004^b

^aPearson's chi-square

^bStudent's t-test

^c One missing value

Abbreviation: BMI=body mass index; VO₂max = maximum oxygen consumption

Data are expressed as the mean with the standard deviation in parentheses.

Table 4. 2 - Pre-post changes for BMI and VO₂max

Variables	Exercise (n=12)		Control (n=10)		Group Differences		
	Pre	Post	Pre	Post	<i>F</i>	<i>p</i>	<i>d_{ppc2}</i>
BMI (kg/m ²)	24.66 (3.68)	24.98 (3.19)	22.90 (4.42)	22.64 (4.35)	.040	.84	.14
VO ₂ max (mL/kg/min)	17.06 (6.12)	25.79 (11.29)	26.17 (6.53)	25.42 (3.24) ^a	7.90	.011^a	1.48
BDNF (pg/ml)	9079 (3479)	8680 (3781)	8751 (2198)	9528 (2612)	1.29	.27	.39
CTHB (pg/ml)	36,011 (10,778)	36,332 (15,178)	40,972 (18,366)	37,526 (10,826) ^a	.81	.379	.25

^aOne missing value

Abbreviations: BMI=body mass index; VO₂max = maximum oxygen consumption; BDNF = brain derived neurotrophic factor; CTHB = cathepsin B

Data are expressed as the mean with the standard deviation in parentheses.

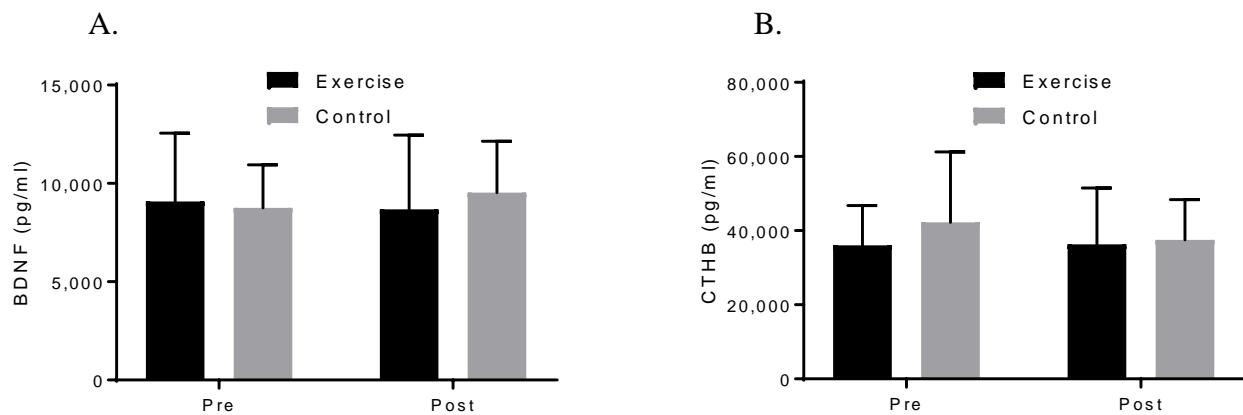


Figure 4. 1 - Group plots illustrating pre-post biomarker changes for (A) plasma BDNF concentrations, (B) plasma CTHB concentrations. Abbreviations: BDNF=brain-derived neurotrophic factor; CTHB=cathepsin B

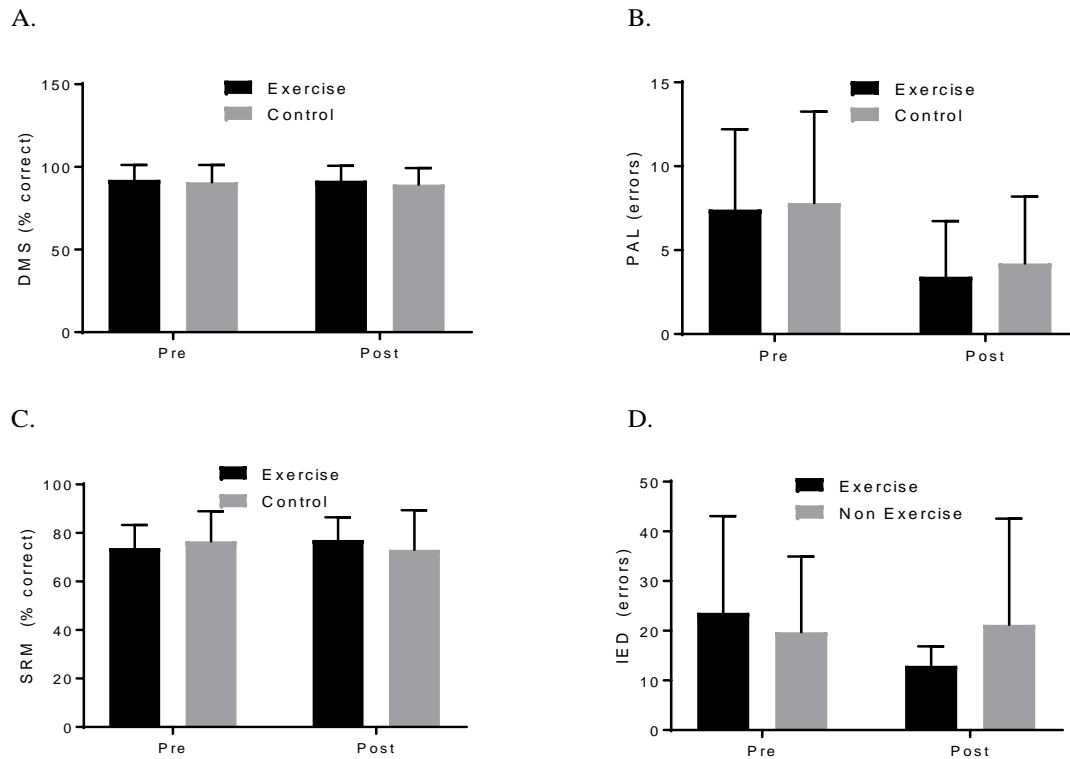


Figure 4. 2 - Group plots illustrating pre-post CANTAB changes for (A) DMS, (B) PAL, (C) SRM, (D) IED. Abbreviations: DMS=delayed matching to sample; PAL=paired associates learning; SRM= spatial recognition memory; IED= intra-extra dimensional set shift

4.5 Discussion

This present study demonstrated that an eight-week exercise intervention, based on the minimum recommended guidelines, was able to significantly improve cardiorespiratory fitness in young and healthy adults who were untrained. We provide evidence that exercise did not significantly improve cognitive function or change resting plasma BDNF or CTHB concentrations, despite improvements in fitness. Our findings suggest that if biomarker

levels are within normal ranges at baseline, then exercise does not change these ranges in young and healthy adults. Cognitive function peaks during this time and thus to show effects of exercise on brain function may require more sensitive tests than provided by standardize cognitive testing batteries.

Our findings that we did not observe a significant pre-post change in cognitive function for the exercise group collaborates with a previous meta-analysis that used meta-regression techniques to examine the relationship between cardiorespiratory fitness and cognitive performance in elderly and young adults. Researchers found that although elderly adults showed improvements in cognitive function following an exercise intervention, young adults did not. However, cross-sectional analyses revealed that cardiorespiratory fitness was negatively predictive of cognitive performance for children and young adults, and not the elderly. These results are of significant importance as they provide evidence that the exercise-cognition relationship changes across the life span. These same researchers also suggested that the lack of behavioural findings in the exercise-cognition literature, might be a consequence from using cognitive performance measures alone which may not be a sensitive enough to detect changes in high-functioning young adults (Etnier, Nowell, Landers, & Sibley, 2006).

To help understand the exercise-cognition relationship in young and healthy adults, electrophysiological studies have examined the effects of physical activity levels and cardiorespiratory fitness on behavioral and neuroelectric indices of executive control processes. Using a task-switching paradigm, researchers measured the error-related negativity (ERN) component of an event related potentials (ERP), as well as behavioural

measures of response time (RT) and accuracy. Despite no difference in cognitive performance between the groups, there were decreases in ERN amplitude and increases in post-error response slowing for high-active and high-fit participants compared to their sedentary counterparts (Themanson & Hillman, 2006; Themanson, Hillman, & Curtin, 2006). A similar study conducted by Kamijo and Takeda investigated the effects of physical activity on executive control in young adults, using measures of RT and the P3 component of an ERP during a task switching task. Researchers observed a smaller task switching cost on RTs and P3 amplitudes for the active group relative to the sedentary group. Taken together, these data suggest that physically active individuals require less demands on neural networks and have more efficient neural processes associated with executive function than their sedentary counterparts (Kamijo & Takeda, 2010). Further supporting that long-term exercise is associated with decreases neural activity despite no change in overt cognitive performance, a recent fMRI study used a subsequent memory paradigm to investigate the effects of an eight-week exercise intervention on hippocampal function and overall brain activity in depressed adults and young and healthy adults. Although no pre-post changes in memory performance were observed, fMRI data revealed that both the depressed and healthy young adults had a consistent pre-post deactivation pattern in the hippocampus and across several other memory-associated brain regions, suggestive of an increase in neural network efficiency during the memory encoding process (Gourgouvelis, Yelder, & Murphy, 2017).

In an attempt to link a physiological mechanism underlying the effects of exercise on cognitive function, we measured plasma BDNF and CTHB concentrations. We did not

observe any change in plasma BDNF concentrations following the exercise intervention agreeing with previous research conducted in young and healthy adults (Griffin et al., 2011; Schiffer et al., 2009). Though our study did not replicate Moon et al., who observed an increase in plasma CTHB following four months of aerobic exercise, our intervention was much shorter in duration. It is worth noting that the animal literature has reported reduced CTHB gene expression in the cardiac muscle of mice following five days of treadmill running (Smuder, Kavazis, Min, & Powers, 2013) and no change in CTHB activity in skeletal muscle following eight hours of exhaustive exercise (Salminen, 1984). However, little is known about the role that CTHB plays in cognitive function.

4.6 Limitations

This study was limited by the small sample size. Second, while our eight-week exercise intervention was able to significantly increase in cardiorespiratory fitness in young and healthy adults who were untrained, all participants in the exercise group remained in the poor fitness category following the intervention. As such, significant improvements in cognitive function may have been observed with a longer intervention. Future research should investigate the dose–response effects of exercise on cardiorespiratory fitness, cognitive function and biomarkers by comparing various durations of exercise.

Furthermore, the CANTAB battery used for this study might not have been sensitive enough to detect changes in this high-functioning group of young and healthy adults. It is possible that the effects of exercise on cognitive behavior may only emerge when the task is extremely difficult (Voss, Nagamatsu, Liu-Ambrose, & Kramer, 2011).

4.7 Conclusion

This study provides evidence that eight weeks of the minimum recommended dose of exercise does not change cognitive function, BDNF or CTHB concentrations in young and healthy adults who are untrained. Our sample is representative of the a 95% of the adult population in the United States and Canada who do not meet the recommended physical activity guidelines for health benefits (Colley et al., 2011; Troiano et al., 2008). As such, neurodegenerative changes observed in aging and psychiatric populations are likely confounded by sedentary behaviour and poor cardiorespiratory fitness. In order to understand the magnitude of the effects of exercise on cognitive function in neurodegenerative disorders, it is critical that we understand the impact of exercise on cognitive function young and healthy population who are trained and untrained.

4.8 Conflict of interest disclosure

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Chapter 5: General Discussion

Human and animal experiments have shown long-term exercise to improve mood, sleep quality, cognitive function and neural function in both aging populations and those affected with neuropathological disease including MDD. The MDD and exercise literature have also identified a convergence of mechanisms that are associated with neuroplasticity and neural function (see Figure 5.1). However, it remains unclear whether exercise-related variables such as physical activity and cardiorespiratory levels underlie the symptoms and mechanisms associated with MDD. It is also unknown whether exercise affects cognitive and neural function in young and healthy adults who are considered low active and cardiorespiratory unfit. To address these gaps, this thesis investigated the effects of exercise, and mechanisms associated with both MDD and exercise, on cognitive and neural function in low-active MDD patients and young and healthy individuals. Using a multi-disciplinary research approach, this study examined the relationship between cognitive behavioural performance, neural function and physiological mechanisms to identify biomarkers that are unique to MDD independent of fitness levels. This thesis also examined the effects of exercise as an add-on therapy to ADM and CBT to identify exercise-related mechanisms underlying treatment response. fMRI results showed a similar deactivation pattern in several memory-related brain regions, despite no pre-post change in memory performance, for both the MDD and healthy groups following the eight weeks of exercise. These results suggest that low levels of cardiorespiratory fitness may potentially be an underlying variable that contributes to the alterations in neural function reported in the MDD neuroimaging literature. The increase in plasma BDNF concentrations observed

exclusively in the MDD group following exercise, suggests plasma BDNF to be a candidate mechanism underlying the clinical recovery of MDD. This study also showed that exercise did not significantly improve cognitive function in young and healthy adults despite changes in neural activation. These results indicate that exercise changes brain function in high-functioning, young, healthy adults and future work must consider using a more sensitive cognitive measure to identify behavioural changes. This research study provides clinical implications that eight weeks of exercise, based on the minimum recommended guidelines, in addition to ADM and cognitive therapy leads to significantly better clinical outcomes in those suffering with MDD.

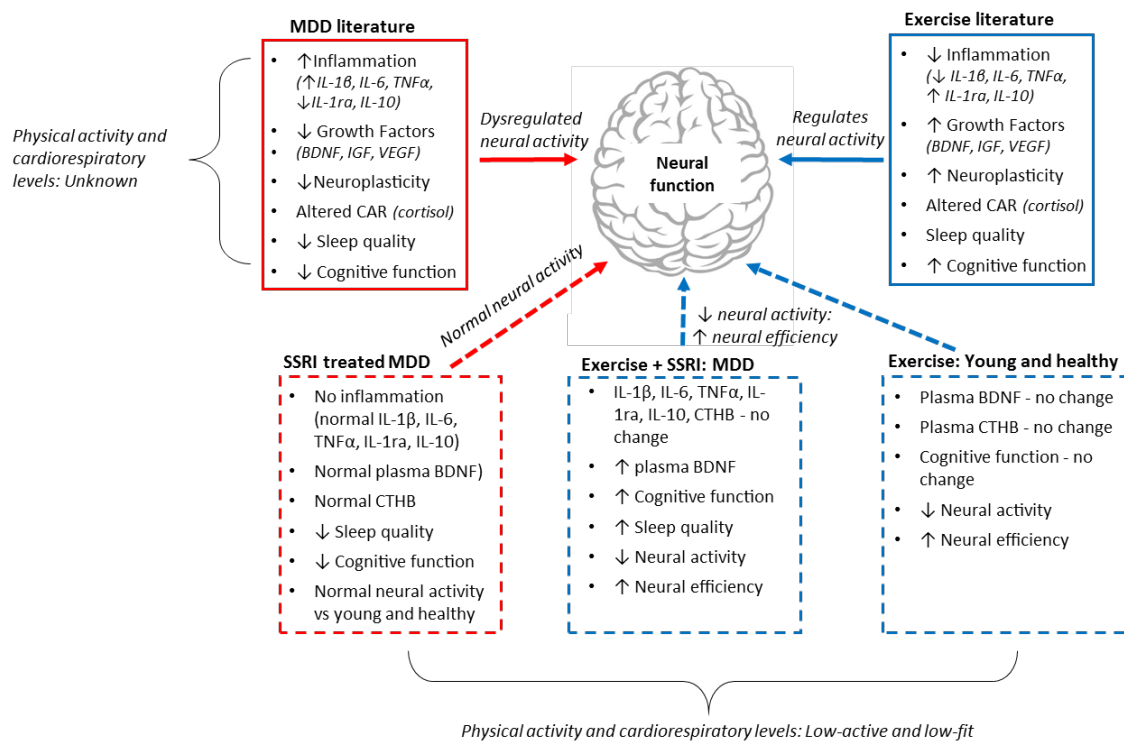


Figure 5. 2 - Converging mechanisms associated with MDD and exercise on neural function: Previous and current findings.

Although this study revealed a large effect (Cohen's $d=6.46$) for exercise and increased plasma BDNF, this relationship remains unclear. Previous studies have found no change in serum BDNF concentrations following a supervised aerobic exercise intervention based on a public health dose, despite significant improvements in depression (Toups, Greer et al. 2011b, Krogh, Rostrup et al. 2014). The inconsistent results between studies may be explained by the variation in methodologies to quantify circulatory BDNF concentrations, particularly plasma versus serum. For instance, circulatory BDNF concentrations have been shown to increase exclusively in plasma but not in the serum of MDD patients, in response to ECT (Haghighi, Salehi et al. 2013) and ADM (Piccinni, Marazziti et al. 2008). Additionally, a recent study also showed that a four week aerobic exercise intervention of moderate intensity, significantly improved depressive symptoms and increased plasma BDNF concentrations in MDD patients (Salehi, Hosseini et al. 2016). Over 90% of BDNF in the circulatory is stored in blood platelets and is released into the plasma via activation or clotting processes (Fujimura, Altar et al. 2002). This suggests that the inconsistent research findings between serum and plasma BDNF concentrations during the clinical recovery of MDD, may be an increase in platelet release of BDNF that is more easily detected in plasma (Castren and Rantamaki 2010). Since exercise did not increase plasma BDNF in the young and healthy group, it suggests that the BDNF increases in MDD may be associated with a dysfunction in the platelet release of BDNF that may be upregulated with exercise. Further studies examining the differences between serum and plasma BDNF during the course of illness in MDD, would provide further insight.

No signs of inflammation were observed in the MDD patients at study enrolment. These results provide direction for future studies, to consider whether cytokine analysis is feasible when using a sample of MDD patients with no comorbid inflammatory disorder and undergoing SSRI therapy. Despite the mounting evidence that implicates chronic inflammation in the pathophysiology of MDD, there are several limitations to consider. First, not all patients with MDD show signs of inflammation (Yoon, Kim et al. 2012) and not all patients with inflammatory disorders or undergoing cytokine therapy develop MDD. SSRI treatment has been shown to reduce inflammation yet many people still suffer with depressive symptoms (Sacre, Medghalchi et al. 2010, Tynan, Weidenhofer et al. 2012). There is an extensive gap in the cytokine literature investigating inflammatory biomarkers throughout the course of depression, and there is gap in the research indicating healthy normal levels for comparison. There are no cut-off criteria for cytokine concentrations that are considered to be toxic or beneficial, and no values that indicate normal, healthy variations (Kim, Na et al. 2016). Additionally, the various immunoassay methodologies within the literature, makes it challenging for researchers to conduct cross-study comparisons (Leonard 2007, Kim, Na et al. 2016).

A strength of this study was the multi-modal scientific approach in measuring psychological and neurobiological mechanisms that identified changes at the behavioural, neural and physiological levels in recovering with MDD. It demonstrated very large effect sizes for exercise-related improvements in depression, cognitive function, sleep quality and plasma BDNF for the MDD patients. This study is able to provide a solid foundation for future work. It has shown that an exercise prescription based on the minimum guidelines,

is able to improve cardiorespiratory fitness and is well tolerated by low active MDD patients. Findings also suggests that a lower dose of exercise for low active individuals may be better tolerated, yet still effective, since the MDD patients remained in the poor cardiorespiratory fitness range following the eight weeks of exercise. In fact, findings suggest that it may be the engagement and increase in physical activity levels that underlie the anti-depressant effects of exercise. This study highlights feasible biomarkers in MDD patients undergoing SSRI treatment providing a framework for future study designs. Nonetheless, the present research findings must be replicated with future research and limitations of this study need to be addressed before implementing the clinical use of biomarkers such as sleep quality, plasma BDNF and neural activity during the recovery of MDD.

5.1 Limitations

This study did not include no-intervention control groups and therefore it cannot be certain that the deactivation pattern observed in both the MDD and healthy groups was exercise-induced. The inclusion of both MDD and healthy control groups would confirm the deactivation pattern to be exercise induced. Also, the MDD and healthy groups were not age-matched and it cannot be certain that the pre-post changes observed in the MDD group were not age-related. Furthermore, this study measured total BDNF and not the ratio of pro-BDNF to mature BDNF. Therefore, it is unknown whether there was an alteration in mature BDNF to pro-BDNF underlying the improvements in depression and sleep quality. This study was also limited to individuals who were considered low active with low levels

of cardiorespiratory fitness. As such, it remains unclear whether physical activity and fitness levels were associated with the treatment response in the MDD group. The relationship between fitness and MDD would be clearer with the inclusion of patients with higher levels of physical activity and cardiorespiratory fitness for comparison.

5.2 Future directions

An initial objective of this research study was to investigate HPA axis functioning through measures of morning saliva. Participants were instructed to provide morning salivary samples immediately upon awakening and 30 minutes post awakening. Our findings revealed that several participants in the healthy and MDD groups did not provide saliva samples for all time points, and several participants showed a negative CAR. These findings indicate methodological issues, particularly adhering to sampling protocols. The literature has shown that when in ambulatory settings, reliance upon self-sampling at required times can often lead to invalid results (Elder, Wetherell et al. 2014). A negative CAR may be valid, however, it is more likely a result of poor adherence to the timing of sampling during the CAR period. Future outpatient studies, should consider measuring salivary cortisol at several time points throughout the day that will identify levels and variability of daily life cortisol secretion and HPA activity (Peeters, Nicolson et al. 2004).

Although the young and healthy participants in this study revealed no change in cognitive function following exercise, we did observe a decrease in brain activity during the memory encoding process. The absence of behavioural findings could be that the CANTAB battery is not sensitive enough to detect subtle changes in cognitive function in

this high-functioning group. Future research must consider to build on this literature base throughout the lifespan. The inclusion of young and healthy adults in future studies, will not only provide normal data for comparison, but will illustrate how cognitive function changes throughout adulthood.

Finally, MDD is a clinically and biologically heterogeneous disorder and it is likely to be a multifaceted interaction of psychological and neurobiological mechanisms that underlie the antidepressant effects of exercise. Future research must adopt a multi-disciplinary scientific approach to converge the mechanisms between exercise, depression, and neuroplasticity that will elucidate novel biomarkers. Once we are able to elucidate these key biomarkers unique to MDD, novel treatment strategies can be developed.

5.3 Clinical implications

Poor sleep quality is a frequently reported symptom of depression and a core residual symptom following remission. This study showed that sleep quality significantly improved following exercise. This finding has practical implications for mental health practitioners, highlighting the importance of measuring sleep quality during routine visits. It must be recognized that sleep quality is a potential biomarker of treatment response in MDD and also a risk factor for relapse.

Furthermore, there is a lack of attention to physical activity during routine visits to mental health practitioners, reducing the opportunity to improve both the physical and mental health of their patients (Janney, Brzoznowski et al. 2017). This study provides evidence that low active depressed individuals are able to tolerate an exercise prescription

based on the minimum recommended guidelines. This study also shows that by incorporating physical activity into mental health care, improves both cardiorespiratory fitness and clinical outcomes in patients suffering with severe MDD.

5.4 Qualitative observations

Understanding patient perspectives and preferences is critical if exercise is to be effectively implemented into the treatment plan for MDD (Janney, Brzoznowski et al. 2017). The following section summarizes some qualitative observations that were observed during this research study. In order to improve clinical outcomes for all patients in this research study, the non-exercise group was offered four personal training sessions following study completion. As such, the following observations were based on 16 patients.

Specifically I will discuss the attitudes, current knowledge and barriers to perform regular exercise that were discussed among participants. First, the term ‘exercise’ was perceived negatively among the MDD sample in this study and therefore the term physical activity was substituted. Several patients perceived exercise to be analogous to marathon running or something that only bodybuilders do. Many patients expressed that they were intimidated fitness facilities as they were not educated on the use of the equipment. Most patients indicated that their low mood and negative body image was a barrier to participate in exercise. Interestingly, very few patients indicated that lack of time was a barrier, however, cost of a gym membership was a frequently mentioned barrier. Many patients in this study indicated that they had never been educated on the positive impact of exercise on

mood during routine mental health visits, nor had their clinician recommended them to increase their physical activity levels. All patients indicated that they did not know how to exercise or how to initiate an exercise program.

At study enrolment, all patients were very motivated to participate in this research study with the expectation they would recover from their debilitating disease. The inclusion of an exercise professional to educate and supervise them was well accepted. Participants expressed that the exercise professional was able to increase their knowledge about the benefits of exercise and how to perform exercise safely and effectively. Motivation to attend exercise sessions was maintained throughout the eight weeks through positive feedback from both the exercise professionals and exercise log that illustrated their progress. Surprisingly, very few patients missed an exercise session.

Worth noting, there were distinguishable features between the two groups. The exercise group entered the study during a period of severe depression. Consequently, attending both CBGT and the exercise sessions concurrently, was overwhelming for some during the initial weeks. However, this was not observed in the non-exercise group who performed their four exercise sessions following the eight weeks of CBGT. Based on these observations, it may be beneficial to delay the introduction of regular exercise in the early phase of severe depression in clinical practice.

Finally, the increases in self-efficacy for exercise and overall improvements in emotional and physical well-being that I observed in each participant throughout the study was beyond rewarding. Although few patients indicated that adhering to the eight week exercise prescription was a challenge, all participants completed the study with high levels

of satisfaction. Overall, patients indicated that learning how to exercise was a life-changing experience for them and that exercise improved their overall quality of life.

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Appendix 1: BDI

Beck's Depression Inventory

This depression inventory can be self-scored. The scoring scale is at the end of the question.

1.
 - 0 I do not feel sad.
 - 1 I feel sad.
 - 2 I am sad all the time and I can't snap out of it.
 - 3 I am so sad and unhappy that I can't stand it.
2.
 - 0 I am not particularly discouraged about the future.
 - 1 I feel discouraged about the future.
 - 2 I feel I have nothing to look forward to.
 - 3 I feel the future is hopeless and that things cannot improve.
3.
 - 0 I do not feel like a failure.
 - 1 I feel I have failed more than the average person.
 - 2 As I look back on my life, all I can see is a lot of failures.
 - 3 I feel I am a complete failure as a person.
4.
 - 0 I get as much satisfaction out of things as I used to.
 - 1 I don't enjoy things the way I used to.
 - 2 I don't get real satisfaction out of anything anymore.
 - 3 I am dissatisfied or bored with everything.
5.
 - 0 I don't feel particularly guilty.
 - 1 I feel guilty a good part of the time.
 - 2 I feel quite guilty most of the time.
 - 3 I feel guilty all of the time.
6.
 - 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.
 - 0 I don't feel disappointed in myself.
 - 1 I am disappointed in myself.
 - 2 I am disgusted with myself.
 - 3 I hate myself.
8.
 - 0 I don't feel I am any worse than anybody else.
 - 1 I am critical of myself for my weaknesses or mistakes.
 - 2 I blame myself all the time for my faults.
 - 3 I blame myself for everything bad that happens.
9.
 - 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.
 - 0 I don't cry any more than usual.
 - 1 I cry more now than I used to.
 - 2 I cry all the time now.
 - 3 I used to be able to cry, but now I can't cry even though I want to.

11.
 0 I am no more irritated by things than I ever was.
 1 I am slightly more irritated now than usual.
 2 I am quite annoyed or irritated a good deal of the time.
 3 I feel irritated all the time.
12.
 0 I have not lost interest in other people.
 1 I am less interested in other people than I used to be.
 2 I have lost most of my interest in other people.
 3 I have lost all of my interest in other people.
13.
 0 I make decisions about as well as I ever could.
 1 I put off making decisions more than I used to.
 2 I have greater difficulty in making decisions more than I used to.
 3 I can't make decisions at all anymore.
14.
 0 I don't feel that I look any worse than I used to.
 1 I am worried that I am looking old or unattractive.
 2 I feel there are permanent changes in my appearance that make me look unattractive.
 3 I believe that I look ugly.
15.
 0 I can work about as well as before.
 1 It takes an extra effort to get started at doing something.
 2 I have to push myself very hard to do anything.
 3 I can't do any work at all.
16.
 0 I can sleep as well as usual.
 1 I don't sleep as well as I used to.
 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
 3 I wake up several hours earlier than I used to and cannot get back to sleep.
17.
 0 I don't get more tired than usual.
 1 I get tired more easily than I used to.
 2 I get tired from doing almost anything.
 3 I am too tired to do anything.
18.
 0 My appetite is no worse than usual.
 1 My appetite is not as good as it used to be.
 2 My appetite is much worse now.
 3 I have no appetite at all anymore.
19.
 0 I haven't lost much weight, if any, lately.
 1 I have lost more than five pounds.
 2 I have lost more than ten pounds.
 3 I have lost more than fifteen pounds.

Appendix 2: HADS

When you answer the following questions we ask that you please chose only **one response** for each question and give the response that **immediately** comes into your head.
Place a tick or mark beside the answer that best relates to how **you** feel.

<p>I feel tense or 'wound up':</p> <ul style="list-style-type: none"> <input type="radio"/> Most of the time <input type="radio"/> A lot of the time <input type="radio"/> From time to time, occasionally <input type="radio"/> Not at all 	<p>I still enjoy the things I used to enjoy:</p> <ul style="list-style-type: none"> <input type="radio"/> Definitely as much <input type="radio"/> Not quite so much <input type="radio"/> Only a little bit <input type="radio"/> Hardly at all
<p>I get a sort of frightened feeling as if something awful is about to happen:</p> <ul style="list-style-type: none"> <input type="radio"/> Very definitely and quite badly <input type="radio"/> Yes, but not too badly <input type="radio"/> A little, but it doesn't worry me <input type="radio"/> Not at all 	<p>I can laugh and see the funny side of things:</p> <ul style="list-style-type: none"> <input type="radio"/> As much as I always could <input type="radio"/> Not quite so much now <input type="radio"/> Definitely not so much now <input type="radio"/> Not at all
<p>Worrying thoughts go through my mind:</p> <ul style="list-style-type: none"> <input type="radio"/> A great deal of the time <input type="radio"/> A lot of the time <input type="radio"/> From time to time, but not too often <input type="radio"/> Only occasionally 	<p>I feel cheerful:</p> <ul style="list-style-type: none"> <input type="radio"/> Not at all <input type="radio"/> Not often <input type="radio"/> Sometimes <input type="radio"/> Most of the time
<p>I can sit at ease and feel relaxed:</p> <ul style="list-style-type: none"> <input type="radio"/> Definitely <input type="radio"/> Usually <input type="radio"/> Not often <input type="radio"/> Not at all 	<p>I feel as if I am slowed down:</p> <ul style="list-style-type: none"> <input type="radio"/> Nearly all the time <input type="radio"/> Very often <input type="radio"/> Sometimes <input type="radio"/> Not at all
<p>I get a sort of frightened feeling like 'butterflies' in the stomach:</p> <ul style="list-style-type: none"> <input type="radio"/> Not at all <input type="radio"/> Occasionally <input type="radio"/> Quite often <input type="radio"/> Very often 	<p>I have lost interest in my appearance:</p> <ul style="list-style-type: none"> <input type="radio"/> Definitely <input type="radio"/> I don't take as much care as I should <input type="radio"/> I may not take quite as much care <input type="radio"/> I take just as much care as ever
<p>I feel restless as I have to be on the move:</p> <ul style="list-style-type: none"> <input type="radio"/> Very much indeed <input type="radio"/> Quite a lot <input type="radio"/> Not very much <input type="radio"/> Not at all 	<p>I look forward with enjoyment to things:</p> <ul style="list-style-type: none"> <input type="radio"/> As much as I ever did <input type="radio"/> Rather less than I used to <input type="radio"/> Definitely less than I used to <input type="radio"/> Hardly at all
<p>I get sudden feelings of panic:</p> <ul style="list-style-type: none"> <input type="radio"/> Very often indeed <input type="radio"/> Quite often <input type="radio"/> Not very often <input type="radio"/> Not at all 	<p>I can enjoy a good book or radio or TV programme:</p> <ul style="list-style-type: none"> <input type="radio"/> Often <input type="radio"/> Sometimes <input type="radio"/> Not often <input type="radio"/> Very seldom

(Modified from Zigmond & Snaith, 1983)

Appendix 3: MoCA

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME: _____
Education: _____ Date of birth: _____
Sex: _____ DATE: _____

VISUOSPATIAL / EXECUTIVE		Copy cube	Draw CLOCK (Ten past eleven) (3 points)	POINTS																		
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> Contour Numbers Hands	___/5																		
NAMING																						
	<input type="checkbox"/>		<input type="checkbox"/>																			
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	___/3																			
MEMORY		Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td></td> <td style="text-align: center;">FACE</td> <td style="text-align: center;">VELVET</td> <td style="text-align: center;">CHURCH</td> <td style="text-align: center;">DAISY</td> <td style="text-align: center;">RED</td> </tr> <tr> <td style="text-align: center;">1st trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> <tr> <td style="text-align: center;">2nd trial</td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </table>		FACE	VELVET	CHURCH	DAISY	RED	1st trial						2nd trial						No points
	FACE	VELVET	CHURCH	DAISY	RED																	
1st trial																						
2nd trial																						
ATTENTION		Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order <input type="checkbox"/> 2 1 8 5 4 Subject has to repeat them in the backward order <input type="checkbox"/> 7 4 2	___/2																			
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		<input type="checkbox"/> FBACMNAAJKLBAFAKDEAAAJAMOF AAB																				
Serial 7 subtraction starting at 100 <input type="checkbox"/> 93 <input type="checkbox"/> 86 <input type="checkbox"/> 79 <input type="checkbox"/> 72 <input type="checkbox"/> 65 4 or 5 correct subtractions: 3 pts , 2 or 3 correct: 2 pts , 1 correct: 1 pt , 0 correct: 0 pt		___/3																				
LANGUAGE		Repeat : I only know that John is the one to help today. <input type="checkbox"/> The cat always hid under the couch when dogs were in the room. <input type="checkbox"/>																				
Fluency / Name maximum number of words in one minute that begin with the letter F <input type="checkbox"/> _____ (N ≥ 11 words)		___/1																				
ABSTRACTION		Similarity between e.g. banana - orange = fruit <input type="checkbox"/> train - bicycle <input type="checkbox"/> watch - ruler																				
DELAYED RECALL		Has to recall words WITH NO CUE	<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="text-align: center;">FACE</td> <td style="text-align: center;">VELVET</td> <td style="text-align: center;">CHURCH</td> <td style="text-align: center;">DAISY</td> <td style="text-align: center;">RED</td> </tr> <tr> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> <td style="text-align: center;"><input type="checkbox"/></td> </tr> </table>	FACE	VELVET	CHURCH	DAISY	RED	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Points for UNCUED recall only								
FACE	VELVET	CHURCH	DAISY	RED																		
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>																		
Optional Category cue																						
Multiple choice cue																						
ORIENTATION		<input type="checkbox"/> Date <input type="checkbox"/> Month <input type="checkbox"/> Year <input type="checkbox"/> Day <input type="checkbox"/> Place <input type="checkbox"/> City	___/6																			
© Z.Nasreddine MD www.mocatest.org Normal $\geq 26 / 30$		TOTAL ___/30 Add 1 point if ≤ 12 yr edu																				

Appendix 4: PSQI

Sleep Quality

Instructions: *The following questions relate to your usual sleep habits during the past two weeks ONLY. Your answers should indicate the most accurate reply for the majority of days and nights in the past 2 weeks. Please answer all questions.*

1. During the past 2 weeks, when have you usually gone to bed at night?

USUAL BED TIME _____

2. During the past 2 weeks, how long (in minutes) has it usually taken you to fall asleep each night?

NUMBER OF MINUTES _____

3. During the past 2 weeks, when have you usually gotten up in the morning?

USUAL GETTING UP TIME _____

4. During the past 2 weeks, how many hours of *actual sleep* did you get at night?
(This may be different than the number of hours you spend in bed)

HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer *all* questions.

5. During the past 2 weeks, how often have you had trouble sleeping because you.....	Not during the past 2 weeks	Less than once a week	Once or twice a week	Three or more times a week
Cannot get to sleep within 30 minutes				
Wake up in the middle of the night or early morning				
Have to get up to use the bathroom				
Cannot breathe comfortably				
Cough or snore loudly				
Feel too cold				
Feel too hot				
Had bad dreams				
Have pain				
Other reason(s) please describe _____				

6. During the past 2 weeks how would you rate your sleep quality overall? (please circle)

Very bad.....Fairly bad.....Fairly good.....Very good

7. During the past 2 weeks, how often have you taken medicine (prescribed or “over the counter”) to help you sleep? (Please circle)

Not during the	Less than	Once or	Three or more
past 2 weeks	once a week	twice a week	times a week

8. During the past 2 weeks, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity? (Please circle)

Not during the	Less than	Once or	Three or more
past 2 weeks	once a week	twice a week	times a week

9. During the past 2 weeks, how much of a problem has it been for you to keep up enough enthusiasm to get things done? (Please circle)

No problem	Only a very	Somewhat	A very
at all	slight problem	of a problem	big problem

10. Do you have a bed partner or share a room?

No bed partner or do not share a room _____

Partner/flat mate in other room _____

Partner in the same room, but not same bed _____

Partner in the same bed _____

11. If you have a bed partner or share a room, ask him/her how often in the past 2 weeks you have had....

	Not during the	Less than once a	Once or twice a	Three or more
Loud snoring				
Long pauses between breaths while asleep				
Legs twitching or jerking while you sleep				
Episodes of disorientation or confusion during sleep				
Other restlessness while you sleep (please describe)				

(Modified from (Buysse, Reynolds et al. 1989)

Appendix 5: Saliva collection instructions

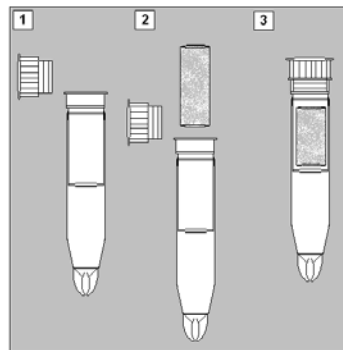
SALIVA COLLECTION METHOD

Exercise and Brain Function Study

During this study, you will be collecting saliva samples to be tested for the stress hormone cortisol. Levels of cortisol change in a predictable way throughout the day. Because of this, you need to collect saliva samples at the exact times instructed for the results to be accurate. Also, activities such as eating and drinking can affect your saliva, so please make sure you follow the instructions for how to collect your sample. Please tell us if you have any sores in your mouth.

W **Week 0 and**

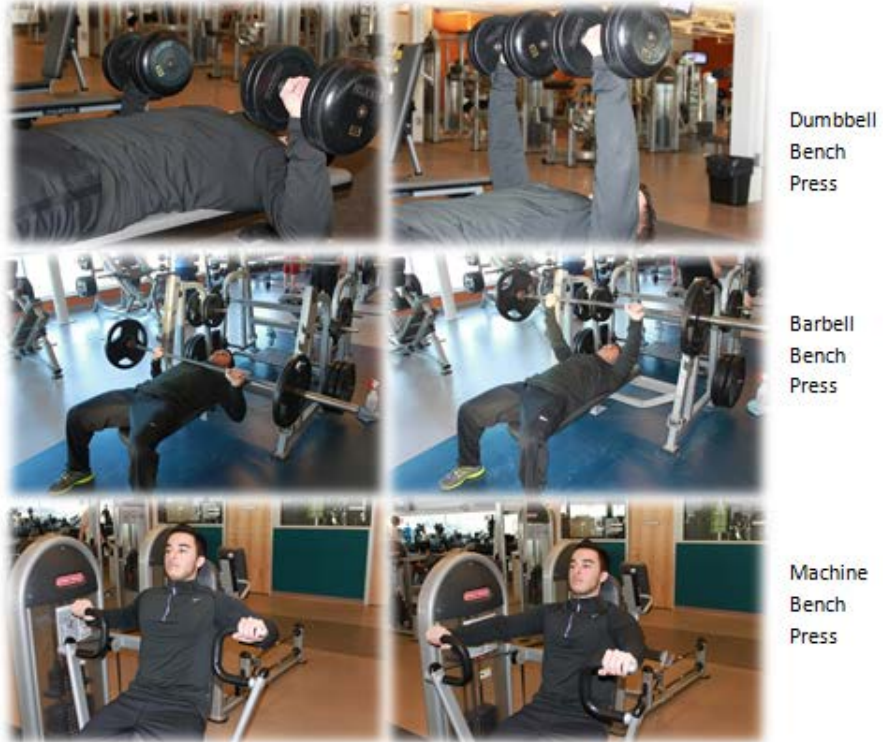
- You will be given two Salimetrics Oral Swab devices and an insulation pack at your orientation session at the UOIT fitness centre
- You will be collecting saliva samples on the **WEDNESDAY** following this appointment
- These vials will be labelled “Weds – waking” , “Weds – 30 min”
- Collect **ONE** sample using the two “Weds – waking” vials immediately on awakening on Wednesday
- Remove swab from tube leaving tube insert in place. Place into mouth under tongue. Keep in place for 1-2 minutes.
- Collect **ONE** more sample in the same way 30 min later in the “Weds– 30min” vial
- **DO NOT** consume caffeinated drinks, eat, brush teeth, smoke or use steroid creams/inhalers between collection of first two samples
- Freeze both samples immediately in your freezer
- Bring samples with you to your first exercise session in the insulated pack provided



Appendix 6: Resistance exercises

Appendix 12: Resistance Exercise Options

Horizontal Push Exercises



Anterior Lower Body Exercises





Dumbbell
Split Squat

Vertical Pull Exercises



Under-
Hand Grip
Pulldown



Over-Hand
Wide-Grip
Pulldown



Over-Hand
Close-Grip
Pullup



Cable
Triceps
Extension

Posterior Lower Body Exercises



Machine
Leg Curl



One-Legged
Calf Raises



Machine
Calf Raises

Horizontal Pull Exercises



Machine
Row



Dumbbell
Row



Machine
Preacher
Curl



Barbell
Biceps Curl



Dumbbell
Jack-
Hammer
Curls

Vertical Push Exercises



Dumbbell
Shoulder
Press

Appendix 7: Pre-scanning questionnaire

Exercise and Depression Screening Form

Please check the appropriate response

SECTION A	YES	NO
1. Does the participant have only one Axis One disorder, i.e. Major Depressive Disorder (MDD)? **Anxiety is the one allowable secondary diagnosis for inclusion. If YES go to question 2	<input type="checkbox"/>	<input type="checkbox"/>
2. "We currently have a free three month exercise study running as part of the Day Treatment program. Is this something you might be interested in?" If YES go to question 3	<input type="checkbox"/>	<input type="checkbox"/>
3. Does the participant have any current substance abuse? If NO go to question 4	<input type="checkbox"/>	<input type="checkbox"/>
4. "Are you between the ages of 18 to 50?" If YES go to question 5	<input type="checkbox"/>	<input type="checkbox"/>
5. "Are you currently sedentary (i.e. do you do less than 20 minutes of exercise a day, less than 3 times per week)?" If YES, go to question 6	<input type="checkbox"/>	<input type="checkbox"/>
6. Does the participant have any inflammatory disease (i.e. rheumatoid arthritis, lupus or other autoimmune conditions)? If NO, go to question 7	<input type="checkbox"/>	<input type="checkbox"/>
7. Will the pharmacological treatment be stabilized 4 weeks prior to enrolment (if not how long have they been on their treatment) Please proceed to Section B	<input type="checkbox"/>	<input type="checkbox"/>
SECTION B	YES	NO
"As part of this study you get a free MRI scan of your brain at the beginning and end of the study. I just need to ask a few quick screening questions to make sure that it is safe for you to go in the scanner."	<input type="checkbox"/>	<input type="checkbox"/>
1. Do you have a cardiac pacemaker?	<input type="checkbox"/>	<input type="checkbox"/>
2. Do you have an aneurysm clip?	<input type="checkbox"/>	<input type="checkbox"/>
3. Do you have a cochlear implant?	<input type="checkbox"/>	<input type="checkbox"/>
4. Have you had any injury that might have left a metal fragment in your eye?	<input type="checkbox"/>	<input type="checkbox"/>

If answer is NO to the scanner questions, please provide the participant with the information form and get them to hand it back you with their contact details filled in. Please forward contact details to UOIT research coordinator at joanne.gourgouvelis@uoit.ca

PARTICIPANT NAME: DATE:



Appendix 8: MRI safety form

York University Neuroimaging Laboratory Magnetic Resonance (MR) Safety Screening Form

Name _____ Weight _____
 Last First MI Height _____
 Date of Birth ____/____/____ Male Female
 Month Day Year

Do you have: Cardiac pacemaker or implantable cardioverter defibrillator (ICD) Yes No
 Aneurysm clip Yes No
 Are you: Claustrophobic Yes No
 Are you currently taking any medications? Yes No
 List: _____

Have you ever had an injury to the eye involving a metallic object or fragment? Yes No
 Have you ever worked in a metal shop? Yes No
 Possibility of pregnancy? Yes No Not applicable

Brain/Head Surgery Yes No **Artificial Implants/Mechanical Devices**
 List type/date _____ List type/date _____ Yes No

Heart/Chest Surgery Yes No **Other Surgery**
 List type/date Retained pacer wires Yes No List type/date _____ Yes No

Ear Surgery Yes No Pierced body parts (earrings, etc.) Yes No
 List type/date _____ Hearing aid or cochlear implant Yes No
 Permanent retainer or braces Yes No
 Dentures or partials Yes No
 History of bullets, shrapnel or BBs Yes No
 History of seizures Yes No
 Hair piece, wig or hair extensions Yes No
 Medication or transdermal patch Yes No
 Tattoo or permanent makeup Yes No
 Stent, filter Yes No

WARNING: Certain implants, devices, or objects may be hazardous to you and/or may interfere with the MR procedure (i.e., MRI, MR angiography, functional MRI, MR spectroscopy). **Do not enter** the MR system room or MR environment if you have any questions or concerns regarding an implant, device, or object. Consult the MRI Technologist or Researcher **BEFORE** entering the MR system room. **The MR system magnet is ALWAYS on.**

I attest that the above information is correct to the best of my knowledge. I have read and understood the contents of this form and had the opportunity to ask questions regarding the information on this form and regarding the MRI procedure that I am about to undergo.

Signature of person completing form: _____ Date ____/____/____
 M D Y

Form completed by: MRI participant Other (specify) _____

Reviewed by: _____ PI of study _____

Appendix 9: Par-Q & You

Physical Activity Readiness
Questionnaire - PAR-Q
(revised 2002)

PAR-Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly: check YES or NO.

YES	NO	
<input type="checkbox"/>	<input type="checkbox"/>	1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor?
<input type="checkbox"/>	<input type="checkbox"/>	2. Do you feel pain in your chest when you do physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	3. In the past month, have you had chest pain when you were not doing physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	4. Do you lose your balance because of dizziness or do you ever lose consciousness?
<input type="checkbox"/>	<input type="checkbox"/>	5. Do you have a bone or joint problem (for example, back, knee or hip) that could be made worse by a change in your physical activity?
<input type="checkbox"/>	<input type="checkbox"/>	6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition?
<input type="checkbox"/>	<input type="checkbox"/>	7. Do you know of any other reason why you should not do physical activity?

If
you
answered

YES to one or more questions

Talk with your doctor by phone or in person BEFORE you start becoming much more physically active or BEFORE you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want — as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow his/her advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active — begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal — this is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively. It is also highly recommended that you have your blood pressure evaluated. If your reading is over 144/94, talk with your doctor before you start becoming much more physically active.

DELAY BECOMING MUCH MORE ACTIVE:

- if you are not feeling well because of a temporary illness such as a cold or a fever — wait until you feel better; or
- if you are or may be pregnant — talk to your doctor before you start becoming more active.

PLEASE NOTE: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

No changes permitted. You are encouraged to photocopy the PAR-Q but only if you use the entire form.

NOTE: If the PAR-Q is being given to a person before he or she participates in a physical activity program or a fitness appraisal, this section may be used for legal or administrative purposes.

"I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction."

NAME _____

SIGNATURE _____

DATE _____

SIGNATURE OF PARENT
or GUARDIAN (for participants under the age of majority) _____

WITNESS _____

Note: This physical activity clearance is valid for a maximum of 12 months from the date it is completed and becomes invalid if your condition changes so that you would answer YES to any of the seven questions.



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Appendix 10: ParMED-X

Physical Activity Readiness
Medical Examination
(revised 2002)

PARmed-X PHYSICAL ACTIVITY READINESS MEDICAL EXAMINATION

The PARmed-X is a physical activity-specific checklist to be used by a physician with patients who have had positive responses to the Physical Activity Readiness Questionnaire (PAR-Q). In addition, the Conveyance/Referral Form in the PARmed-X can be used to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. The PAR-Q by itself provides adequate screening for the majority of people. However, some individuals may require a medical evaluation and specific advice (exercise prescription) due to one or more positive responses to the PAR-Q.

Following the participant's evaluation by a physician, a physical activity plan should be devised in consultation with a physical activity professional (CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™). To assist in this, the following instructions are provided:

PAGE 1: Sections A, B, C, and D should be completed by the participant BEFORE the examination by the physician. The bottom section is to be completed by the examining physician.

PAGES 2 & 3: A checklist of medical conditions requiring special consideration and management.

PAGE 4: Physical Activity & Lifestyle Advice for people who do not require specific instructions or prescribed exercise.

Physical Activity Readiness Conveyance/Referral Form - an optional tear-off tab for the physician to convey clearance for physical activity participation, or to make a referral to a medically-supervised exercise program.

This section to be completed by the participant									
<p>A PERSONAL INFORMATION:</p> <p>NAME _____</p> <p>ADDRESS _____</p> <p>TELEPHONE _____</p> <p>BIRTHDATE _____ GENDER _____</p> <p>MEDICAL No. _____</p>	<p>B PAR-Q: Please indicate the PAR-Q questions to which you answered YES</p> <p><input type="checkbox"/> Q 1 Heart condition</p> <p><input type="checkbox"/> Q 2 Chest pain during activity</p> <p><input type="checkbox"/> Q 3 Chest pain at rest</p> <p><input type="checkbox"/> Q 4 Loss of balance, dizziness</p> <p><input type="checkbox"/> Q 5 Bone or joint problem</p> <p><input type="checkbox"/> Q 6 Blood pressure or heart drugs</p> <p><input type="checkbox"/> Q 7 Other reason:</p>								
<p>C RISK FACTORS FOR CARDIOVASCULAR DISEASE: <i>Check all that apply</i></p> <p><input type="checkbox"/> Less than 30 minutes of moderate physical activity most days of the week.</p> <p><input type="checkbox"/> Excessive accumulation of fat around waist.</p> <p><input type="checkbox"/> Currently smoker (tobacco smoking 1 or more times per week).</p> <p><input type="checkbox"/> Family history of heart disease.</p> <p><input type="checkbox"/> High blood pressure reported by physician after repeated measurements.</p> <p><input type="checkbox"/> High cholesterol level reported by physician.</p> <p><i>Please note: Many of these risk factors are modifiable. Please refer to page 4 and discuss with your physician.</i></p>	<p>D PHYSICAL ACTIVITY INTENTIONS:</p> <p>What physical activity do you intend to do?</p> <p>_____</p> <p>_____</p> <p>_____</p>								
This section to be completed by the examining physician									
<p>Physical Exam:</p> <table border="1"> <tr> <td>Ht</td> <td>Wt</td> <td>BP I)</td> <td>/</td> </tr> <tr> <td></td> <td></td> <td>BP II)</td> <td>/</td> </tr> </table> <p>Conditions limiting physical activity:</p> <p><input type="checkbox"/> Cardiovascular <input type="checkbox"/> Respiratory <input type="checkbox"/> Other</p> <p><input type="checkbox"/> Musculoskeletal <input type="checkbox"/> Abdominal</p> <p>Tests required:</p> <p><input type="checkbox"/> ECG <input type="checkbox"/> Exercise Test <input type="checkbox"/> X-Ray</p> <p><input type="checkbox"/> Blood <input type="checkbox"/> Urinalysis <input type="checkbox"/> Other</p>	Ht	Wt	BP I)	/			BP II)	/	<p>Physical Activity Readiness Conveyance/Referral:</p> <p>Based upon a current review of health status, I recommend:</p> <p><input type="checkbox"/> No physical activity</p> <p><input type="checkbox"/> Only a medically-supervised exercise program until further medical clearance</p> <p><input type="checkbox"/> Progressive physical activity:</p> <p><input type="checkbox"/> with avoidance of: _____</p> <p><input type="checkbox"/> with inclusion of: _____</p> <p><input type="checkbox"/> under the supervision of a CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™</p> <p><input type="checkbox"/> Unrestricted physical activity—start slowly and build up gradually</p> <p>Further Information:</p> <p><input type="checkbox"/> Attached</p> <p><input type="checkbox"/> To be forwarded</p> <p><input type="checkbox"/> Available on request</p>
Ht	Wt	BP I)	/						
		BP II)	/						

Appendix 11: Consent forms



Professor Bernadette Murphy
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Email: Bernadette.Murphy@uoit.ca
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The role of exercise in improving brain function: Part A: Exercise MHDT group

You are invited to participate in a research study entitled “The role of exercise in improving brain function”. This study (# REB 10-104) has been reviewed by the University of Ontario Research Ethics Board and has been approved as of May 13, 2013. Please read this form carefully, and feel free to ask any questions you might have. If you have any questions about your rights as a participant in this study, please contact the Compliance Officer at 905 721 8668 ext 3693 or compliance.uoit.ca.

Researchers

Dr. Bernadette Murphy, Professor, Head-Kinesiology Specialization, Faculty of Health Sciences, University of Ontario Institute of Technology, Phone: (905) 721-8668 ext 2778, email: Bernadette.Murphy@uoit.ca, Fax: (905) 721-3179

Dr. Paul Yelder, Professor, Director-Bachelor of Health Sciences, Faculty of Health Sciences, University of Ontario Institute of Technology, Phone: (905) 721-8668 ext 2768, email: Paul.Yelder@uoit.ca, Fax: (905) 721-3179

Dr. Nancy Wilkinson, Client Care Manager/Psychologist, Mental Health and Pinewood Program, Lakeridge Health, Phone: (905) 576-8711 ext 6233, email: nwilkinson@lakeridgehealth.on.ca

Dr. Stephen Strother, Professor, Dept. of Medical Biophysics, University of Toronto, Senior Scientist, Rotman Research Institute, Baycrest, Phone: (416) 785-2500 ext 2956, email: sstrother@rotman-baycrest.on.ca

Dr. Ron Heslegrave, Chair, Research Ethics Board, Baycrest, Phone: (416) 785-2500 ext. 2440, email: hesgrave@uhnres.utoronto.ca

Joanne Gourgouvelis, PhD Candidate, Faculty of Science, University of Ontario Institute of Technology, Phone: (905) 550-4055, email: Joanne.Gourgouvelis@uoit.ca, Fax: (905) 721-3179

Purpose of the Study

This research study is being conducted to study the effect of exercise on your levels of the stress hormone cortisol and a number of other biomarkers known to be altered in depression. We will also be looking at the way your brain functions during certain memory tasks. We are interested in how exercise may change these things in depressed participants. We are also interested in how exercise may affect the intensity of depression symptoms. These will be assessed over the course of a 8 week structured, supervised exercise program, in addition to the treatment you already receiving as part of the Lakeridge Mental Health Day Treatment program. Once this phase of the study is complete we will be recruiting a group of patients in the Mental Health Day Treatment program who are of a similar age and gender to investigate the effects of the Day Treatment program on its own in order to compare to the results of the exercise group.

Potential Benefits to Participants and/or to Society

Exercise has been shown in past studies to be an effective treatment for depression. In this study we want to learn more about how and why it works in order to help us design the most effective types of exercise interventions. Following the exercise program, participants may receive additional relief from their depression. This study offers a structured exercise program suitable for beginners and may also help you resolve any physical issues you have. If we show a strong effect, it may become a future part of the Day Treatment program and you will be making an important contribution to improving treatment options for future patients.

Participation and Withdrawal

Your participation to take part in this study is voluntary. You may choose not to participate or you may withdraw from the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first. The staff here is very flexible about meeting your needs and if there is anything we can do to accommodate your needs, we are more than willing to help. You are still free to withdraw at any time without giving a reason, and your decision not to participate will not affect your care at this center.

Rights of Research Participants

You are free to ask any questions that you may have about your treatment and your rights as a research participant. You may withdraw your consent at any time and discontinue participation without penalty.

If any questions come up during or after the study or if you have a research-related injury, contact the study researchers listed on the first page.

Should you have any questions or concerns regarding your rights as a participant in this research study, or if you wish to speak with someone who is not related to this study, you may contact the Chair of the Lakeridge Health Corporation Research Ethics Board at (905) 576-8711 or UOIT Research Ethics Board through the Compliance Office (905) 721-8668 ext 6393.

You are one of 20 individuals being asked to participate in this study and have been referred to us by Lakeridge Mental Health Day Treatment program with a diagnosis of depression and you are between the ages of 18 and 50. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this

study and you may discuss it with your friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Eligibility

In order to be eligible for either group, you must not be currently doing regular exercise; that means your levels of exercise should be less than 20 minutes, three times per week. People suffering from mental conditions other than depression, or with physical conditions that would prevent them from doing exercise, such as heart disease, will be excluded from the study. An understanding of English sufficient to answer questionnaires is required.

If you have questions the stated procedures, timeline or exclusion criteria please feel free to discuss them with the study coordinator, Joanne Gourgouvelis or the investigators (contact details provided on page 1).

The following sections will outline the various tests and procedures of the study, including: 1) the purpose of each test or procedure; 2) the respective timelines; 3) exclusion criteria (factors that might make you ineligible to participate).

If you take part in this study, you will need to participate in several procedures. Please read the following pages and tick the boxes to indicate if any of the exclusion criteria pertain to you: A) Questionnaire completion (page 3), B) Cognitive tasks (see Page 3) C) Saliva samples (page 4), D) Bloodwork (see page 4), E) Brainscan (see page 5), F) Exercise (see page 7).

A. QUESTIONNAIRES

1. Purpose

To determine the severity of your symptoms associated with depression, you will complete some demographic information and you will then complete two Questionnaires, called the Beck Depression Inventory II (BDI-II) and the Hospital Anxiety and Depression Scale (HADS).

2. Timeline

Questionnaires will be given at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Do not understand English

4. Risks: There are no risks from completing these questionnaires, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

B. COGNITIVE TASKS

1. Purpose

To determine overall cognitive functioning, you will perform a series of computer generated tasks which will assess your ability to identify simple objects in space. The benefits to you are that you will learn more about how your memory works and you will be increasing our knowledge of how exercise affects memory.

2. Timeline

Cognitive tasks will be given at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Do not understand English

Risks: There are no risks from completing these computer generated tasks, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

C. SALIVA

1. Purpose

Cortisol is a hormone which is known to be elevated in depressed individuals, and chronically high levels of cortisol have been linked with changes in the way the brain functions. It is possible that exercise may help depression by decreasing cortisol secretion. You will be given labelled tubes to collect a sample of your saliva (spit) to be tested at a laboratory for the stress hormone cortisol, which you will collect on the morning after your interview as soon as you wake up and then again 30 minutes after you wake up. The samples will then be put in the freezer and you will be given a small Styrofoam cooler to bring the samples back to the researcher on the next day that you attend the Lakeridge program. You will be given a set of simple instructions in case you forget what to do.

2. Timeline

Saliva samples will be taken at:

- i. Week 0: the day after your interview (when you wake up and 30 minutes after waking up)
- ii. Week 8: after completion of the exercise program (when you wake up and 30 minutes after waking up)

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Ulcers or sores in your mouth

5. Risks

- i. There are no complications or side effects when collecting saliva. Your samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study. They will be disposed of once they have been analyzed.

D. BLOODWORK

1. Purpose

A number of biomarkers found in blood are also known to be altered in depression and exercise may act to normalize their levels. A technician from the Medical Laboratory Science Program at the University of Ontario Institute of Technology will collect blood samples from each participant twice during the study.

2. Timeline

Blood samples will be taken at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Bleeding disorder
- ii. Medications that may interfere with blood clotting (heparin, wafarin)
- iii. Phobia of needles

4. Risks

Complications are very rare when acquiring blood samples through a sterile syringe. However, the following side effects have been reported:

- A. Excessive bleeding at site of puncture
- B. Bruising
- C. Feeling light-headed, fainting
- D. Infection

Your blood and saliva samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study when they will be analyzed. Any unused sample will be disposed of. Once the samples have been analyzed and disposed they cannot be withdrawn.

E. BRAIN SCAN (functional MRI)

1. Purpose

Prior to commencing your program, fMRI images of your brain will be obtained to investigate the way that your brain activates when you are performing a task requiring your concentration. We will also look at anatomical details of brain structures known to be involved in depression such as the hippocampus. Once you come out of the scanner, you will go to a separate room and be asked to go through some of the images from the task that you did in the scanner. The scan will take about one hour and will be carried out at Baycrest hospital attached to the Rotman Brain Research Institute. We will then retest you at the end of your program (8 weeks) to see if exercise has changed the way your brain processes information. There will be no cost to you for the scans and you will be provided with parking and gasoline vouchers to cover travel costs for each session.

The MRI scan being done is designed to answer research questions, not to examine your brain medically. This MRI scan is not a substitute for one that a doctor would order, and it may not show problems that would be picked up by a medical MRI scan. However, in the

unlikely event that we note an atypical finding on your MRI scan, we will contact you to help you arrange medical follow-up to interpret the significance of the findings, if any. We may also ask a radiologist, or other health professional, to look at your scan, and by signing this consent form you agree to releasing the scan for review. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

The MRI technique uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that you may be wearing. For the procedure, you will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the MRI scan of your brain. Since you will be inside the machine during the scan, and a screen will be in place for viewing the visual images, you may not be able to see the technicians operating the machine or the investigators. However, there is an intercom system that will allow you to talk with them at any time. If you feel uncomfortable during the scan and you wish to discontinue the procedure, you will be taken out of the machine at your request.

We will obtain a series of MRI scans, separated by short breaks, and the entire procedure will take approximately one hour. During the scans we will ask you to carry out a variety of tasks. You should try to remain as still as possible during each scan. Movement will not be dangerous to you in any way, but would blur the picture of your brain. You will hear moderately loud knocking or beeping during the scan when the MRI machine is in operation. Although you may find this to be unsettling, the machine cannot hurt you in any way.

Please note: Prior to your first scan you will also be required to sign an additional consent form required by Baycrest hospital which provides similar information about fMRI as this consent form.

2. Timeline

Brain scans will be taken at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Phobia of small confined spaces
- i. Metal Implants, pieces of shrapnel, aneurysm clips, or wires in your head. etc.
- ii. Implanted Pace Maker
- iii. Pregnant
- iv. Inability to get to the scanner at Rotman Baycrest*.

*We will compensate you for your parking and gasoline costs but you will need to be able to drive yourself or have someone else able to drive you in order to participate.

4. Risks and Discomforts

The MRI scan is not associated with any known risks to your health and there is no evidence that there will be either short-term or long-term side effects. Participants undergoing fMRI may feel uncomfortable or claustrophobic in the confined space. Furthermore, the

machine makes a loud noise which some people may find distressing. There will be someone with you at all times during the brain imaging, in case you should experience any adverse effects. If you have a tattoo, there is a very small possibility that you will feel a tingling or burning sensation at the tattoo site.

F. EXERCISE PROGRAM

1. Description

You will complete an exercise safety screening questionnaire called the Par-Q. If there are any concerns about the safety of your participation, you will have the option of withdrawing or getting your family doctor to complete the ParMed-X to ensure it safe for you to exercise.

Once enrolled and baseline assessments have been carried out you will commence a 8 week exercise program as part of the Mental Health Treatment program. The exercise sessions will take place at the Flex Center at Durham College/UOIT. All sessions will be in groups of 2 to 5 participants and will be supervised by the Exercise Supervisor for three sessions per week and you must be prepared to commit to attending at least 80% of the exercise sessions. The role of the supervisor will be to give you verbal encouragement, monitor you for any possible adverse effects and provide aid as needed, and to help you monitor your heart rate to ensure they you are working at the correct intensity. The exercise prescription will be individualized based on your starting fitness levels. One session per week will be aerobic exercise only, and the remaining two will be resistance exercise followed by a shorter aerobic bout. Based on your experience and ability, one resistance exercise will be selected from each of six categories – horizontal push, anterior lower body, vertical pull, posterior lower body, horizontal pull, and vertical push in order to establish a balanced, whole-body exercise prescription. Exercises will be changed after four weeks, to avoid adaptation. The aerobic bout following resistance sessions will be 20 minutes in the first week, and 30 minutes in subsequent weeks. Sessions containing a resistance component will be performed at least 24 hours apart. All sessions begin with a ten-minute aerobic warm-up, and are supervised by a kinesiologist. Participants are advised to bring a drink bottle and keep well hydrated. Opportunities will be provided to make up missed sessions.

2. Timeframe

- i. 3 one hour sessions per week for 8 weeks

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. Already exercise more than 20 minutes, three times per week
- ii. Physical conditions such as heart disease, or exclusions identified based on ParQ or ParMedX questionnaires.
- iii. I am unable to attend at least 80% of the exercise sessions

4. Risks and Discomforts

You may experience some physical discomfort both during exercise or stretching and following exercise or stretching, such as muscle soreness. There is a small risk of injury occurring during any exercise program; however, the kinesiologists involved are trained in modifying exercise programs to minimize this risk and you will be supervised at all times. There will be someone with you at all times during the exercise sessions, in case you should experience any adverse effects.

RESULTS

You will also be given a log to keep track of each procedure required from you. This log is to be completed and given to the researcher at the end of the study (see attached).

Once the information has been collected from all participants, the questionnaire responses will be examined to establish the effect of exercise on depression, cortisol secretion, several biomarkers, cognitive performance, TMS and fMRI results will be analyzed and a report will be written up. A short version of this report will be available to participants who would like a copy. You can indicate at the bottom of the consent form whether you would like to receive your report by email or by regular mail.

If you have depression and you experience any worsening of your depression during your participation in the study, you will be referred immediately to the treatment team at Lakeridge Mental Health. If you are concerned about any aspect of your participation, do not hesitate to contact the researchers at the numbers provided.

Compensation for Participation

There will be no direct compensation for participating in this research study, although you will be given a free supervised exercise program and you will be compensated for parking and gasoline costs.

Disclosure

Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. This legal obligation includes a number of circumstances, such as suspected child abuse and infectious disease, elevated risk or harm to you or others, and a court order by authorized agencies. For your information, the research consent form will be inserted in the patient health record.

Medical records that contain your identity will be treated as confidential in accordance with Ontario's privacy legislation, the Personal Health Information Protection Act, 2004.

The only people who will be accessing your patient records are the Lakeridge clinicians involved in your treatment. The other information collected by the researchers is separate and will be seen only by the researchers and all identifying information will be removed in any publications.

The Lakeridge Health Corporation Research Ethics Board and the University of Ontario Institute of Technology Research Ethics Board may review records related to the study for quality assurance purposes, as it oversees the conduct of this study at Lakeridge Health.

Please read the following before signing the consent form and remember to keep a copy for your own records.

By signing this form, I agree that:

- The study has been explained to me. All my questions were answered to my satisfaction.
- The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
- I know about the alternatives to taking part in this study. I understand that I have the right not to participate and the right to stop at any time. The decision about whether or not to participate will not affect my health care at Lakeridge Health.
- I am free now, and in the future, to ask any questions about the study.
- I have been told that my medical records will be kept confidential, except where release of information is required by law

- I understand that no information that would identify me, will be released without asking me first, unless the disclosure is required by law
- I hereby consent to participate.

I have completed the individual procedure assessments on pages 3 to 8 of this form and hereby consent to participate in the following procedures (please tick the box):

- A. Questionnaire completion
- B. Cognitive tasks
- C. Saliva samples
- D. Blood samples
- E. fMRI
- F. Exercise

Dissemination

Information gathered in this research study may be published or presented in public forums; however your name and other identifying information will not be used or revealed. We hope the information learned from this study will benefit other people and support the use of exercise as a treatment for depression in future patients.

You will be provided with a summary of findings at the end of the study, if you so desire. We will do our best to explain the findings to you in way that you understand and what these changes mean. Often in research we don't get the findings we expect. This is often because we didn't study enough participants or the changes are of a different nature then we expected. This is okay and still makes a very important contribution to science and to our understanding of depression. If you are concerned about any of the study findings or you would like more information, please contact Dr. Bernadette Murphy or Dr. Paul Yelder to discuss.

Please advise us of your preferable format for communication (check one and provide details in the space provided):

Please indicated by ticking the box whether you wish to receive your summary by email or regular mail Please provide either the land or email address you would like it sent to:

Participant Signature _____
 Date _____

Participant Printed Name _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

Printed Name

Date

Signature

Role in the Study (only authorized / qualified member of the research team)



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The role of exercise in improving brain function: Part B: MHDTP control group

You are invited to participate in a research study entitled “The role of exercise in improving brain function”. This study (# REB 10-104) has been reviewed by the University of Ontario Research Ethics Board and has been approved as of May 13, 2013. Please read this form carefully, and feel free to ask any questions you might have. If you have any questions about your rights as a participant in this study, please contact the Compliance Officer at 905 721 8668 ext 3693 or compliance.uoit.ca.

Researchers

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Purpose of the Study

This research study is being conducted to study the effect of the Lakeridge Mental Health Day Treatment Program on your levels of the stress hormone cortisol and a number of other biomarkers known to be altered in depression. We will also be looking at the way your brain functions during certain memory tasks. We are interested in how the treatment may change these things in depressed participants. We are also interested in how exercise may affect the intensity of depression symptoms. Previously we recruited participants from the Lakeridge program who also performed a 8 week exercise program. This phase of the study is now complete and we will be recruiting a group of patients in the Mental Health Day Treatment program who are of a similar age and gender to investigate the effects of the Day Treatment program on its own in order to compare to the results of the exercise group.

Potential Benefits to Participants and/or to Society

Exercise has been shown in past studies to be an effective treatment for depression. In this study we want to learn more about how and why it works in order to help us design the most effective types of exercise interventions. The control group will still receive the benefits of the Mental Health Day Treatment program. Additionally you will have the opportunity to see your scans and learn more about how your brain functions. If we show a strong effect between exercise and depression, it may become a future part of the Day Treatment program and you will be making an important contribution to improving treatment options for future patients.

Participation and Withdrawal

Your participation to take part in this study is voluntary. You may choose not to participate or you may withdraw from the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first. The staff here is very flexible about meeting your needs and if there is anything we can do to accommodate your needs, we are more than willing to help. You are still free to withdraw at any time without giving a reason, and your decision not to participate will not affect your care at this center.

Rights of Research Participants

You are free to ask any questions that you may have about your treatment and your rights as a research participant. You may withdraw your consent at any time and discontinue participation without penalty.

If any questions come up during or after the study or if you have a research-related injury, contact the study researchers listed on the first page.

Should you have any questions or concerns regarding your rights as a participant in this research study, or if you wish to speak with someone who is not related to this study, you may contact the Chair of the Lakeridge Health Corporation Research Ethics Board at (905) 576-8711 or UOIT Research Ethics Board through the Compliance Office (905) 721-8668 ext 6393.

You are one of 20 individuals being asked to participate in this study and have been referred to us by Lakeridge Mental Health Day Treatment program with a diagnosis of depression and you are between the ages of 18 and 50. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Eligibility

In order to be eligible for either group, you must not be currently doing regular exercise; that means your levels of exercise should be less than 20 minutes, three times per week. People suffering from mental conditions other than depression, or with physical conditions that would prevent them from doing exercise, such as heart disease, will be excluded from the study. An understanding of English sufficient to answer questionnaires is required.

If you have questions the stated procedures, timeline or exclusion criteria please feel free to discuss them with the study coordinator, Joanne Gourgouvelis or the investigators (contact details provided on page 1).

The following sections will outline the various tests and procedures of the study, including: 1) the purpose of each test or procedure; 2) the respective timelines; 3) exclusion criteria (factors that might make you ineligible to participate);

If you take part in this study, you will need to participate in several procedures. Please read the following pages and tick the boxes to indicate if any of the exclusion criteria pertain to you: A) Questionnaire completion (page 3), B) Cognitive tasks (page 3), C) Saliva samples (page 4), D) Bloodwork (see page 4), E) Brainscan (see page 5).

E. QUESTIONNAIRES

4. Purpose

To determine the severity of your symptoms associated with depression, you will complete some demographic information and you will then complete two Questionnaires, called the Beck Depression Inventory II (BDI-II) and the Hospital Anxiety and Depression Scale (HADS).

5. Timeline

Questionnaires will be given at:

- iii. Week 0
- iv. Week 8

6. Exclusion Criteria *(please check box if you have any of the following)*

- ii. Do not understand English

- 6. **Risks:** There are no risks from completing these questionnaires, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

F. COGNITIVE TASKS

4. Purpose

To determine overall cognitive functioning, you will perform a series of computer generated tasks which will assess your ability to identify simple objects in space. The benefits to you are that you will learn more about how your memory works and you will be increasing our knowledge of how exercise affects memory.

5. Timeline

Cognitive tasks will be given at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

6. Exclusion Criteria *(please check box if you have any of the following)*

- i. Do not understand English

Risks: There are no risks from completing these computer generated tasks, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

G. SALIVA

4. Purpose

Cortisol is a hormone which is known to be elevated in depressed individuals, and chronically high levels of cortisol have been linked with changes in the way the brain functions. It is possible that exercise may help depression by decreasing cortisol secretion. You will be given labelled tubes to collect a sample of your saliva (spit) to be tested at a laboratory for the stress hormone cortisol, which you will collect on the morning after your interview as soon as you wake up and then again 30 minutes after you wake up. The samples will then be put in the freezer and you will be given a small Styrofoam cooler to bring the samples back to the researcher on the next day that you attend the Lakeridge program. You will be given a set of simple instructions in case you forget what to do.

5. Timeline

Saliva samples will be taken at:

- iii. Week 0: the day after your interview (when you wake up and 30 minutes after waking up)
- iv. Week 8: when you wake up and 30 minutes after waking up

6. Exclusion Criteria *(please check box if you have any of the following)*

- ii. Ulcers or sores in your mouth

7. Risks

- ii. There are no complications or side effects when collecting saliva. Your samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study. They will be disposed of once they have been analyzed.

D. BLOODWORK

4. Purpose

A number of biomarkers found in blood are also known to be altered in depression and exercise may act to normalize their levels. A technician from the Medical Laboratory Science Program at the University of Ontario Institute of Technology will collect blood samples from each participant twice during the study.

5. Timeline

Blood samples will be taken at:

- iii. Week 0
- iv. Week 8

6. Exclusion Criteria *(please check box if you have any of the following)*

- iv. Bleeding disorder
- v. Medications that may interfere with blood clotting (heparin, wafarin)
- vi. Phobia of needles

5. Risks

Complications are very rare when acquiring blood samples through a sterile syringe. However, the following side effects have been reported:

- G. Excessive bleeding at site of puncture
- H. Bruising
- I. Feeling light-headed, fainting
- J. Infection

Your blood samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study when they will be analyzed. Any unused sample will be disposed of.

K. BRAIN SCAN (functional MRI)

2. Purpose

Prior to commencing your program, fMRI images of your brain will be obtained to investigate the way that your brain activates when you are performing a task requiring your concentration. We will also look at anatomical details of brain structures known to be involved in depression such as the hippocampus. Once you come out of the scanner, you will go to a separate room and be asked to go through some of the images from the task that you did in the scanner. The scan will take about one hour and will be carried out at Baycrest hospital attached to the Rotman Brain Research Institute. We will then retest you at the end of your program (8 weeks) to see if exercise has changed the way your brain processes information. There will be no cost to you for the scans and you will be provided with parking and gasoline vouchers to cover travel costs for each session.

The MRI scan being done is designed to answer research questions, not to examine your brain medically. This MRI scan is not a substitute for one that a doctor would order, and it may not show problems that would be picked up by a medical MRI scan. However, in the unlikely event that we note an atypical finding on your MRI scan, we will contact you to help you arrange medical follow-up to interpret the significance of the findings, if any. We may also ask a radiologist, or other health professional, to look at your scan, and by signing this consent form you agree to releasing the scan for review. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

The MRI technique uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that

you may be wearing. For the procedure, you will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the MRI scan of your brain. Since you will be inside the machine during the scan, and a screen will be in place for viewing the visual images, you may not be able to see the technicians operating the machine or the investigators. However, there is an intercom system that will allow you to talk with them at any time. If you feel uncomfortable during the scan and you wish to discontinue the procedure, you will be taken out of the machine at your request.

We will obtain a series of MRI scans, separated by short breaks, and the entire procedure will take approximately one hour. During the scans we will ask you to carry out a variety of tasks. You should try to remain as still as possible during each scan. Movement will not be dangerous to you in any way, but would blur the picture of your brain. You will hear moderately loud knocking or beeping during the scan when the MRI machine is in operation. Although you may find this to be unsettling, the machine cannot hurt you in any way.

Please note: Prior to your first scan you will also be required to sign an additional consent form required by Baycrest hospital which provides similar information about fMRI as this consent form.

4. Timeline

Brain scans will be taken at:

- iii. Week 0
- iv. Week 8

5. Exclusion Criteria *(please check box if you have any of the following)*

- ii. Phobia of small confined spaces
- v. Metal Implants, pieces of shrapnel, aneurysm clips, or wires in your head. etc.
- vi. Implanted Pace Maker
- vii. Pregnant
- viii. Inability to get to the scanner at Rotman Baycrest*.

*We will compensate you for your parking and gasoline costs but you will need to be able to drive yourself or have someone else able to drive you in order to participate.

5. Risks and Discomforts

The MRI scan is not associated with any known risks to your health and there is no evidence that there will be either short-term or long-term side effects. Participants undergoing fMRI may feel uncomfortable or claustrophobic in the confined space. Furthermore, the machine makes a loud noise which some people may find distressing. There will be someone with you at all times during the brain imaging, in case you should experience any adverse effects. If you have a tattoo, there is a very small possibility that you will feel a tingling or burning sensation at the tattoo site.

RESULTS

You will also be given a log to keep track of each procedure required from you. This log is to be completed and given to the researcher at the end of the study (see attached).

Once the information has been collected from all participants, the questionnaire responses will be examined to establish the effect of the MHDTP on depression, cortisol secretion, several biomarkers, cognitive performance, and fMRI results will be analyzed and a report will be written up. A short version of this report will be available to participants who would like a copy. You can indicate at the bottom of the consent form whether you would like to receive your report by email or by regular mail.

If you have depression and you experience any worsening of your depression during your participation in the study, you will be referred immediately to the treatment team at Lakeridge Mental Health. If you are concerned about any aspect of your participation, do not hesitate to contact the researchers at the numbers provided.

Compensation for Participation

There will be no direct compensation for participating in this research study, although you will be given a free supervised exercise program and you will be compensated for parking and gasoline costs.

Disclosure

Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. This legal obligation includes a number of circumstances, such as suspected child abuse and infectious disease, elevated risk or harm to you or others, and a court order by authorized agencies. For your information, the research consent form will be inserted in the patient health record.

Medical records that contain your identity will be treated as confidential in accordance with Ontario's privacy legislation, the Personal Health Information Protection Act, 2004.

The only people who will be accessing your patient records are the Lakeridge clinicians involved in your treatment. The other information collected by the researchers is separate and will be seen only by the researchers and all identifying information will be removed in any publications.

The Lakeridge Health Corporation Research Ethics Board and the University of Ontario Institute of Technology Research Ethics Board may review records related to the study for quality assurance purposes, as it oversees the conduct of this study at Lakeridge Health.

Please read the following before signing the consent form and remember to keep a copy for your own records.

By signing this form, I agree that:

- The study has been explained to me. All my questions were answered to my satisfaction.
- The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
- I know about the alternatives to taking part in this study. I understand that I have the right not to participate and the right to stop at any time. The decision about whether or not to participate will not affect my health care at Lakeridge Health.
- I am free now, and in the future, to ask any questions about the study.

- I have been told that my medical records will be kept confidential, except where release of information is required by law
- I understand that no information that would identify me, will be released without asking me first, unless the disclosure is required by law
- I hereby consent to participate.

I have completed the individual procedure assessments and hereby consent to participate in the following procedures (please tick the box):

- A. Questionnaire completion
- B. Cognitive task
- C. Saliva samples
- D. Blood samples
- E. fMRI

Dissemination

Information gathered in this research study may be published or presented in public forums; however your name and other identifying information will not be used or revealed. We hope the information learned from this study will benefit other people and support the use of exercise as a treatment for depression in future patients.

You will be provided with a summary of findings at the end of the study, if you so desire. We will do our best to explain the findings to you in way that you understand and what these changes mean. Often in research we don't get the findings we expect. This is often because we didn't study enough participants or the changes are of a different nature then we expected. This is okay and still makes a very important contribution to science and to our understanding of depression. If you are concerned about any of the study findings or you would like more information, please contact Dr. Bernadette Murphy or Dr. Paul Yelder to discuss.

Please indicated by ticking the box whether you wish to receive your summary by email or regular mail Please provide either the land or email address you would like it sent to:

Participant Signature _____

Date _____

Participant Printed Name _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

Printed Name

Date

Signature

Role in the Study (only authorized / qualified member of the research team)



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The role of exercise in improving brain function: Part C: Non-depressed exercise control group

You are invited to participate in a research study entitled “The role of exercise in improving brain function”. This study (# REB 10-104) has been reviewed by the University of Ontario Research Ethics Board and has been approved as of May 13, 2013. Please read this form carefully, and feel free to ask any questions you might have. If you have any questions about your rights as a participant in this study, please contact the Compliance Officer at 905 721 8668 ext 3693 or compliance.uoit.ca.

Researchers

Dr. Bernadette Murphy, Professor, Head-Kinesiology Specialization, Faculty of Health Sciences, University of Ontario Institute of Technology, Phone: (905) 721-8668 ext 2778, email: Bernadette.Murphy@uoit.ca, Fax: (905) 721-3179

Dr. Paul Yelder, Professor, Director-Bachelor of Health Sciences, Faculty of Health Sciences, University of Ontario Institute of Technology, Phone: (905) 721-8668 ext 2768, email: Paul.Yelder@uoit.ca, Fax: (905) 721-3179

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Dr. Ron Heslegrave, Chair, Research Ethics Board, Baycrest, Phone: (416) 785-2500 ext. 2440, email: hesgrave@uhnres.utoronto.ca

Joanne Gourgouvelis, PhD Candidate, Faculty of Science, University of Ontario Institute of Technology, Phone: (905) 550-4055, email: Joanne.Gourgouvelis@uoit.ca, Fax: (905) 721-3179

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Purpose of the Study

This research study is being conducted to study the effect of exercise on your levels of the stress hormone cortisol and a number of other biomarkers known to be altered in depression. We will also be looking at the way your brain functions during certain memory tasks. We are interested in how exercise may change these things in depressed participants as well as non depressed individuals. These will be assessed over the course of a 8 week structured, supervised exercise program.

Potential Benefits to Participants and/or to Society

Exercise has been shown in past studies to be an effective treatment for depression. In this study we want to learn more about how and why it works in order to help us design the most effective types of exercise interventions. Following the exercise program, you may be rewarded with several benefits that exercise is associated with. This study offers a structured exercise program suitable for beginners and may help you resolve any physical issues you have. If we show a strong effect, it may become a future part of the Mental Health Day Treatment program at Lakeridge Health and you will be making an important contribution to improving treatment options for future patients.

Participation and Withdrawal

Your participation to take part in this study is voluntary. You may choose not to participate or you may withdraw from the study at any time. However, if you decide to stop participating in the study, we encourage you to talk to the study staff first. The staff here is very flexible about meeting your needs and if there is anything we can do to accommodate your needs, we are more than willing to help. You are still free to withdraw at any time without giving a reason, and your decision not to participate will not affect your care at this center.

Rights of Research Participants

You are free to ask any questions that you may have about your treatment and your rights as a research participant. You may withdraw your consent at any time and discontinue participation without penalty.

If any questions come up during or after the study or if you have a research-related injury, contact the study researchers listed on the first page.

Should you have any questions or concerns regarding your rights as a participant in this research study, or if you wish to speak with someone who is not related to this study, you may contact the Chair of the Lakeridge Health Corporation Research Ethics Board at (905) 576-8711 or UOIT Research Ethics Board through the Compliance Office (905) 721-8668 ext 6393.

You are one of 20 individuals being asked to participate in this study and you are between the ages of 18 and 50. Please take your time to review this consent form and discuss any questions you may have with the study staff. You may take your time to make your decision about participating in this study and you may discuss it with your friends, family or your doctor before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

Eligibility

In order to be eligible for this study, you must not be currently doing regular exercise; that means your levels of exercise should be less than 20 minutes, three times per week. People suffering from any

mental conditions including depression, or with physical conditions that would prevent them from doing exercise, such as heart disease, will be excluded from the study. An understanding of English sufficient to answer demographic information is required.

The following sections will outline the various tests and procedures of the study, including: 1) the purpose of each test or procedure; 2) the respective timelines; 3) exclusion criteria (factors that might make you ineligible to participate);

If you have questions the stated procedures, timeline or exclusion criteria please feel free to discuss them with the study coordinator, Joanne Gourgouvelis or the investigators (contact details provided at bottom of page 1).

If you take part in this study, you will need to participate in several procedures. Please read the following pages and tick the boxes to indicate if any of the exclusion criteria pertain to you: A) Questionnaire completion (page 3), B) Cognitive tasks (see Page 3) C) Saliva samples (page 4), D) Bloodwork (see page 4), E) Brainscan (see page 5), F) Transcranial Magnetic Stimulation (TMS) (see page 6) G) Exercise (see page 7).

H. QUESTIONNAIRES

7. Purpose

Since we will be comparing your results to a group of depressed individuals, we need you to complete the complete some demographic information and as well as the same two Questionnaires, called the Beck Depression Inventory II (BDI-II) and the Hospital Anxiety and Depression Scale (HADS).

8. Timeline

Questionnaires will be given at:

- v. Week 0 (prior to the exercise program)
- vi. Week 8 (after completion of the exercise program).

9. Exclusion Criteria *(please check box if you have any of the following)*

- iii. Do not understand English

8. Risks: There are no risks from completing these questionnaires, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

I. COGNITIVE TASKS

7. Purpose

To determine overall cognitive functioning, you will perform a series of computer generated tasks which will assess your ability to identify simple objects in space. The benefits to you are that you will learn more about how your memory works and you will be increasing our knowledge of how exercise affects memory.

8. Timeline

Cognitive tasks will be given at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

9. Exclusion Criteria *(please check box if you have any of the following)*

- i. Do not understand English

Risks: There are no risks from completing these computer generated tasks, data will not contain any personal information that can identify you. Privacy and confidentiality will be maintained and data will be stored in a secured location.

J. SALIVA

7. Purpose

Cortisol is a hormone which is known to be elevated in depressed individuals, and chronically high levels of cortisol have been linked with changes in the way the brain functions. It is possible that exercise may help depression by decreasing cortisol secretion. You will be given labelled tubes to collect a sample of your saliva (spit) to be tested at a laboratory for the stress hormone cortisol, which you will collect on the morning after your interview as soon as you wake up and then again 30 minutes after you wake up. The samples will then be put in the freezer and you will be given a small Styrofoam cooler to bring the samples back to the researcher on the next day that you attend the Lakeridge program. You will be given a set of simple instructions in case you forget what to do.

8. Timeline

Saliva samples will be taken at:

- v. Week 0: the day before your first exercise session (when you wake up and 30 minutes after waking up)
- vi. Week 8: after completion of the exercise program (when you wake up and 30 minutes after waking up)

9. Exclusion Criteria *(please check box if you have any of the following)*

- iii. Ulcers or sores in your mouth

9. Risks

- iii. There are no complications or side effects when collecting saliva. Your samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study. They will be disposed of once they have been analyzed.

K. BLOODWORK

7. Purpose

A number of biomarkers found in blood related to brain function may be improved by exercise and we want to find out if similar changes in the level of these biomarkers happen with exercise for both depressed and non-depressed individuals. A technician from the

Medical Laboratory Science Program at the University of Ontario Institute of Technology will collect blood samples from each participant twice during the study.

8. Timeline

Blood samples will be taken at:

- v. Week 0 (prior to the exercise program)
- vi. Week 8 (after completion of the exercise program).

9. Exclusion Criteria (please check box if you have any of the following)

- vii. Bleeding disorder
- viii. Medications that may interfere with blood clotting (heparin, wafarin)
- ix. Phobia of needles

6. Risks

Complications are very rare when acquiring blood samples through a sterile syringe. However, the following side effects have been reported:

- L. Excessive bleeding at site of puncture
- M. Bruising
- N. Feeling light-headed, fainting
- O. Infection

Your blood and saliva samples will be coded in a way that does not identify you, frozen in a special freezer and stored until the end of the study when they will be analyzed. Any unused sample will be disposed of. Once the samples have been analyzed and disposed they cannot be withdrawn.

P. BRAIN SCAN (functional MRI)

3. Purpose

Prior to commencing your program, fMRI images of your brain will be obtained to investigate the way that your brain activates when you are performing a task requiring your concentration. We will also look at anatomical details of brain structures known to be involved in depression such as the hippocampus. Once you come out of the scanner, you will go to a separate room and be asked to go through some of the images from the task that you did in the scanner. The scan will take about one hour and will be carried out at Baycrest hospital attached to the Rotman Brain Research Institute. We will then retest you at the end of your program (8 weeks) to see if exercise has changed the way your brain processes information. There will be no cost to you for the scans and you will be provided with parking and gasoline vouchers to cover travel costs for each session.

The MRI scan being done is designed to answer research questions, not to examine your brain medically. This MRI scan is not a substitute for one that a doctor would order, and it may not show problems that would be picked up by a medical MRI scan. However, in the unlikely event that we note an atypical finding on your MRI scan, we will contact you to help you arrange medical follow-up to interpret the significance of the findings, if any. We may also ask a radiologist, or other health professional, to look at your scan, and by signing this

consent form you agree to releasing the scan for review. It is possible that you could be unnecessarily worried if a problem were suspected, but not actually found.

The MRI technique uses magnets and radiowaves to construct a picture of the brain on a computer. Before the scan begins, you will be asked to remove any magnetic metals that you may be wearing. For the procedure, you will be asked to lie on a padded bed that will be moved into a tunnel-like machine for the MRI scan of your brain. Since you will be inside the machine during the scan, and a screen will be in place for viewing the visual images, you may not be able to see the technicians operating the machine or the investigators. However, there is an intercom system that will allow you to talk with them at any time. If you feel uncomfortable during the scan and you wish to discontinue the procedure, you will be taken out of the machine at your request.

We will obtain a series of MRI scans, separated by short breaks, and the entire procedure will take approximately one hour. During the scans we will ask you to carry out a variety of tasks. You should try to remain as still as possible during each scan. Movement will not be dangerous to you in any way, but would blur the picture of your brain. You will hear moderately loud knocking or beeping during the scan when the MRI machine is in operation. Although you may find this to be unsettling, the machine cannot hurt you in any way.

Please note: Prior to your first scan you will also be required to sign an additional consent form required by Baycrest hospital which provides similar information about fMRI as this consent form.

6. Timeline

Brain scans will be taken at:

- v. Week 0 (prior to the exercise program)
- vi. Week 8 (after completion of the exercise program).

7. Exclusion Criteria (please check box if you have any of the following)

- iii. Phobia of small confined spaces
- ix. Metal Implants, pieces of shrapnel, aneurysm clips, or wires in your head. etc.
- x. Implanted Pace Maker
- xi. Pregnant
- xii. Inability to get to the scanner at Rotman Baycrest*.

*We will compensate you for your parking and gasoline costs but you will need to be able to drive yourself or have someone else able to drive you in order to participate.

6. Risks and Discomforts

The MRI scan is not associated with any known risks to your health and there is no evidence that there will be either short-term or long-term side effects. Participants undergoing fMRI may feel uncomfortable or claustrophobic in the confined space. Furthermore, the machine makes a loud noise which some people may find distressing. There will be someone with you at all times during the brain imaging, in case you should experience any adverse effects. If you have a tattoo, there is a very small possibility that you will feel a tingling or burning sensation at the tattoo site.

Q. Transcranial Magnetic Brain Stimulation (TMS)

1. Purpose

Prior to commencing your program, transcranial magnetic stimulation (TMS) data will be collected to investigate the way that your brain activates output to your muscles. We will evaluate this again at the end of the program to determine if the exercise intervention has altered the excitability of certain brain pathways. Your participation in the TMS experiments will contribute to our understanding of how the brain and associated structures aids in the control of bodily movement. You will also further our knowledge of how motor training tasks can evoke cognitive learning, and how this subsequently affects the neural system.

Should you agree to participate you will need to attend two evaluation sessions at the beginning and end of the exercise program. During the evaluation session we will collect some information about the way your brain is controlling a distal hand muscle. To do this it will be necessary to place some electrodes over the investigated muscle to record the signals from your brain to the muscle. Each evaluation session will take about 2-3 hours and you will be given feedback about your results following the procedure.

2. Timeline

TMS data will be collected at:

- i. Week 0 (prior to the exercise program)
- ii. Week 8 (after completion of the exercise program).

3. Exclusion Criteria *(please check box if you have any of the following)*

- i. History of epilepsy
- ii. Metal Implants, pieces of shrapnel, aneurysm clips, or wires in your head. etc.
- iii. Implanted Pace Maker
- iv. Pregnant
- v. Previous brain surgery

4. Risks and Discomforts

The surface EMG techniques have low risks such as the person getting a skin irritation from the alcohol swab or electrode gel, but these are uncommon and not serious. Magnetic stimulation is a safe procedure that allows us to study the nerve pathways that go to the muscles of the hand. The stimulator produces a clicking sound and then a mild twitching feeling can sometimes be felt in the scalp muscles as well as the hand muscles. Occasionally, some people experience mild, transient scalp discomfort, due to the activation of the scalp muscles by the stimulation. Some people may also experience nausea or a mild headache. Both these reactions are uncommon and not serious. If you experience any of these effects let the investigator know. Certain people such as those with epilepsy, metal plates in their skull or prior brain surgery are not suitable candidates for magnetic brain stimulation, and this will be determined through the use of a screening questionnaire prior to your participation in this aspect of the study. Because the magnetic field discharges so quickly there is far less electromagnetic radiation than that from a television or mobile phone. At any time during the experiment, at your request we will stop the stimulation immediately.

G. EXERCISE PROGRAM

4. Description

You will complete an exercise safety screening questionnaire called the Par-Q. If there are any concerns about the safety of your participation, you will have the option of withdrawing or getting your family doctor to complete the ParMed-X to ensure it safe for you to exercise.

Once enrolled and baseline assessments have been carried out you will commence a 8 week exercise program. The exercise sessions will take place at the Flex Center at Durham College/UOIT. All sessions will be in groups of 2 to 5 participants and will be supervised by the Exercise Supervisor for three sessions per week and you must be prepared to commit to attending at least 80% of the exercise sessions. The role of the supervisor will be to give you verbal encouragement, monitor you for any possible adverse effects and provide aid as needed, and to help you monitor your heart rate to ensure they you are working at the correct intensity. The exercise prescription will be individualized based on your starting fitness levels. One session per week will be aerobic exercise only, and the remaining two will be resistance exercise followed by a shorter aerobic bout. Based on your experience and ability, one resistance exercise will be selected from each of six categories – horizontal push, anterior lower body, vertical pull, posterior lower body, horizontal pull, and vertical push in order to establish a balanced, whole-body exercise prescription. Exercises will be changed after four weeks, to avoid adaptation. The aerobic bout following resistance sessions will be 20 minutes in the first week, and 30 minutes in subsequent weeks. Sessions containing a resistance component will be performed at least 24 hours apart. All sessions begin with a ten-minute aerobic warm-up, and are supervised by a kinesiologist. Participants are advised to bring a drink bottle and keep well hydrated..

5. Timeframe

ii. 3 one hour sessions per week for 8 weeks

6. Exclusion Criteria *(please check box if you have any of the following)*

iv. Already exercise more than 20 minutes, three times per week

v. Physical conditions such as heart disease, or exclusions identified based on ParQ or ParMedX questionnaires.

vi. I am unable to attend at least 80% of the exercise sessions

5. Risks and Discomforts

You may experience some physical discomfort both during exercise or stretching and following exercise or stretching, such as muscle soreness. There is a small risk of injury occurring during any exercise program; however, the kinesiologists involved are trained in modifying exercise programs to minimize this risk and you will be supervised at all times. There will be someone with you at all times during the exercise sessions, in case you should experience any adverse effects.

RESULTS

You will also be given a log to keep track of each procedure required from you. This log is to be completed and given to the researcher at the end of the study (see attached).

Once the information has been collected from all participants, cortisol secretion, several biomarkers, and fMRI results will be analyzed and a report will be written up. A short version of this report will be available to participants who would like a copy. You can indicate at the bottom of the consent form whether you would like to receive your report by email or by regular mail.

If you are concerned about any aspect of your participation, do not hesitate to contact the researchers at the numbers provided.

Compensation for Participation

There will be no direct compensation for participating in this research study, although you will be given a free supervised exercise program and you will be compensated for parking and gasoline costs.

Disclosure

Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law. This legal obligation includes a number of circumstances, such as suspected child abuse and infectious disease, elevated risk or harm to you or others, and a court order by authorized agencies. For your information, the research consent form will be inserted in the patient health record.

Medical records that contain your identity will be treated as confidential in accordance with Ontario's privacy legislation, the Personal Health Information Protection Act, 2004.

All information collected by the researchers will be seen only by the researchers and all identifying information will be removed in any publications.

The University of Ontario Institute of Technology Research Ethics Board may review records related to the study for quality assurance purposes, as it oversees the conduct of this study.

Please read the following before signing the consent form and remember to keep a copy for your own records.

By signing this form, I agree that:

- The study has been explained to me. All my questions were answered to my satisfaction.
- The possible harms and discomforts and the possible benefits (if any) of this study have been explained to me.
- I am free now, and in the future, to ask any questions about the study.
- I have been told that my medical records will be kept confidential, except where release of information is required by law
- I understand that no information that would identify me, will be released without asking me first, unless the disclosure is required by law
- I hereby consent to participate.

I have completed the individual procedure assessments and hereby consent to participate in the following procedures (please tick the box):

G. Questionnaire completion

- H. Cognitive tasks
- I. Saliva samples
- J. Blood samples
- K. fMRI
- L. TMS
- M. Exercise

Dissemination

Information gathered in this research study may be published or presented in public forums; however your name and other identifying information will not be used or revealed. We hope the information learned from this study will benefit other people and support the use of exercise as a treatment for depression in future patients.

You will be provided with a summary of findings at the end of the study, if you so desire. We will do our best to explain the findings to you in way that you understand and what these changes mean. Often in research we don't get the findings we expect. This is often because we didn't study enough participants or the changes are of a different nature then we expected. This is okay and still makes a very important contribution to science and to our understanding of depression. If you are concerned about any of the study findings or you would like more information, please contact Dr. Bernadette Murphy or Dr. Paul Yelder to discuss.

Please indicated by ticking the box whether you wish to receive your summary by email or regular mail Please provide either the land or email address you would like it sent to:

Participant Signature _____
 Date _____

Participant Printed Name _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their consent.

 Printed Name

 Date

 Signature

Role in the Study (only authorized / qualified member of the research team)