Mechanisms by which exercise promotes hippocampal function in both depressed and non-depressed individuals: A feasibility study

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Abstract

Depression is one of the top ten health problems in the world, affecting millions of Canadians. Research indicates that exercise is an effective treatment for depression but it is not clear on exactly how and why it works. Animal studies show that exercise improves the ability of the brain to function. It can even lead to new cell formation in a part of the brain called the hippocampus, which is important for memory processing. This study is investigating whether exercise may also improve hippocampal function in depressed humans. One way exercise may improve brain function is by normalizing levels of the hormone cortisol, and its toxic effects on the hippocampus. Exercise may also normalize levels of biochemical markers called cytokines involved in inflammation, while improving levels of growth factors important to brain cell function. This feasibility study aimed to develop protocols to investigate changes in hippocampal activity while participants are performing memory tests involving association of images and words in a functional magnetic resonance scanner before and after a 12 week exercise program. It also aimed to develop and validate protocols to measure changes in cortisol, cytokines and growth factors which are likely to be affected by exercise. Our preliminary imaging results revealed hippocampal dysregulation in the depressed brain, and biomarker analysis revealed abnormal concentrations of interleukin-6, vascular endothelial growth factor and salivary cortisol when compared to normal healthy controls. However, following the 12-week exercise program a more normalized pattern of hippocampal activation associated with successful memory encoding was observed. Additionally, biomarker concentrations either resembled or were closer to normal healthy values. Over the long term, the project arising from this feasibility study has the potential to provide a
tool to improve exercise prescription, to predict exercise responders and to guide development of combined treatment approaches related to biochemical markers in order to optimize depression outcomes for Canadians.
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<tbody>
<tr>
<td>BB</td>
<td>Barbell</td>
</tr>
<tr>
<td>BBB</td>
<td>Blood-brain barrier</td>
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<td>BDI-II</td>
<td>Beck Depression Inventory – Second edition</td>
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<td>BDNF</td>
<td>Brain Derived Neurotrophic Factor</td>
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<td>BOLD</td>
<td>Blood oxygenation level-dependent</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>bpm</td>
<td>(Heart) beats per minute</td>
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<tr>
<td>BrdU</td>
<td>bromodeoxyuridine</td>
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<tr>
<td>CA</td>
<td>Cornu Ammonis</td>
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<tr>
<td>CAR</td>
<td>Cortisol awakening response</td>
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<td>CNS</td>
<td>Central nervous system</td>
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<td>CPAFLA</td>
<td>Canadian Physical Activity, Fitness &amp; Lifestyle Approach</td>
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<tr>
<td>DB</td>
<td>Dumbbell</td>
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<tr>
<td>DG</td>
<td>Dentate Gyrus</td>
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<tr>
<td>EPI</td>
<td>Echo-Planar Image</td>
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<tr>
<td>EIA</td>
<td>Enzyme immunoassay</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-linked immunoassay</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<td>GAIN-SS</td>
<td>Global Appraisal of Individual Needs – Short Screener</td>
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<tr>
<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<tr>
<td>HADS-A</td>
<td>Hospital Anxiety and Depression Scale - Anxiety</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>HADS-D</td>
<td>Hospital Anxiety and Depression Scale - Depression</td>
</tr>
<tr>
<td>HC</td>
<td>High-confidence</td>
</tr>
<tr>
<td>HR\text{max}</td>
<td>Maximum heart rate</td>
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<tr>
<td>HPA</td>
<td>Hypothalamic-pituitary-adrenal</td>
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<td>HRP</td>
<td>Horseradish peroxidase</td>
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<tr>
<td>ID</td>
<td>Identification</td>
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<tr>
<td>IGF</td>
<td>Insulin Growth Factor</td>
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<td>IL-1</td>
<td>Interleukin 1</td>
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<td>Interleukin 6</td>
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<tr>
<td>IFN</td>
<td>Interferon</td>
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<td>Kcals</td>
<td>Kilocalories</td>
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<tr>
<td>LMHDT</td>
<td>Lakeridge Mental Health Day Treatment</td>
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<tr>
<td>MHDT</td>
<td>Mental Health Day Treatment</td>
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<td>MHR</td>
<td>Maximum heart rate</td>
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<td>MoCA</td>
<td>Montreal Cognitive Assessment</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<td>PAR-Q</td>
<td>Physical Activity Readiness Questionnaire</td>
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<td>PARmed-X</td>
<td>Physical Activity Readiness Medical Examination</td>
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<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
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<tr>
<td>REB</td>
<td>Research Ethics Board</td>
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<tr>
<td>RPE</td>
<td>Rating of Perceived Exertion</td>
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<tr>
<td>RPM</td>
<td>Revolutions per minute</td>
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<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>SCID-I</td>
<td>Structural Clinical Interview for DSM-IV Axis I Disorders</td>
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<tr>
<td>SF-36</td>
<td>36-item Short-form questionnaire</td>
</tr>
<tr>
<td>SOS</td>
<td>Salimetrics® Oral Swab</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>VEGF</td>
<td>Vascular Endothial Growth Factor</td>
</tr>
<tr>
<td>VO2 max</td>
<td>Maximal oxygen uptake</td>
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Chapter 1  Introduction

1.1 Background to the study

The effects of depression are profound and far-reaching, being the 3rd largest contributor to the burden of disease in high income and 7th in middle and low income countries (Lopez et al. 2006) and affecting millions of Canadians (Canada 2006). Exercise has proven benefits in the treatment of depression (Blumenthal et al. 1999; Dunn et al. 2005), but there are several competing hypotheses in our understanding of its mechanism of action. Major Depressive Disorder (MDD) is associated with a wide array of physiological, psychological and cognitive symptoms particularly impairments in memory (Burt et al. 1995; Ilsley et al. 1995; Zakzanis et al. 1998; Airaksinen et al. 2004). Exercise has been shown to improve memory in people with MDD (Ernst et al. 2006; Cotman et al. 2007), suggesting an underlying mechanism that improves neural function however it has been difficult to ascribe the improvement to the physiological effects of exercise because of a lack of a physiological test that is clearly linked to improved neural function (Sperling et al. 2003; Fairhall et al. 2010). Recently, Fairhall (2010) and colleagues were the first to demonstrate decreased activation of the hippocampus during the encoding phase of a memory task in depressed individuals compared to control subjects using functional magnetic resonance imaging (fMRI)(Fairhall et al. 2010). Researchers compared differences in hippocampal function (as opposed to volume differences) between eight people with MDD and eight age and gender matched controls. An associative memory task was designed based on work that showed robust modulation
of the right anterior hippocampus during the encoding of events that are subsequently successfully remembered (Sperling et al. 2003). Likewise, pilot results confirmed robust activation in the right hippocampus during encoding. Controls showed the predicted pattern of increased activation in the right anterior hippocampus during the associative encoding of stimuli that are successfully remembered with confidence compared to those that are not remembered. However, this pattern was absent in the MDD group, thus supporting the hypothesis that the normal modulation of right hippocampal activation by encoding strength is dysregulated in MDD. An additional analysis showed that this dysfunction was specific to the hippocampus and that a double dissociation between groups in the hippocampus and intraparietal sulcus suggest that compensatory mechanisms may exist. These findings provide a cutting edge tool linking memory impairments and hippocampal changes in MDD and to integrate several current threads of research to differentiate those factors which are able to be mediated by exercise and are correlated with improved neural function.

One way that exercise may improve brain function in depression is by restoring normal hypothalamic-pituitary-adrenal (HPA) axis and immune functioning by reducing cortisol and pro-inflammatory cytokines levels and their toxic effects on the hippocampus in addition to increasing neurotrophic growth factors known to enhance neural plasticity, and new cell formation (neurogenesis). However the relationship between new cell growth, increased hippocampal volume and more efficient functional activity in the hippocampus has only been presumed thus far.

With the ability to demonstrate improved hippocampal activation concomitant with improved memory, it is possible to determine which of the biochemical markers
including cortisol, inflammatory cytokines and growth factors relate to changes in hippocampal function. This work has the potential to provide a tool to improve exercise prescription, to predict exercise responders and guide development of a synergistic treatment approach.

Figure 1.1: Overview of the effects of depression and exercise on dependant variables
1.2 Experimental objectives and hypotheses

1.2.1 Original Objectives

The objectives of the proposed study are to investigate the effect of a moderate-intensity structured, supervised 12 week exercise program combined with a mental health day treatment (MHDT) program, as compared to the MHDT on its own, and exercise in a non-depressed group. The outcome measures will include: Intensity of depressive symptoms, sleep quality, overall cognitive function, plasma IL-1β, IL-6, IFN-γ, TNF-α and IL-10, VEGF, BDNF and IGF, salivary cortisol, performance on an associative memory task and concomitant fMRI hippocampal activation. A non-depressed exercise group will be included to determine if the effects of exercise on the outcome measures are generic. All outcome measures will be assessed at baseline and 12 weeks.

The specific objectives of this research are:

a) To determine whether depressed individuals who perform moderate exercise perform better on cognitive memory tasks and demonstrate a return towards the profile of hippocampal activation found in non-depressed individuals:

   Hippocampal activation will be assessed using functional magnetic resonance imaging (fMRI) and measuring activation in the hippocampus during the encoding phase of a cognitive memory task.

b) To determine whether the depressed exercise group demonstrates lower levels of cortisol, IL-1β, IL-6, IFN-γ, TNF-α and higher levels of IL-10, DHEA, VEGF, BDNF and IGF after 12 weeks compared to their own
baseline and to any changes in the control group, and the baseline levels in the non-depressed group: Participant will be sampled mid-week at waking and 30 minutes post-awakening samples for saliva which will be brought to the investigators when they present for their fMRI scan. Both waking cortisol and the awakening response (waking – 30 minutes post awakening) will be assayed along with growth factors and cytokines which will be measured from plasma and assayed using ELISA test kits for all three groups.

c) **To investigate the relationship between changes in biochemical markers and changes in hippocampal function with exercise:** Regression analysis will be used to determine whether there is any relationship between biochemical markers and hippocampal function.

d) **Determine whether there is relationship between improved fitness and improved hippocampal function:** Aerobic fitness will be measured at 0 and 12 weeks using submaximal tests of oxygen uptake ($V_{O2\ max}$). Improvement in fitness will be compared to improvement in memory and hippocampal activation to determine if there is any correlation between the two for both exercise groups.

### 1.2.2 Original Hypotheses

The overall goal of this research is to investigate whether a structured, supervised 12 week exercise program can promote changes in hippocampal function in depressed individuals and whether this is associated with improvements in depression, memory and the status of biochemical markers known to be altered in MDD. This study will be comparing depressed individuals who perform moderate exercise for 12 weeks in
addition to attending an outpatient day program to a control group who attend the day program only. This study will also have a matched non-depressed exercise group to provide normative data for comparison and to determine whether exercise also improves hippocampal activation and biomarker status in non-depressed individuals.

It is hypothesized that:

a) Improved cardiovascular fitness as measured by change in maximal oxygen consumption (VO2max) will be correlated with decreased cortisol levels in both exercise groups.

b) Participants who receive exercise in addition to the MHDT will show greater improvements in depression and hippocampal function as well as lower levels of cortisol than those in the MHDT only group.

c) Performance on cognitive memory tasks with concomitant hippocampal activation (assessed using fMRI) will be positively correlated with improvements in depression scores following the 12 week exercise intervention.

d) Changes in cortisol, IL-1β, IL-6, IFN-γ, TNF-α will be negatively correlated and changes in IL-10, VEGF, BDNF and IGF will be positively correlated with changes in hippocampal function following the 12 week exercise intervention.

### 1.3 Revised Thesis objectives

As the planning for the study began in collaboration with our partners at the Lakeridge MHDT (LMHDT) program it became clear that there were a large number of preliminary steps that would need to be completed prior to the initiation of the original aims.

These preliminary steps included:
1. Completion of an in depth literature review to ensure the most relevant biomarkers relating to both exercise and depression would be assayed and the most up to date evidence based protocols for exercise and depression are utilized.

2. Applying for grant funding to cover the costs of the fMRI scans and biomarker assays.

3. Obtaining Ethical approval from three different Ethics committees (Lakeridge Health where patients will be sampled, UOIT and Rotman Baycrest where the fMRI scans would take place).

4. Validating and piloting the planned fMRI protocol previously piloted in New Zealand on a 1.5 Tesla General Electric MRI scanner at the 3.0 Tesla Siemens MRI scanner at the Rotman Baycrest hospital.

5. Developing a recruitment protocol from the LMHDT program to minimize the number of steps required for staff and potential participants.

6. Developing protocols for blood collection, storage and biomarker assays.

7. Preliminary testing of the baseline samples of the initial recruits to determine the sensitivity of the assays.

8. Development of an organizational plan to match exercise supervisors to participants as each participant will be performing three one hour exercise sessions per week.

Additionally, because it is clear that in order to differentiate the effects of exercise specific to depression from the general effects of exercise it is important to include a non-depressed exercise group in the final study which would have been beyond the timeframe of a Masters’ thesis. Therefore it was decided that that this Masters’ thesis would become
a feasibility study for the larger study with the aims of completing the preliminary steps described above, writing an in depth methods chapter to be used in the larger study, and summarizing and discussing the results of the feasibility study and any implications that this would have for the larger study.

1.4 Significance of the study

The effects of depression are far-reaching, having become one of the leading contributors to the global burden of disease (WHO, 2008). Depression affects 1 in 20 Canadians (Canada 2006) with an economic burden, estimated at over 14 billion dollars annually in 2001 (Stephens and Joubert 2001). The poor remission rates of existing antidepressant therapies as well as the social stigma associated with seeking medical help leaves many individuals undertreated (Shelton 2006). With a recent meta-analysis suggesting that there are minimal benefits of medication vs placebo for mild to moderate depression (Fournier et al. 2010), the role of non-pharmacologic treatment for depression becomes increasingly important. Exercise is a therapeutic intervention with proven benefits in the treatment of depression, but there is minimal research on its mechanism of action. Therefore it is fundamental to understand why and how exercise works, in order to better focus the exercise prescription and identify those most likely to benefit from exercise in place of, or in addition to, other therapies.

It is well established that impaired episodic memory and reduced hippocampal volume is associated with depression, however there is controversy about the meaning and mechanism of these findings. Previous pilot data suggest that hippocampal fMRI can distinguish between depressed and non-depressed individuals and may prove to be
sensitive marker of the effect of an intervention on neural function. A potential candidate mechanism for hippocampal and memory changes are the elevated cortisol and pro-inflammatory cytokine levels and decreased growth factor levels observed in depressed individuals. This planned study will significantly advance knowledge as it is the first to use fMRI to measure changes in hippocampal activation following an exercise intervention in people with depression. By correlating changes in hippocampal activation with changes in cortisol, pro-inflammatory cytokines and growth factors it is possible to determine which of the biochemical markers is most predictive of improved neural function. This study will also differentiate which markers change in MHDT plus exercise vs MHDT alone as well as measuring whether these same markers change with exercise in a non-depressed group. This will create a much more solid rationale for combined approaches in the future. In the future it may be possible to use a person’s “biochemical signature” to determine the combination of exercise, pharmacotherapy and/or psychological interventions are needed for synergistic effects and optimize treatment outcomes for an individual. This work has the potential to provide a tool to improve exercise prescription, to predict exercise responders and to guide development of synergistic treatment approaches to optimize depression outcomes for Canadians.

1.5 Limitations

Study design

The proposed research will utilize a cohort control design. Participants will be recruited in blocks. Depressed Group 1 will undertake a 12 week structured, supervised exercise program in addition to the MHDT and they will be recruited in the first year of the study. Group 2 from the MHDT will be recruited in the second year so that they can be matched
by age, gender, pharmacotherapy and baseline fitness level to the exercise group using the same inclusion criteria. The reason for running the study as a cohort control rather than a randomized controlled trial is that the LMHDT is a group program and it might affect group cohesion if some participants were offered the exercise program and others were not. This way everyone in the first cohort who meets the inclusion criteria will be given the opportunity to have the exercise program, and this will not interfere with the program in the way that it is currently run. It also allows to age and gender match the control group in the non-exercising LMHDT cohort.

Testing and instrumentation

Cortisol secretion is associated with several variables such as life stressors. Saliva sampling at baseline and 12 weeks took place midweek on a Wednesday, due to the significant cortisol secretion differences on week days, versus weekends (Kunz-Ebrecht et al. 2004).

Although indirect submaximal cardiorespiratory fitness tests estimating VO$_{2\text{max}}$ are less accurate than direct maximal measurements, they are more appropriate test to use when evaluating sedentary populations. The validity of VO$_{2\text{max}}$ tests can be questioned with variables such as motivation, however workload and durations for the Astrand-Rhyming cycle ergometer protocol are determined by fixed guidelines and do not allow for subjectivity. Additionally, provide an accurate estimation of VO$_{2\text{max}}$ once adjusted to the Astrand age correction factors (Cink and Thomas 1981).
Participant compliance

To prevent errors associated with self-sampling, participants will be provided with clearly written instructions in conjunction with a verbal explanation, at baseline and at 12 weeks. If a participant forgets to sample or a sampling error occurs, an alternative midweek day (Thursday) will be used to repeat sampling.

To ensure that exercise attendance between-group differences could be accounted for, individual records were kept of session attendance so that attendance rate could be calculated. To remain eligible for the study, a minimum of 75% attendance is required, which translates to a minimum of 27 sessions out of the total 36 allotted.

Controlling for the effects from social contact

It is important to differentiate the benefits of group exercise which are specific to exercise as opposed to the psychosocial benefits due to the social interaction that occurs within the group. A meta-analysis of 14 randomised controlled trials in this area, while finding a positive overall effect for exercise, identified a lack of randomisation concealment, blinding and intention to treat analysis in the research to date (Lawlor and Hopker 2001). A point raised is that positive social interactions occurring during exercise may be more important to the treatment effect than exercise per se, and most research is lacking the inclusion of contact only groups to control for the psychosocial benefits of exercise, an issue will be addressed as the LMHDT program provides an ideal solution to this.
Chapter 2  Literature Review

Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it. - Plato (423 BC - 347 BC)

2.1 Depression

Major depressive disorder (MDD) is a global public-health problem and is among the most prevalent and burdensome of all psychiatric disorders. In Canada, it is estimated that 1 in 20 Canadians are affected by depression and its economic burden is estimated at over 14 billion dollars annually (Stephens and Joubert 2001). Depression is the fourth leading cause of disease burden globally and is projected to be the second leading cause by the year of 2030 (WHO, 2004). It has been estimated that 12% of men and 25% of women will experience a clinically significant depressive episode at least once in their lives (Shelton 2006; Gadalla 2009).

Depression is also a severely undertreated and under recognized disorder in the primary care setting (Diverty and Beaudet 1997; Insel and Charney 2003; Patten and Beck 2004). The majority of individuals with mental illness do not consult health professionals (Insel and Charney 2003; Gadalla 2009) and it is estimated that only 56% of depressed Canadians seek medical help. Of those patients who seek medical help and receive treatment with antidepressant drug therapy, only half achieve full remission of symptoms (i.e. absence of symptoms and return to normal functioning) (Fava and Ruini 2002). 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). The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-
TR) defines a depressive episode as a period greater than 2 weeks that is characterized by five or more symptoms ranging from 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, decreased ability to think or concentrate (APA and DSM-IV 2000). These symptoms are often associated with higher suicide rates and higher mortality rates (Kalia, 2005; Wulsin, Vaillant, & Wells, 1999). There is also strong evidence implicating depression in the later development of other medical illnesses such as increased abdominal fat, decreased bone density, hypertension, peptic ulcers and diabetes (Brown, Varghese, & McEwen, 2004). Therefore, the need for non-pharmacologic treatments for depression is becoming increasingly important.

2.2.1 Depression and memory

Of the wide array of cognitive deficits associated with depression, memory impairment is the most frequently reported (Airaksinen et al. 2004). However, research in this area has presented ambiguous findings in terms of the type, severity and specificity of memory deficits. One finding that has consistently been replicated is that of impaired 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 other facets of memory such as short-term memory (Ilsley et al. 1995; Tulving and Markowitsch 1998; Sweeney et al. 2000). However, some studies have found equivalence between depressed and control individuals for both semantic and episodic memory (Danion et al. 1995). These conflicting findings may be due somewhat to differences in the sampling populations, and methodological weaknesses. A meta-analysis of 147 studies examining memory dysfunction in depression (Burt et al. 1995) found a significant, stable association between depression and memory impairment. A more recent meta-
analysis of 22 studies supports the relationship between depression and memory impairment, and furthermore reveals that depression has the greatest effect on episodic memory as compared to semantic and short-term memory (Zakzanis et al. 1998). Research identifying the stage of the memory deficit, in encoding or retrieval, has been equivocal (Ilsley et al. 1995; Airaksinen et al. 2004). A meta-analysis of studies on depression and memory suggests that both encoding and retrieval processes are impaired somewhat in depression (Zakzanis et al. 1998). More recent, behavioural and neuroimaging studies have found that both the encoding and retrieval processes in memory are impaired in depression (Zakzanis et al. 1998; Airaksinen et al. 2004; Behnken et al. 2010; Fairhall et al. 2010; Milne et al. 2012). Although the neural underpinnings of impaired memory in MDD are not completely understood, the majority of evidence implicates abnormal activity in the hippocampal region critical for normal memory formation (Heckers et al. 2002; Sperling et al. 2003).

2.2 The role of the hippocampus

The role of the hippocampus in the formation of memories has long been recognized. The hippocampus is located in the medial temporal lobe and is critical for learning and the formation of stable declarative memory in humans. However, the exact function of the hippocampus in forming successful memories remains unknown (Scoville and Milner 2000; Kim et al. 2006). The laminae that comprise the hippocampal complex include the dentate gyrus (DG) and hippocampal proper, four regions of the cornu Ammonis (CA) termed CA1–CA4 which are based on pyramidal neuron morphology and sensitivity to anoxia (Sperling et al. 2003; Campbell and MacQueen 2004; Duvernoy 2005). The critical functions of the hippocampus were first
discovered over 50 years ago when severe amnesia and the inability to form new memories occurred in a patient following removal of this brain region (Scoville and Milner 2000).

At the time of memory formation a connection must be made between the to-be-remembered stimulus and its context. It is the process of encoding that forms new associations between previously unrelated items of information and the ability to retain relational information across time that is considered the heart of declarative memory and the function of the hippocampal region (Zola et al. 2000; Sperling et al. 2003). Although the exact function of the hippocampus in creating successful memories is not yet fully understood, converging results from animal models of amnesia (Zola et al. 2000) and neuroimaging studies in humans have implicate the hippocampus in the process of encoding episodic memories (Köhler et al. 2000; Heckers et al. 2002; Sperling et al. 2003). It has been assumed that long-term potentiation (LTP), a form of synaptic plasticity within the hippocampus, contributes to the acquisition and retention of memories although the exact mechanism remains unknown (Bliss and Collingridge 1993; Lamprecht and LeDoux 2004; Leuner et al. 2006; Fairhall et al. 2010).

2.3.1 Hippocampus and depression
Brain imaging studies demonstrate that psychiatric disorders such as MDD are associated with structural alterations such as reduced brain volume to structures that control mood and contribute to stress related psychiatric illnesses (Pittenger and Duman 2007). Combining evidence from animal models and post-mortem studies investigating brain tissue from depressed subjects further detail alterations at the cellular level, such as atrophy of dendrite processes and reduced neurons and glial elements (Pittenger and Duman 2007; Krishnan and Nestler 2008). However the specific mechanisms underlying these structural changes have not been determined (Banasr et al. 2011).
The hippocampus is particularly vulnerable to structural, functional, and neurogenic change in response to stress and stress-related diseases, such as depression. (Conrad 2008). To date, MRI studies have revealed compelling evidence that the hippocampus undergoes selective volume reduction in stress-related neuropsychiatric disorders such as schizophrenia and MDD (Sheline et al. 1996; Duman et al. 1999; Bremner et al. 2000; Czéh et al. 2001; Brown et al. 2004; Videbech and Ravnikle 2004; Hickie et al. 2005; McKinnon et al. 2009; Pajonk et al. 2010). Likewise, several meta analyses confirm that individuals with MDD have hippocampal volumes that are approximately 5-8% smaller than healthy controls (Videbech and Ravnikle 2004; McKinnon et al. 2009). Importantly, hippocampal volume is negatively correlated with depression duration and morphological changes in the hippocampus are not evident in patients with a first episode of depression, suggesting cumulative damage to this area. (MacQueen et al. 2003). This work has recently been extended to indicate that duration of illness plays an important role as a predictor in hippocampal volume reduction if left untreated by antidepressant drug therapy since medication status may also play a central role in modulating hippocampus volume in MDD (McKinnon et al. 2009). Hence, treatment early in disease progression may minimize the volumetric reductions that are associated with multiple episodes of depression. Hippocampus volumes are also associated with clinical outcome (MacQueen et al. 2008). Recently, MacQueen et al. (2008) examined hippocampal volumes in 63 depressed participants who had baseline MRI scans and then completed eight weeks of first-line pharmaceutical treatment. Researchers compared the hippocampal volumes between patients who met the criteria for clinical remission to those who did not meet the criteria for remission. Overall, patients who entered remission had larger hippocampal volumes than those who did not enter remission.
Reduced hippocampal volume is also associated with several other neuropsychiatric conditions, such as schizophrenia, dementia and posttraumatic stress disorder (MacQueen 2009; Pajonk et al. 2010). It still has not been determined whether the pathological mechanisms that result in reduced hippocampal volumes in patients with MDD, psychosis or dementia are unique for each condition or involve the same pathophysiological processes (MacQueen 2009). For instance, it has been difficult to determine whether there are reliable differences between individuals with bipolar disorder and healthy controls due to the treatment effects of lithium, comorbidity, course of illness and variability in subtypes of patients which may partly explain the mixed finding reported (MacQueen 2009).

### 2.3.2 Hippocampus, depression and memory

Memory impairments often accompany depression and are considered to be a direct result from structural changes in the hippocampus (Hickie et al. 2005). Hippocampal recruitment is linked with greater hippocampal activation as indicated by regional cerebral blood flow within the hippocampus (Heckers et al. 2002). In healthy individuals, fMRI revealed that there is an expected pattern of increased activation in the anterior hippocampus during the encoding of stimuli that are subsequently remembered with confidence compared to items that are not remembered. However, this hippocampal activation pattern is absent in depressed individuals suggesting a dysregulation of hippocampal function (Fairhall et al. 2010). Similarly, abnormal hippocampal activation was found during the memory retrieval process in depressed individuals (Milne et al. 2012). Given that most studies investigating the hippocampus in depression use volumetric imaging analysis there is limited literature regarding hippocampal function. Therefore, it is still unclear how or whether structural abnormalities of the hippocampus turn into functional abnormalities. A combination of functional and structural imaging techniques may be
helpful in understanding whether structural brain abnormalities translate into function abnormalities as well as the underlying neural basis of cognitive processes such as memory.

## 2.4 Neurogenesis

The hippocampus is a highly reactive brain structure that exhibits rapid plasticity at the molecular, cellular, structural and functional levels in response to a specific stimuli (DeCarolis and Eisch 2010). One specific feature of hippocampal plasticity noteworthy is the ability of the DG in the hippocampus to generate new neurons throughout life (Gould et al. 1999; Leuner et al. 2006). In healthy brains, neurogenesis occurs mainly in two distinct areas: the subventricular zone, which generates new neurons in the olfactory bulb; and the subgranular zone, which generates new neurons in the DG of the hippocampus (Ming and Song 2005).

Rodent studies are among the first to demonstrate the ability of neurogenesis in specific areas in the brain (Gould et al. 1999; van Praag et al. 1999; Deng et al. 2010). For instance, environmental enrichment such as larger living space, physical exercise and social interaction with other rodents helped to stimulate cell proliferation in the adult hippocampus as well as significantly increase survival time for newly generated hippocampal neurons (van Praag et al. 1999). Behavioural studies in rodents in which neurogenesis has been experimentally interrupted support the idea that the newly generated cells play a critical role in some forms of hippocampus-dependent learning (Winocur et al. 2006).

Neurogenesis can also be regulated by several factors associated with an organism’s behavioural states. For instance, learning of hippocampal-dependent tasks such as maze-learning not only increased the number of adult-generated hippocampal granule cells (Gould et al. 1999) but also
increased network activity while also improving cognition (Deng et al. 2010). However, whether increases neurogenesis is responsible for cognitive improvements remains to be investigated.

In the rodent hippocampus, it has been well established that exposure to chronic stress alters the number and morphology of neurons; however, very little is known about the likely changes that occur in the hippocampal vasculature. Importantly, stress-induced reductions in hippocampal neurogenesis occurs mainly near capillaries suggesting that decreased blood flow and capillary density in the hippocampus results in the onset of depression (Heine et al. 2005; Kiuchi et al. 2012). Furthermore, the local microvasculature of hippocampus in chronically stressed mice show decreased capillary density in the DG (Czéh et al. 2010). Together these findings suggest that the development and improvement of depressive symptoms may be closely associated to alterations in hippocampal neurogenesis and angiogenesis (Heine et al. 2005; Kiuchi et al. 2012).

Neurogenesis in humans is affected by a variety neurological disorders and mental illnesses, such as epilepsy, Alzheimer’s disease, Parkinson’s disease, cerebral ischemia, schizophrenia and depression (Zhao et al. 2008; Pajonk et al. 2010). In depression, researchers suggest that hippocampal atrophy is, in part, a result of suppressed neurogenesis (Sapolsky 2000; McEwen 2005). While antidepressant pharmaceutical agents have been found to promote hippocampal neurogenesis and improve depressive symptom (McEwen 2005; Sahay and Hen 2007) the mechanism of action is unknown. However increased hippocampal neurogenesis is tightly correlated with other variables presumed to promote hippocampal health, such as angiogenesis, blood flow, growth factor production and pro-inflammatory cytokine reduction (Pereira et al. 2007). Hippocampal neurogenesis has been proposed as a target mechanism for the amelioration and prevention of mental illness (DeCarolis and Eisch 2010).
Together, these findings implicate the hippocampus in the aetiological, rather than purely symptomatic, role in MDD (Fairhall et al. 2010). However, the relationship between these findings of macro and microscopic changes and evidence for alterations in hippocampal function has remained elusive (Werner et al. 2009). Therefore, a better understanding of how newly generated neurons function and integrate into existing hippocampal circuitry is needed (DeCarolis and Eisch 2010). Assessing hippocampal function by neuroimaging techniques such as fMRI during a behavioural task will help fill this gap in research.

2.5 The stress response
The stress response is a multifaceted biochemical cascade of diverse chemicals that can affect brain structures, physiological processes and memory (Kim and Diamond 2002). The secretion of glucocorticoids hormones, cortisol (in humans) or corticosterone (in rodents) is the most important endocrine component of the response to stress and the one that is most necessary for successful adaptation (Checkley 1996). Brief episodes of stress are beneficial for an organism as it increases focus, alertness and enhances memory and learning in order to cope with threatening situations (McEwen and Sapolsky 1995; Krugers and Hoogenraad 2009). Although the stress response is an essential survival mechanism, the inability to respond appropriately to intense or prolonged periods of stress can have deleterious physiological and psychological consequences (Kim et al. 2006). For instance, elevated cortisol has been associated with increased risk of several diseases such as cardiovascular disease, Type 2 diabetes, reduced immune functioning and psychiatric illnesses such as depression (Lundberg 2005).
2.5.1 Stress and the HPA axis

A characteristic feature of MDD that has been found over the past several years is the disturbance in the HPA functionality (Herbert et al. 2006). Glucocorticoids have been associated with the regulation of neuronal survival, neurogenesis, the acquisition of new memories, the emotional appraisal of events and the immune response to stress (Herbert et al., 2006). Consequently, the role of glucocorticoids in both the stress response and brain functioning could partly elucidate the HPA abnormalities associated with psychiatric disorders such as depression. HPA axis activation results in the increased secretion of adrenal glucocorticoids such as cortisol. Stress is perceived by the brain cortex and the amygdala and is transmitted to the hypothalamus to release corticotropin-releasing hormone (CRH). CRH then stimulates the anterior pituitary gland to secrete corticotropin into the bloodstream. Corticotropin then stimulates the adrenal cortexes to secrete the glucocorticoid hormone cortisol. Cortisol sequentially induces feedback inhibition in the hypothalamus and the pituitary, suppressing the production of CRH and corticotropin, respectively (Figure 2.5) (Belmaker and Agam 2008). Under normal conditions, increased circulating cortisol inhibits HPA axis activity via a negative feedback mechanism by binding to glucocorticoid receptors at the levels of the hypothalamus and the pituitary (Blume et al. 2011). However, in chronic stress and psychiatric disorders such as depression, it has been proposed that this feedback mechanism may be impaired (Belmaker and Agam 2008).
Cortisol

Cortisol is a steroid hormone that is produced by the adrenal cortex (Saladin 2001). Cortisol is associated with the response and adaptation to stress and is regulated through a HPA axis negative feedback inhibition by corticotropin (Saladin 2001). Cortisol concentrations can be measured in blood, urine and saliva (Saladin 2001). In blood, approximately 20% of cortisol is unbound and biologically active while the remaining 80% of cortisol is bound to cortisol-binding globulin (le Roux et al. 2003). Unbound cortisol enters the saliva via intracellular mechanisms where the majority remains unbound (Vining et al. 1983). As a result, salivary measures of cortisol accurately represent free cortisol and are more sensitive to subtle changes when compared to measuring cortisol in plasma or serum (Guechot et al. 1982; Vining et al. 1983;
Gozansky et al. 2005). Cortisol production has a distinct circadian rhythm with levels peaking in the early morning and dropping to the lowest concentration at night (Stone et al. 2001). Typically, a secretory burst in cortisol, referred to as the cortisol awakening response (CAR), occurs 30 minutes post awakening in which free cortisol concentration increases by approximately 50-75% (Schmidt-Reinwald et al. 1999; Wust et al. 2000b; Wilhelm et al. 2007). The CAR is considered a reliable biomarker of HPA axis activity (Pruessner et al. 1999; Wust et al. 2000a) and can be altered with psychological disorders such as depression (Stetler and Miller 2005; Adam et al. 2006; Foley 2006; Huber et al. 2006). Similarly, chronic elevations of cortisol are associated with a wide array of health consequences such as cardiovascular disease, bone loss, immune dysfunction and metabolic syndrome (Brunner et al. 2002; Lundberg 2005; Reynolds et al. 2005).

Cortisol secretion is a highly variable function that is associated with variables such as sex, socioeconomic status, sleep disturbance and increased perceived stress particularly on workdays compared to weekends (van Eck et al. 1996; Wust et al. 2000b; Backhaus et al. 2004; Kunz-Ebrecht et al. 2004). Table 2.6 illustrates the wide range of values that represent cortisol concentrations in normal healthy individuals which will be used as normative data in this study (Clow et al. 2004).

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>± SD</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>0 min post-waking (nmol/L)</td>
<td>11.6</td>
<td>4.6</td>
<td>4.7 – 18.5</td>
</tr>
<tr>
<td>30 min post-waking (nmol/L)</td>
<td>20</td>
<td>5.9</td>
<td>8.6 - 28</td>
</tr>
<tr>
<td>Percentage increase 0-30 min (%)</td>
<td>91.4</td>
<td>42.4</td>
<td>50 - 156</td>
</tr>
<tr>
<td>Change 0-30 min (nmol/L)</td>
<td>9.3</td>
<td>3.1</td>
<td>3.9 - 15</td>
</tr>
</tbody>
</table>
2.6.1 Cortisol, stress and depression

Chronic stress is known to be a strong causal factor in the onset of depression (Kendler 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 et al. 2004; Phillips et al. 2006). It has been well established that inventories of stressful events predict subsequent depression (Kessler 1997) and stressful events are often associated with the onset of MDD (Kendler et al. 2000). The glucocorticoid cortisol is a major mediator of the physiological stress response. Excess cortisol secretion is reported to be one of the risk factors for subsequent depression (Herbert et al. 2006). Not surprisingly, elevated cortisol is a hallmark finding in patients with MDD (Davis et al. 1987; Newcomer et al. 1999; Sapolsky 2000; Young et al. 2001; Brown et al. 2004; Krishnan and Nestler 2008).

HPA axis dysregulation is commonly implicated in the course of depressive illness. The hypothalamic-pituitary-cortisol hypothesis of depression (see Figure 2.6) postulates that abnormalities in the cortisol response to stress may underlie depression (Belmaker and Agam 2008). The hippocampus participates in the termination of the stress response through the glucocorticoid-mediated negative feedback that inhibits the HPA axis (Kim and Diamond 2002; Sapolsky et al. 2002). In depression, the negative feedback mechanism is impaired resulting in an increased activity of the HPA axis and elevated cortisol secretion. (Belmaker and Agam 2008; Hinkelmann et al. 2009). It is still disputed whether these phenomena are a consequence of MDD or whether they represent a vulnerability marker existing before the illness onset (Dedovic et al. 2010). However, it has been shown that normalization of circulating cortisol levels with antiglucocorticoid therapy alleviates depressive symptomatology in both patients with Cushing’s disease and hypercortisolemic depressed patients and has been associated with successful clinical
treatment outcomes (Murphy and Beverley 1997; Reus et al. 1997; Herbert et al. 2006). Furthermore, the diurnal rhythm of cortisol secretion is also blunted in depression; pulses tend to be longer and more frequent, with levels remaining consistently high over the day (Stokes 1995). However findings have been inconsistent across studies (Chida and Steptoe 2009). A recent meta-analysis found that the magnitude of the CAR is related to a number of psychosocial factors. Specifically, researchers found that the CAR was positively associated with job stress and general life stress and was negatively associated with fatigue, burnout, and exhaustion (Chida and Steptoe 2009).

**2.6.2 Cortisol and memory**

Stress-induced elevated cortisol levels have well-known effects on cognition. Increasing evidence has found that exposures to stress and/or stress hormones impair hippocampal-dependent forms of memory in both humans and animals. Both chronic and acute elevations in cortisol due to either prolonged stress or experimental injections have consistently been linked with cognitive deficits such as effortful processing and episodic memory impairment (Rubinow et al. 1984; Bemelmans et al. 1996; Lupien et al. 1998; Newcomer et al. 1999; Dominique et al. 2003; Sauro et al. 2003; Buss et al. 2004; Herbert et al. 2006; Hinkelmann et al. 2009). This pattern of increased cortisol and memory deficits has been replicated in Lupien’s work in hypercortisolemic aged populations (Lupien et al. 1998), and in those with Cushing’s Disease, a state characterised by hypercortisolemia (Starkman et al. 2001). Chronically high levels of cortisol have been associated with memory deficits in those with depression, and successful treatment has been associated with decreases in cortisol secretion and subsequent improvement in episodic memory function (Vythilingam et al. 2004). Also, cortisol is known to reduce hippocampal long-term potentiation (LTP), a form of synaptic plasticity essential for

2.6.3 Cortisol and the hippocampus

The biological mechanisms leading to hippocampal volume reduction in depressive disorders are currently unclear. One possible mechanism of injury to the hippocampus is corticosteroid exposure (Brown et al. 1999). Chronic stress, hyperactivation of the HPA axis and elevated cortisol levels have all been suggested to play a role in the down-regulation of neurogenesis, the volumetric changes of the hippocampus and the deficits in functional capacity of the hippocampus (Starkman et al. 1992; Sheline et al. 1996; Brown et al. 1999; Duman et al. 1999; McEwen 2000; Sapolsky 2000; Herbert et al. 2006; Mondelli et al. 2010).

The hippocampus also plays a role in terminating the HPA stress response, however, injury to the hippocampus impairs this negative feedback mechanism resulting in a more prolonged HPA response to psychological stressors (Brown et al. 1999; McEwen 2007). The “glucocorticoid cascade hypothesis” (Sapolsky et al. 2002) suggests that there is an association between cumulative exposure to high cortisol levels and hippocampal atrophy. Increases in cortisol levels produce hippocampal damage resulting in even greater increases in cortisol secretion due to impaired feedback mechanisms to suppress cortisol release. The “neurotoxicity hypothesis” (Gilbertson et al. 2002), suggests that chronic secretion of elevated glucocorticoids results in the neurotoxic effects on the hippocampus, such as disruptions in glucose metabolism, dendrite branching and neurogenesis which ultimately leads to hippocampal atrophy (Lupien et al. 2009).

The hippocampus is one of the main glucocorticoid target sites in the brain, with copious amounts of corticosteroid receptors (Sapolsky 2000; McEwen 2005; Hinkelmann et al. 2009).
making it extremely sensitive to increased glucocorticoid levels. Stress hormones such as cortisol modulate function within the hippocampus by plasticity (adaptation, changing or remodelling the structure of neurons) to possibly avoid over-exposure to elevated glucocorticoid levels (Duman et al. 1999; McEwen 2000; Lee et al. 2002; Campbell and MacQueen 2004; McEwen 2005; Conrad 2008). As a result, excessive exposure to glucocorticoids have profound effects on the hippocampus such as volume loss, dendritic atrophy, inhibiting neurogenesis and neuron death (Brown et al. 1999; Duman et al. 1999; Newcomer et al. 1999; Bremner et al. 2000; Sapolsky 2000; Lee et al. 2002; Brown et al. 2004; McEwen 2005; Pittenger and Duman 2007; Mondelli et al. 2010).

To test the hypothesis that dysregulation of the HPA axis and hippocampal volume abnormalities would represent vulnerability factors for depression, Dedovic et al., (2010) compared the CAR and hippocampal volume in healthy control subjects and individuals at risk for depression. Supporting their hypothesis, a dysregulated CAR and smaller hippocampal volume was observed in the subclinical high risk group (Dedovic et al. 2010).

2.6.4 Cortisol and neurogenesis
In rodents, exposure to high levels of glucocorticoids decreases neurogenesis of DG granule neurons in the hippocampus (Gould et al. 1998; Ekstrand et al. 2008). Therefore, it has been proposed that the down-regulation of neurogenesis is a potential mechanism for the observed decrease in hippocampal size as seen with neuroimaging of depressed individuals (MacQueen et al. 2003; Belmaker and Agam 2008). Likewise, the down-regulation of neurogenesis in response to increased levels of glucocorticoids could contribute to deficits in the functional capacity of the hippocampus resulting in learning and memory impairments (Kim et al. 2006).
Although there is a relationship between high cortisol levels and reduced hippocampal volume, this does not suggest that cortisol alone is the only cause but instead the underlying mechanisms may be associated to the activation of the stress response (Dedovic et al. 2010; Mondelli et al. 2010). For example, glucocorticoids increase the release, as well as decrease the clearance of glutamate. Glutamate is the major excitatory neurotransmitter in the brain and at elevated levels becomes neurotoxic leading to the neuronal atrophy associated with chronic stress and depression (Banasr et al. 2011).

The causal relationship between hypercortisolism and depressive symptoms such as memory impairment has not been established and is it likely to dissociate the effects of depression and hypercortisolism on memory impairment in MDD (Egeland et al. 2005). For instance, findings of memory deficits in other clinical groups suffering from hypercortisolism such as Cushing’s disease implies a direct relationship between cortisol and memory dysfunction that is not facilitated by depression (Egeland et al. 2005). Additionally, depression is only seen in 50% of Cushing’s disease patients indicating that depression is secondary to hypercortisolism (Checkley 1996). However, conclusive evidence linking hippocampal dysfunction with elevated cortisol to determine whether hippocampal alterations are secondary to increased cortisol and if these changes are reversible for early intervention therapy levels has not yet been determined (Sherwood 1997). The hippocampus may be a possible candidate for mediating the effects of cortisol on episodic memory however there is a lack of understanding about the differences between rodent and human hippocampal neurogenesis.
2.7 *Inflammation and cytokines*

Previously, the majority of research on depression, neurodegeneration and decreased neurogenesis investigated the effects of elevated glucocorticoids. More recently, MDD has been suggested to be a psychoneuroimmunological disorder, in which peripheral immune activation, via cytokine release, is responsible for the array of behavioural, neuroendocrine and neurochemical changes that occur with this disorder (Schiepers et al. 2005).

Cytokines are proteins that are released by a variety of cells and serve as intercellular signals regulating immune responses. Cytokines encompass a heterogeneous group of messenger molecules that are produced by immunocompetent cells, such as lymphocytes and macrophages, to regulate immune responses (Schiepers et al. 2005). Similar to hormones of the endocrine system, cytokines transmit messages by interacting with receptors on cell surfaces to communicate throughout the body (Robles et al. 2005). Cytokines can be divided into two broad classes based on their effects on the immune response: pro-inflammatory (stimulating inflammation) and anti-inflammatory (reducing inflammation) (Robles et al. 2005; Schiepers et al. 2005). Pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, tumor necrosis factor-α (TNF-α) and interferon (IFN), are produced by cells at the site of infection or injury to attract other immune cells and signal them to activate and respond. Anti-inflammatory cytokines reduce this immune response, inhibiting immune-cell activities, such as replication, activation, and synthesis of other cytokines (Robles et al. 2005).

Since peripheral cytokines are relatively large molecules and do not freely pass through the blood-brain barrier (BBB) research has focussed on the pathways by which peripheral cytokine signals reach the brain (Raison et al. 2009). Animal research indicates that cytokines administered peripherally can access the brain and affect function through several pathways via:
vagal nerve activation, a leaky or compromised BBB, active transport across the BBB, or binding to cell-surface proteins on brain endothelial cells. (Dantzer et al. 2008; Miller et al. 2009; Loftis et al. 2010). Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α that sub serve inflammation in the periphery have complex and contrasting functional roles in the CNS (Miller et al. 2009). Under normal physiological conditions, these cytokines are important for providing trophic support to neurons, enhancing neurogenesis, and contribute to cognitive functioning such as memory (Miller et al. 2009). However, in the milieu of excessive and/or prolonged activation, cytokine networks in the CNS can encourage an interconnected group of abnormalities that are thought to be partly responsible for the pathophysiology of depression, such as reduced neurotrophic support, decreased neurogenesis, increased glutamatergic activation, oxidative stress, induction of cell apoptosis and impaired cognitive function (Miller et al. 2009).

Overall, cytokines have been found to access the brain and interact with nearly every pathophysiologic domain relevant to depression, including neuroendocrine function, neurotransmitter metabolism, and neural plasticity (Miller et al. 2009). There is a growing body of evidence that activation of pro-inflammatory cytokines and/or inhibition of anti-inflammatory factors cytokines have been reported to modulate CNS functions and contribute to the changes involved in psychiatric and neurodegenerative diseases such as depression (Song et al. 2003; Hayley et al. 2005; Irwin and Miller 2007; Song and Wang 2010).

2.7.1 Cytokines and depression
Depression is a multifaceted disorder and the pathogenesis of the disease likely involves alterations in several systems which interact with one another. Findings that cytokine-mediated inflammatory processes play a critical role in the development of depression is quite robust (Zunszain et al. 2011). Depression is highly prevalent among patients suffering from infectious,
autoimmune and neurodegenerative diseases, and this co-morbidity cannot be attributed solely to the psychological distress of the initial disease (Pollak and Yirmiya 2002; Rook and Lowry 2008).

The “Cytokine Hypothesis of Depression” proposes that inflammation may be a causal mechanism in the development of depressive symptomatology (Dantzer et al. 2008; Miller et al. 2009). Research indicates that individuals with depression and other psychiatric disorders express elevated immune markers (Archer et al. 2010). An experimental model for assessing the acute immune response to infection in humans is the administration of the endotoxin lipopolysaccharide (LPS) (Reichenberg et al. 2001). Both acute and chronic administration of cytokines (or cytokine inducers such as LPS or vaccination) can result in behavioural symptoms similar to those found in major depression. Likewise, data in humans are consistent with animal findings, acute administration of LPS to humans leads to a host of behavioural changes, including depressed mood, anhedonia, sleep disturbance, fatigue, and cognitive dysfunction (Reichenberg et al. 2001; Dantzer et al. 2008; Harrison et al. 2009; Eisenberger et al. 2010; Loftis et al. 2010; Haroon et al. 2011). Interestingly, the concentration of these cytokines in the blood correlates with the severity of depression and the administration of antidepressant medication normalizes the elevated pro-inflammatory cytokine levels (Miller et al. 2009; Janssen et al. 2010).

The main pro-inflammatory cytokines IL-1β, IL-6, IFN-γ and TNF-α are considered to be one of the most reliable peripheral biomarkers in MDD (Mössner et al. 2007) as they consistently appear to be elevated in depressive states or in response to psychological stress (O'Brien et al. 2004; Schiepers et al. 2005; Raison et al. 2006; Piletz et al. 2009; Dowlati et al. 2010). For instance, depressed patients who had attempted suicide have shown increased IL-6 in
cerebrospinal fluid (Lindqvist et al. 2009) and chronic administration of the inflammatory cytokine IFN-α induces depressive symptoms in up to 30–50% of IFN-α treated patients. (Musselman et al. 2001; Raison et al. 2005; Asnis and De La Garza 2006; Raison et al. 2009). Recent meta-analyses exclusively that examined pro-inflammatory markers determined that circulating peripheral C-reactive protein (CRP), TNF-α, IL-6, and IL-1β were all significantly elevated in association with a diagnosis of MDD (Howren et al. 2009; Dowlati et al. 2010). A prospective study found that an increased inflammatory state at baseline (defined as elevated levels of CRP and increased capacity of leukocytes to produce IL-1), predicted a later onset of depression in elderly individuals with no previous history of depression indicating that excess inflammation precedes depression (van den Biggelaar et al. 2007; McNally et al. 2008).

The ratio of pro-inflammatory to anti-inflammatory cytokines may also be disrupted in depression and result in a net increase in inflammatory activity (Dhabhar et al. 2009). Decreased IL-10 levels, a higher IL-6/IL-10 ratio, and the lack of a counter-balancing, immunoregulatory increase in IL-10 in response to increased IL-6 concentrations underlie the pro-inflammatory physiological environment that is found to be associated with MDD. As a result, a reduction in IL-10 that would normally dampen pro-inflammatory cytokine actions and resolve inflammation, may contribute to the depressogenic, in addition to the inflammatory disease-promoting effects of chronic, low-level elevations in pro-inflammatory cytokines (Dhabhar et al. 2009).

2.7.2 HPA axis and cytokines

The human stress response has a several checks and balances built in place to ensure that various components do not become over or underactive (Kendall-Tackett 2009). The stress response system is intricately linked with pro-inflammatory signalling. In the event of severe stress and
disrupted glucocorticoid signals, the result may be reduced restraint on the immune system and the overproduction of pro-inflammatory cytokines (Raison and Miller 2003).

For example, cortisol is normally anti-inflammatory and keeps pro-inflammatory cytokines in check however under severe stress cortisol can change function and potentiate the actions of IL-1 and IL-6 rather than inhibiting them. As a result, pro-inflammatory cytokines may themselves disrupt cortisol signaling and negative feedback regulation of the HPA axis, further increasing risk for depression (Robles et al. 2005)

particularly, IL-1, IL-6, TNF-α and IFN-γ induce a cascade of behavioural, neuroendocrine and central neurotransmitter changes including direct stimulation of the HPA axis and secretion of cortisol (Song 2002; O'Brien et al. 2004; Hayley et al. 2005; Schiepers et al. 2005; Dantzer et al. 2008). Increased glucocorticoid levels found in depression are partly a result of increased production of pro-inflammatory cytokines, such as IL-1β and IL-6 (Maes et al. 2009). For example, chronic administration of IFN-α to humans led to increased cortisol levels and flattening of the diurnal cortisol slope which was also associated with depression and fatigue (Raison et al. 2008). These findings parallel the correlations between flattening of the cortisol curve and plasma IL-6 in patients with advanced cancer (Capuron et al. 2003; Bower et al. 2005; Rich et al. 2005)

As previously mentioned, it is becoming increasingly evident that in certain disorders, such as depression, these inhibitory feedback loops become impaired, allowing for chronic immune activation and the persistence of sickness symptoms that present from this activation (Irwin and Miller 2007). In depression, both cortisol and pro-inflammatory cytokine levels are elevated,
which also indicates a failing or dysregulation of HPA-axis feedback mechanism (Raison and Miller 2003; O'Brien et al. 2004; Pace et al. 2007; Leonard and Myint 2009).

2.7.3 Cytokines, neuroplasticity and memory
Accumulating evidence indicates that cytokines are critical to the regulation of neuronal plasticity and survival, and that prolonged disruption of the balance of these cytokines can lead to alterations in brain structures and function (Loftis et al. 2010). In clinical populations, a consistent finding is that hepatitis patients treated with IFN therapy often develop a wide array of cognitive impairments (Reichenberg et al. 2005; Lieb et al. 2006). It has been proposed that inflammation impacts cognitive function through effects on neurogenesis and synaptic plasticity (Bernardino et al. 2008; Dantzer et al. 2008; Maes et al. 2009; McAfoose and Baune 2009; Dantzer 2012). A possible mechanism for the negative effects of pro-inflammatory cytokines is their ability to modulate hippocampal neurogenesis through their activity on cytokine pathways and messenger systems (Dowlati et al. 2010). Specifically, elevations in pro-inflammatory cytokines influence neuronal functioning via cell apoptosis, oxidative stress, metabolic derangement, and by impairing processes of neuronal branching (Hayley et al. 2005).

Cognitive-behavioural studies in animals have shown that inflammatory manipulations which substantially increase IL-1 in the hippocampus (either endogenously or exogenously) result in impairments of hippocampal-dependent memory consolidation, inhibit LTP and cell proliferation and promote cell atrophy in the DG and CA regions of the hippocampus (Vereker et al. 2000; Song 2002; Avital et al. 2003; Barrientos et al. 2006; Goshen et al. 2007; Hennigan et al. 2007; Pickering and O’Connor 2007; Chen et al. 2008).
The involvement of IL-1 in hippocampal-dependent memory processes follows an inverted U-shape pattern, such that basal levels of IL-1 are required for memory formation, and any deviation from this physiological range either by an excessive increase in IL-1 levels or by blockade of IL-1 signaling, impairs memory (Avital et al. 2003; Goshen et al. 2007). What’s more, the memory impairments following central administration of IL-1 may be associated with hypercortisolemia, as the cognitive disturbances were reversed not only by IL-1 receptor agonist, but also by a glucocorticoid receptor antagonist (Song 2002). Therefore, cortisol alone may provide an incomplete estimate of the effects of hypercortisolemia (Bauer et al. 2009).

2.8 Neurotropic growth factors
Neurotrophic growth factors such as BDNF, IGF and VEGF contribute to a variety of neural processes including neural development, neuronal survival, synaptic signalling and synaptic consolidation making them attractive candidates for the cellular mechanisms underlying both depression-induced changes and antidepressant responses (Allen and Dawbarn 2006; Warner-Schmidt and Duman 2008). Stress has been found to decrease levels of VEGF and BDNF in the hippocampus, as well as produce neuronal atrophy and reduce neurogenesis, which may contribute to a depressogenic state (Duman and Monteggia 2006). Several studies that have assessed BDNF levels in MDD found important correlations between stress, MDD and neurotrophic growth factor levels. A post-mortem study of depressed patients who had committed suicide found reduced hippocampal BDNF (Karege et al. 2005) and several biochemical studies have found low BDNF levels in depressed subjects (Shimizu et al. 2003; Lee et al. 2007; Bocchio-Chiavetto et al. 2010) as well as a negative correlation with the depression severity (Shimizu et al. 2003).
The “neurotrophic model” of depression (Duman and Monteggia 2006) postulates that reduced hippocampal BDNF activity, caused by stress or elevated glucocorticoids, impairs the ability of stem cells in the subgranular zone of the DG to proliferate into mature cells that remain viable (Duman and Monteggia 2006; Wolkowitz et al. 2010). There is also evidence that the downregulation of BDNF by acute stress is mediated by the pro-inflammatory cytokine IL-1β (Barrientos et al. 2003).

However, antidepressants have been shown to increase levels of VEGF, BDNF, IGF-1, restore neuronal atrophy, and increase neurogenesis (Warner-Schmidt and Duman 2006; Wolkowitz et al. 2010). BDNF has anti-inflammatory and antioxidant effects as well as attenuating glucocorticoid-induced neuronal death by promoting the growth of developing neurons (Wolkowitz et al. 2010). The suggested role of BDNF in antidepressant mechanisms is supported by research that hippocampal neurogenesis (in animals) and serum BDNF concentrations (in depressed humans) increase with antidepressant therapy (Hashimoto et al. 2004). In rodents, BDNF administration to the DG of adult rats leads to increased neurogenesis of granule cells (Scharfman et al. 2005) in addition to having antidepressant-like effects (Shirayama et al. 2002). In depressed humans, antidepressants increase BDNF levels (Shimizu et al. 2003) as well as improve depression scores (Brunoni et al. 2008). Research has also found that stress-induced decreases in neurogenesis and the expression of relevant nerve growth factors which support neurogenesis, can be reversed by the administration of an IL-1 receptor antagonist (Barrientos et al. 2003; Duman 2009).

It has been hypothesized that the regulation of neuroplasticity is mediated by various growth factors (Duman et al. 2009; Paslakis et al. 2012). Similar to BDNF, IGF-1, produces antidepressant-like behavioural effects (Duman et al. 2009) as well as increases adult
hippocampal neurogenesis in the rodent brain (Trejo et al. 2001). Interestingly, researchers suggest that at BDNF plus IGF-I act synergistically producing a more robust effect than either neurotrophin alone in activating neurotrophic cascades that alter ongoing neuroplasticity mechanisms which promote the survival of new and existing hippocampal neurons (Cotman et al. 2007; Paslakis et al. 2012). In support of this, researchers have shown that the maximal survival of new neurons in the rat hippocampus is achieved when both growth factors are present (Johnson-Farley et al. 2006).

Astroglia also play a part in neuroplasticity through the secretion of neurotrophic factors (McNally et al. 2008). Reduced astroglia numbers, another feature of depression, disrupts the balance of anti- and pro-inflammatory mediators and further impairs the elimination process of excitatory amino acids. Microglia activated by increased inflammation, astroglial loss, and abnormal glutamate receptor activation disrupt the delicate balance of neuroprotective vs neurotoxic effects in the brain, possibly leading to depression (McNally et al. 2008).

The majority of research to date found that BDNF levels increase following antidepressant treatment, however the results are mixed. An important research question is whether changes in BDNF levels are specific to certain types of antidepressant treatments or whether BDNF levels are associated with an overall improvement in depressive symptomatology (Brunoni et al. 2008).

2.9 Current therapies for depression

In order to determine whether antidepressant therapy has been successful, the desired outcome must be clearly defined. Response rate is defined as \( \geq 50\% \) improvement from baseline on a recognized rating scale for depression such as the HADS or the BDI. Nonetheless, many patients with a 50% reduction in HADS score continue to experience significant residual symptoms and
may still meet diagnostic criteria for MDD (Shelton 2006). As a result, remission rate (i.e., recovery) has mostly replaced treatment response (improvement) as the standard for successful therapy. Therefore, patients are considered to be in remission when symptoms are absent and there is a full restoration with no impairments in psychosocial functioning (Shelton 2006).

The mainstream interventions for treating MDD are pharmacological therapy, electroconvulsive therapy (ECT) and psychotherapy. However the effect of these treatments is far from satisfactory. For instance, a placebo-controlled trial compared Cognitive Behavioural Therapy (CBT), a form of psychotherapy, and antidepressant medication in moderately to severely depressed individuals who were randomly assigned to 16 weeks of CBT or pharmaceutical therapy or 8 weeks of pill placebo. At eight weeks, response rates were 50% in the medication group and 43% in the CBT group and both superior to the placebo group (25%). When researchers reassessed patients eight week later they found remission rates were only 46% for the medication group and 40% for the CBT group (DeRubeis et al. 2005).

Generally, ECT is currently considered to be the most effective treatment for major depression (Shelton 2006). Approximately 60% to 80% of all depressed patients who receive a course of ECT respond to this treatment (Remick 2002). Although the mechanism of efficacy of ECT remains unclear and the use of ECT is uncommon and mainly considered a last resort treatment option (Remick 2002; Shelton 2006).

The low remission rates associated with current therapies are mainly a result of poor patient compliance to treatment due to the wide range of side-effects accompanied by antidepressant medication and ECT (Remick 2002; Shelton 2006). For that reason, these trends indicate a need for more effective treatment options and the role of non-pharmacologic treatments for depression
becomes increasingly important. As well, researchers must consider strategies to address the needs of patients with failed initial treatments as well as target individuals who are reluctant to seek medical help.

2.10 Exercise and depression

Due to the unsatisfactory mainstream antidepressant therapies, newer non-pharmacologic therapeutic options are needed for the treatment of MDD. Research has found that higher cardiorespiratory fitness levels and increased habitual physical activity are associated with lower depressive symptomatology and greater emotional well-being (Martinsen 1990; Galper et al. 2006; Boettger et al. 2009). Additionally, lower cardiovascular fitness in adolescents is associated with increased risk of serious depression in adulthood (Åberg et al. 2012) and MDD patients who are moderately physically active are more likely to seek treatment than inactive MDD patients (Diverty and Beaudet 1997). Exercise alone or in combination with other treatment options, such as pharmacotherapy or cognitive behavioural therapy, have all been effective in treating depression (Blumenthal et al. 1999; Perraton et al. 2010). For this reason, the potential use of exercise as an alternative or complementary therapy for depression has received considerable attention recently.

Both aerobic and anaerobic forms of exercise are equally effective in alleviating symptoms associated with depression (Doyne et al. 1987; Martinsen et al. 1989). However, a higher exercise dose leads to greater reductions in depression scores than a low dose (Dunn et al. 2005), indicative of a possible dose-response for exercise, though further replication of this work is needed. Overall, the general consensus from studies that report the aerobic intensity and frequency suggest that 60–80% of maximum heart rate, three 30-minute sessions per week, with
an overall duration of 8 weeks is required for a significant improvement in depressive symptoms (Perraton et al. 2010). It is likely that exercise-mediated amelioration of depression may be explained by synergistically acting psychological and physiological mechanisms (Backhaus et al. 2004). Physical activity reduces self-reported and clinical depressive symptoms (Koehl et al. 2008), improves learning and memory (Ernst et al. 2006) alters physiological function of the hippocampus as demonstrated by increased neurogenesis (Cotman and Berchtold 2002; Ernst et al. 2006; Cotman et al. 2007; Pereira et al. 2007; Koehl et al. 2008; Praag 2008; Wu et al. 2008) and hippocampal BDNF (Ploughman et al. 2007), reduces cortisol secretion (Nabkasorn et al. 2006; Foley et al. 2008) and even has increased brain volume in elderly individuals (Colcombe et al. 2006). Mild group jogging reduced urine cortisol and epinephrine excretions, alleviated MDD, and improved cardio-respiratory fitness (Nabkasorn et al. 2006).

Research in both animal and human subjects suggest that aerobic fitness has a strong biological basis in the role of maintaining and enhancing central nervous system health as well as substantial antidepressant effects in psychiatric patients (Martinsen et al. 1985). In fact, the response rates for exercise were generally comparable to antidepressant medication (Martinsen et al. 1985; Blumenthal et al. 1999; Babyak et al. 2000; Blumenthal et al. 2007) and both tend to be better than placebo (Blumenthal et al. 2007). An earlier study conducted by Martinsen et al. (1985) found that the combination of exercise with tricyclic antidepressants was not more effective than exercise as a monotherapy. In a similar study, the efficacy of 16 weeks of aerobic exercise training was comparable to standard pharmacotherapy in treating MDD. Blumenthal et al., (1999) randomly assigned 156 patients with MDD to 4 months of aerobic physical exercise alone, 4 months of antidepressant treatment (sertraline) or 4 months of combination treatment in the form of both medication and physical exercise. All three groups exhibited significant
reductions in depressive symptoms and no significant differences were observed between groups at 4 months, although, the onset of effect was more rapid with the drug treatment. Remarkably, when researchers reassessed the patients 6 months after completion of treatment they found that the 10-month relapse rate was significantly lower in the exercise group (8%), when compared to the sertraline (38%) or the combination group (31%). Combining exercise with medication adding no additional gain over either treatment alone, suggesting that exercising on one’s own initiative during the follow-up period was associated with a reduced probability of depression diagnosis at the end of that period (Babyak et al. 2000). Consistent with previous findings, a meta-analysis using 11 studies yielded a large combined effect size for the benefit of exercise over control conditions when treating depression ($d = 1.42$) indicating that exercise can be a powerful intervention for clinical depression (Stathopoulou et al. 2006). A recent review of studies investigating the relationship between physical activity and depressive symptoms reveal an inverse relationship between physical activity and depression and that even a low dose of exercise can reduce the probability of developing depression (Teychenne et al. 2008).

It has been well established that exercise is a therapeutic intervention with proven benefits in the treatment of depression however its mechanisms of action remain unclear.

2.10.1 Exercise, neurogenesis and the hippocampus

There are broad speculations as to the possible mechanism which exercise might impact aspects of cognition such as episodic memory. Adult hippocampal neurogenesis has been suggested as a target for the amelioration or prevention of mental illness (De Carolis and Eisch 2010). Voluntary exercise increases cerebral blood flow in the DG of the hippocampus and has been associated with increased adult hippocampal neurogenesis (van Praag et al. 1999; Pereira et al. 2007). For instance, in mice the number of proliferating cells detected by bromodeoxyuridine (BrdU)
injections over 12 consecutive days increases significantly in runners compared to sedentary controls (van Praag et al. 1999). The positive association between voluntary exercise and increased adult hippocampal neurogenesis in rodents has been consistently replicated (van Praag et al. 1999; Pereira et al. 2007; Ekstrand et al. 2008; Fuss et al. 2010). Running also increases the volume of the rodent hippocampus after 8-10 weeks of voluntary exercise (Rhodes et al. 2003). Rhodes et al., (2003) suggest that increases in hippocampal neurogenesis might underlie the 20% hippocampal volume increase observed after 8-10 weeks of exercise. A possible mechanism by which exercise may increase hippocampal neurogenesis is increased cerebral blood volume. Cerebral blood volume, an \textit{in vivo} correlate of neurogenesis and a potential mechanism, is also increased in the hippocampus and correlated with improved memory after a 3 month exercise intervention in mice (Pereira et al. 2007).

Hippocampal neurogenesis has been linked to learning and memory improvements (Leuner et al. 2006; Winocur et al. 2006) and it facilitates LTP in the hippocampus of adult rats (Farmer et al. 2004). In rodents, exercise increases synaptic plasticity and improved retention on tasks mediated by the hippocampus (van Praag et al. 1999; Kramer and Erickson 2007) and enhanced the rate of learning on hippocampal mediated spatial navigation tasks such as the Morris Water maze swimming task that require the use of cues to determine the location of submerged escape platforms (Adlard et al. 2004).

A recently published three month exercise study with schizophrenic patients and healthy controls found significant increases in hippocampal volume in both normal and schizophrenic patients which correlated with improvements in aerobic fitness and no change in a non-exercising schizophrenic group. In the schizophrenia exercise group only, hippocampal volume increase was associated with a 35% increase in the \textit{N}-acetylaspartate to creatine ratio (considered a marker
of healthy neurons) in the hippocampus. Short-term memory improvement correlated with change in hippocampal volume across all groups (Pajonk et al. 2010).

2.10.2 Exercise, inflammation and growth factors

Compelling evidence suggests that exercise training diminishes inflammation (Beavers et al. 2010). Exercise promotes an increase in the systemic levels of a number of cytokines with anti-inflammatory properties and therefore protects against chronic medical disorders associated with low-grade systemic inflammation (Petersen and Pedersen 2007). Specifically, studies have found that exercise not only decreased the levels of pro-inflammatory cytokines IL-6, TNF-α, and CRP but also simultaneously elevated the concentrations of anti-inflammatory cytokines IL-4, IL-10 and TGF-β when compared with controls. IL-4, IL-10 and TGF-β are not only anti-inflammatory in nature but also inhibit the production of pro-inflammatory cytokines IL-1, IL-2, and TNF-α (Das 2004; Das 2006). Exercise also sets into action an interactive cascade of growth factor signalling that has the net effect of stimulating neuroplasticity, enhancing cognitive function, attenuating the mechanisms promoting depression, up-regulating neurogenesis and increasing cerebrovascular perfusion (Cotman et al. 2007). For example, IGF-1 signalling converges on BDNF signalling, which may explain the positive effects of exercise on both memory and depression. Exercise may also improve growth factor signalling by reducing pro-inflammatory cytokines and directly increasing growth factor levels (Cotman et al. 2007; Petersen and Pedersen 2007). BDNF, IGF-1 and VEGF are the main growth factors known to mediate the effects of exercise on the brain (Trejo et al. 2001; Vaynman et al. 2004; Cotman et al. 2007). The effects of exercise on memory, learning and depression are primarily regulated by IGF-1 and BDNF, whereas exercise-dependent stimulation of angiogenesis and hippocampal neurogenesis appear to be regulated by IGF-1 and VEGF (Cotman et al. 2007).
Supporting the critical role of the VEGF signaling pathway in neurogenesis, researchers compared depression-like behaviour, blood vessel density, and neurogenesis in hippocampal DG between stressed and exercising mice with or without administration of VEGF receptor inhibitor. Chronic stress led to the development of depression-like behaviour, decreases in blood vessel density and neurogenesis in the hippocampus, whereas regular exercise training improved depression-like behaviour, limited the decrease of hippocampal blood vessel density and enhanced the survival of newly generated neurons in chronic stress. Interestingly the combination of exercise and VEGF receptor inhibitor cancelled the exercise-induced antidepressant effect (Kiuchi et al. 2012).

2.10.3 Further evidence for exercise and neural function
Exercise enhances cognition and brain function, protects against the development of neurodegenerative diseases and aging (Dishman et al. 2006; Kramer and Erickson 2007) and has been shown to improve sleep quality (Atlantis et al. 2006). Descriptive studies have found that elderly adults with greater levels of physical activity are less likely to develop dementia or other cognitive function impairments compared to those who do not exercise (Kramer and Erickson 2007; Rosano et al. 2010). For instance, aerobic exercise improves cognitive function in aging humans (Colcombe et al. 2003) and has been associated with the sparing of brain tissue in humans (Colcombe et al. 2006). Also, physical activity and higher fitness levels in elderly individuals are associated with increased hippocampal volume and better memory function (Erickson et al. 2009). Importantly, physically fit individuals are reported to have larger left and right hippocampal volumes than unfit individuals. Furthermore, hippocampal volume increases following an exercise protocol are partially mediated the relationship between higher fitness levels and enhanced spatial memory in older adults (Erickson et al. 2009). In elderly humans,
persistent physical activity has also shown to increase psychomotor speed as well as increased brain activation (Rosano et al. 2010). Moreover, aerobic exercise has also been associated with delaying the onset of and decline in several neurodegenerative diseases (Cotman et al. 2007) and known to facilitate neurocognitive recovery from traumatic brain injury (Devine and Zafonte 2009; Mossberg et al. 2010).

In addition to the observed structural changes in the brain, research has found that exercise can alter brain activity and functional connectivity associated with cognitive tasks (Voss et al. 2010). For instance, Voss et al., (2010) used fMRI to examine cognitive relevant brain networks before and after a 12 month aerobic exercise intervention in older adults. Researchers found that aerobic fitness training improved the aging brain’s resting functional efficiency in higher-level cognitive networks. Additionally, changes in functional connectivity was associated with a behavioural change such that increased functional connectivity was correlated with greater improvement in executive function (Voss et al. 2010).

It is quite clear that exercise sets into motion an interactive cascade of biological events that has a net effect of stimulating neural plasticity and neurogenesis, improving cognitive function, and attenuating the mechanisms that drive depression (Cotman et al. 2007). Both human and animal findings suggest that exercise targets many areas of brain function and has a wide array of positive effects on overall brain health, resilience, memory and learning, and depression (Cotman et al. 2007).

Exercise is a new and promising low-cost approach to preserve and protect CNS health. Exercise may be a viable treatment option in treating depression because it can be recommended to most individuals and does not carry a negative social stigma as the other treatment therapies do (Dunn
et al. 2005). Research must identify treatment targets and directions for future studies to identify individuals at risk, decrease relapse rates, and increase long-term favourable outcomes for those suffering from depression.
Chapter 3  Methods

3.1 Experimental design for future pilot study

This future study will utilize a cohort control design. Participants will be recruited in blocks. Group 1 will undertake a 12 week structured, supervised exercise program in addition to the LMHDT and they will be recruited in the first year of the study. Group 2 from the LMHDT will be recruited in the second year so that they can be matched by age, gender, pharmacotherapy and baseline fitness level to the exercise group using the same inclusion criteria.

The reason for running the study as a cohort control rather than a randomized control trial is that the LMHDT is a group program and it might affect group cohesion if some participants were offered the exercise program and others were not. This way everyone in the first cohort who meets the inclusion criteria will be given the opportunity to have the exercise program, and this will not interfere with the program in the way that it is currently run. It also allows us to age and gender match the non-exercising LMHDT cohort (group 2), as well as a cohort of non-depressed individuals who will undergo baseline fMRI scans to provide normative data for comparison for potential fMRI activation changes in the depressed groups.

Outcome measures will be assessed at baseline and week 12 (see Figure 3.1). The primary measures are salivary cortisol, hippocampal activation during a memory task, plasma biomarkers and depression scores. Additional measures will include subjective exercise barriers and self-efficacy questionnaires, a face recognition task evaluating hippocampal function, a cardiorespiratory fitness test, sleep quality questionnaire and a neurocognitive screening test.
Additionally, a precursory investigation will be carried out in a group of non-depressed, active participants, to determine ‘normal’ values.

A sedentary non-depressed group will be recruited from UOIT and Durham College in Oshawa Ontario. Advertisement will be placed throughout the campus. Participants will complete the same assessments as the depressed groups at baseline and week 12. They will receive the same 12 week exercise intervention as the depressed exercise group. The non-depressed control group will provide background data on the normal values and variability of the measures in an asymptomatic group, with particular focus on cortisol and hippocampal function in addition to the effects of exercise on non-depressed sedentary adults. This will enable studies to discriminate the general effects of exercise on neural function and biomarker status as distinct from those unique to depression.

For the non-depressed group, respondents to recruitment advertisements received the Participant Information Sheet (PIS), orientation session, consent form, Par Q, Baycrest Screening Form, and the following questionnaires: BDI-II, HADS, MoCA, PSQI (section 3.2.2, Appendices 1-8). Those who met inclusion criteria attended a baseline assessment, exercise self-efficacy questionnaires, the Astrand-Ryhming fitness test, first set of salivettes accompanied by saliva sampling instructions (Appendix 9), blood collection and fMRI. At this stage, the participants will commence the exercise program, completing three sessions per week. In week 12, all questionnaires, neurocognitive assessment, fMRI, fitness test, saliva samples and blood collection were repeated.
Figure 3.1: Overview of study design for the depressed exercise group, depressed control group and non-depressed exercise group.
3.2 Selection of outcome measures and protocols

3.2.1 Variables

**Independent variables**

1) Exercise intervention
   - Relative training intensity (% HR_{\text{max}})

**Dependent variables**

1) Psychometric evaluation
   - BDI-II - depression rating (out of 63)
   - HADS - anxiety and depression ratings (each out of 21)
   - MoCA - screens for mild cognitive impairment (out of 30)
   - PSQI - Sleep quality rating (out of 21)
   - Barriers and exercise self-efficacy (each out of 100)

2) fMRI
   - Blood oxygenation level-dependent (BOLD) response

3) Associative memory task
   - Hippocampal function – accurate responses (high and low confidence)

4) Salivary cortisol
   - Absolute levels at awakening, 30 minutes post awakening (nmol/L)
   - Wakening response – increase in secretory activity following awakening (Edwards et al. 2001)

5) Plasma biomarkers
• IL-6
• VEGF

6) Anthropometry
• Body mass (kg)
• BMI (kg·m\(^{-2}\))

7) Astrand-Ryhming protocol
• Estimated relative VO\(_{2\text{max}}\) (mL·kg\(^{-1}\)·min\(^{-1}\))

### 3.2.2 Protocols

**Biomarkers**

Presently, immunoassays are the most widely used techniques measuring cytokines and growth factors in human serum and plasma because of their high specificity, sensitivity, rapid turnaround time, convenience, the ease of performance and relatively low costs (Sachdeva and Asthana 2007). Their detection limit is approximately 1-5 pg/ml and they have good reproducibility with a coefficient of variation between 5-10% (Sachdeva and Asthana 2007). The basic cytokine sandwich ELISA based method is a monoclonal antibody specific for each antigen is pre-coated onto a microplate containing 96 wells. Standards, controls and samples are pipetted into the wells and any biomarker present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for each antigen is added to the wells. Following the wash to remove an unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of the antigen bound. The color development is stopped and the intensity of the color is measured.
Salivary cortisol

Salimetrics Oral Swab (SOS: Salimetrics®, State College, Pennsylvania) for saliva collection is an excellent alternative to passive drool because of its ease of use. The SOS is made of a non-toxic, inert polymer shaped into a 30 x 10 mm cylinder. (Salimetrics 2006; Salimetrics and Europe 2011).

Enzyme immunoassay (EIA) is an acceptable widely used method for determining salivary cortisol (Gozansky et al. 2005). This method is advantageous due to the high sensitivity, ease of use, rapid detection and also avoiding the disposal and lifetime issues associated with using radioisotopes (Blackburn et al. 1991).

Beck Depression Inventory – Second Edition (BDI-II)

The BDI-II (Appendix 5) is a 21-item self-reported instrument that corresponds to the criteria for depressive disorders from the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV; American Psychiatric Association, 1994). Each multiple choice question is rated on a 4-point scale of 0-3, ranging in intensity. Total numerical scores are compared to a classification key with higher scores indicating greater depression severity. Total depression scores of 0-13 is minimal, 14-19 is mild, 20-28 is moderate, and 29-63 is severe (Beck et al. 1996). The BDI-II has demonstrated high internal consistency (0.92 and 0.93, respectively), test-retest reliability of 0.93 (p < .001), and has found to have significant correlations (r = 0.68 - 0.93) with three other major instruments used in the assessment of depression in samples of psychiatric outpatients and University students (Beck et al. 1996).

Hospital Anxiety and Depression Scale (HADS)

The HADS (Appendix 6) developed by Zigmond and Snaith (1983), is a 14-item self-report instrument, that assesses anxiety and depression (Snaith 2003). Seven items measure depression
and seven items measure anxiety. Each item is rated on a four-point Likert scale of 0-3, and each subscale has a total possible score of 21 (Snaith 2003). Although there is no set standard of cutoff scores (Herrmann 1997), authors recommend that a score of 0-7 is considered within the normal range, 8-10 indicates a possible case of the respective mood disorder, and a score higher than 11 indicates a probable case.

The HADS has demonstrated good validity and reliability against clinical diagnosis of depression (Mykletun et al. 2001) and has consistently demonstrated high test-retest reliability ($r>0.80$) (Herrmann 1997). Internal reliabilities for the anxiety and depression subscales, and total score have been reported as (Cronbach α’s) 0.82, 0.77, and 0.86 respectively (Crawford et al. 2001). While the average sensitivity and specificity has been reported as 0.8 or higher from 17 different studies (Herrmann 1997).

**Exercise Self-Efficacy Scale**

The 11-item questionnaire (Appendix 10) developed by McAuley and colleagues (1990), measures perceived capabilities to exercise three times per week when faced with barriers. Each item is rated on a scale of 0-100 then averaged to give a total score out of 100. The measure has demonstrated high internal consistency ($\alpha = 0.92$) and has been shown be predictive of exercise adherence (McAuley et al. 1990). The rationale for administering this scale is to help the RC identify and consider barriers that may prevent participants from adhering to the exercise program.

**6-item Exercise Self-efficacy Questionnaire**

The six-item questionnaire (Appendix 11) was developed and validated by Litt and colleagues (2002) to assess the confidence in ability to adhere to an exercise program over an extended
period of time (one and four weeks). Each item is rated on a scale of 0-100 then averaged to give a total score out of 100. The measure has demonstrated high internal reliability ($\alpha = 0.97$). The rationale for administering this scale is to identify participants with a low self-efficacy for exercise that may need extra supervision or encouragement so that the maximum exercise sessions can be completed.

**Pittsburgh Sleep Quality Index (PSQI)**

A sleep quality measure is a valuable tool, since poor sleep quality is associated with depression and HPA axis dysregulation (Backhaus et al. 2004). The PSQI (Appendix 8) developed by Buysse and colleagues (1989) is 19-item questionnaire that assesses sleep quality during the previous month. Seven components of sleep quality are measured including, subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Scoring of the answers is based on a 0 to 3 Likert scale where 3 reflects decreased sleep quality and a global sum of five or greater indicates a poor sleep quality for a total possible global of score of 21 (Buysse et al. 1989).

The PSQI demonstrates both high internal consistency ($\alpha = 0.83$), overall test-retest reliability 0.85 ($p = 0.001$) and was able to differentiate between healthy, depressed and sleep disorder groups, even after covarying for age and gender, with a sensitivity of 89.6% and a specificity of 86.5% (Buysse et al. 1989).

**Montreal Cognitive Assessment (MoCA)**

The Montreal Cognitive Assessment (MoCA) is a brief neurocognitive tool with high sensitivity for screening patients with mild cognitive impairment (Nasreddine et al. 2005). This cognitive assessment was given to identify participants who may have difficulty performing the associative
memory task. It scores from 0 to 30, where higher scores indicate better cognition and a score below 26 indicates cognitive impairment corresponding to mild cognitive impairment (Appendix 9).

**Associative Memory Task:**

To evaluate the encoding and retrieval processes of memory, fMRI studies frequently use a recognition memory paradigm that consists of a ‘study’ and ‘recall’ phase (Sperling et al. 2003; Henson 2005). An associative memory paradigm using face name pairing was used to investigate functional abnormalities of the hippocampus during the encoding process (Sperling et al. 2003; Fairhall et al. 2010). A specific version of a face recognition task known to reliably activate the hippocampus during encoding ($p<.001$) was used (Sharma 2007). The inclusion of confidence judgments during the testing phase was used to account for successfully remembered items and not lucky guesses (Henson 2005).

A LCD projector and rear projection screen was used to present the encoding task during the functional image acquisition. During encoding, participants viewed 240 face name pairs over two nine minute fMRI sequences. To ensure adequate encoding of the stimuli and participant engagement, participants were asked to indicate whether they felt the name suited face. Participants responded using a push-button response box. Each sequence consisted of the presentation of jittered event related face name pairs with 120 stimulus presentations of 3 s, interspersed with 34 fixations periods varying between 3 and 9 s. The retrieval task was performed outside the scanner on a laptop computer. Participants were first asked to indicate which of the two names was originally paired with the presented face and subsequently asked after each judgment if participants were confident or not in their recollection (see Figure 3.2). This allows for the post hoc coding of events during the encoding phase that led to a strong
memory formation. This information is then used to separate fMRI data into successful (confident-correct responses) and unsuccessful (incorrect) events. This procedure has been used by researchers (Sperling et al. 2003; Fairhall et al. 2010) and has revealed that activation in the right anterior hippocampus is tightly coupled to encoding success. Participants were presented with different face name combinations at 0 and 12 weeks to control for the effects of both time and of practice among the three groups.

![Figure 3.2: Associative memory task](image)

**MRI/fMRI Protocols**

Participants were scanned at the Rotman Research Institute, Baycrest Centre, Toronto, Ontario in a Siemens Magnetom Tim Trio Whole Body 3T MR scanner with a 32-channel Avotech Audio head coil. The participant’s head was restrained using a vacuum pillow that fit inside the head coil. To maximise hippocampal signal quality, slices were positioned perpendicular to the long axis of the temporal lobe on an oblique coronal orientation, with phase encoding in the foot to head direction. The MR session included six series of scans. See Table 3.2 for scan details.
For functional scans, 50 oblique coronal 3.5 mm slices with full brain coverage were obtained (TE=27 ms; TR=2.5 s; flip angle 70°; FOV=200 mm; resolution=3.125x3.125x5mm; zero gap using T$_2^*$-weighted EPI sequence). Anatomical images were obtained following the fMRI consisting of 3D T$_1$-weighted pulse sequence (TE=2.63 ms; TR=2 s; FOV=256 mm; 1 mm isotropic voxels; 176 slices).

Table 3.2: fMRI protocol

<table>
<thead>
<tr>
<th>MR Series</th>
<th>Data Acquisition</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Auto align scout</td>
<td>Slice positioning</td>
<td>00:00:46</td>
</tr>
<tr>
<td>2. Localizer</td>
<td>Slice positioning</td>
<td>00:01:26</td>
</tr>
<tr>
<td>3. fMRI</td>
<td>BOLD at rest</td>
<td>00:09:00</td>
</tr>
<tr>
<td>4. fMRI</td>
<td>BOLD during memory encoding task</td>
<td>00:09:00</td>
</tr>
<tr>
<td>5. fMRI</td>
<td>BOLD during memory encoding task</td>
<td>00:09:00</td>
</tr>
<tr>
<td>6. MRI</td>
<td>structural</td>
<td>00:06:26</td>
</tr>
</tbody>
</table>

Instructions between series 00:03:00
Set up 00:15:00

**Total scanner time** 00:53:38

Stimuli were presented using E-Prime software version 2.0 (Psychology Software Tools). Images were back-projected onto a screen behind the scanner and shown to the participant using a mirror mounted on the head coil. The display had a spatial resolution of 1024 x 768 pixels and a visual angle of approximately 14.8° x 12.1° at a viewing distance of 132 cm.
Total time for each scanning session was under one hour (see Table 3.2). Behavioural tasks and fMRI were synchronized according to trigger pulses sent by the scanner. For vision correction MR safe glasses made by SafeVision (Webster Groves, MO, USA) were provided. Participants responded with the right index and middle fingers using buttons on a Fiber-Optic Response Pad System paddle developed by Current Designs Inc. (Philadelphia, PA, USA).

Astrand-Ryhming cycle protocol

The Astrand-Ryhming cycle ergometer protocol is a six minute submaximal exercise test capable of estimating $\text{VO}_2\text{max}$ from heart rate (HR) measurements and perceived exertion (Whaley 2006). It is a single-stage test, with HR measured in the fifth and sixth minute (Whaley 2006). The average of these values is adjusted for age using age correction factors, and an estimation of $\text{VO}_2\text{max}$ is made using a specifically-designed nomogram (Astrand 1960; Whaley 2006, cited in Whaley, 2006).

Cardiovascular fitness was assessed by the RC and final year kinesiology internship students at 0 and 12 weeks. The prescribed intensities of the exercise program in this research are at a level that should lead to improvements in cardiovascular fitness if undertaken correctly. It is expected that cardiovascular fitness will improve in the exercise groups, and not in the MHDT control group.

Body mass index (BMI)

BMI provides a relative anthropometric measurement that is sensitive to changes over time. BMI values were obtained by dividing body weight in kilograms by height in metres squared (kg·m$^{-2}$), (Whaley 2006). The ‘normal’ BMI range is 18.5 – 24.9 kg·m$^{-2}$ (Panel 1998).
Exercise intervention

Review of the literature suggests that both aerobic and resistance exercises are effective in the treatment of depressive disorders (Pedersen and Saltin 2006). For the aerobic component, an initial intensity of 12-13 on the Borg Scale of Perceived Exertion (RPE) is recommended for a duration of 10-20 minutes, gradually increasing to 15-16 RPE for 30 minutes (Pedersen and Saltin 2006). Using maximum heart rate (Whaley 2006), to determine intensity, it is suggested that a minimum of 70% $\text{HR}_{\text{max}}$ is necessary to solicit greater improvements (Dunn et al. 2001). A higher total weekly energy expenditure, obtained through manipulating frequency, duration and intensity, has been shown to be significantly more effective in the treatment of mild to moderate severity depression (Dunn et al. 2005).

Guidelines for resistance training in healthy adults recommend an 8-12 repetition maximum, with large-muscle and multiple-joint exercises being performed before small-muscle and single-joint exercises, and increases of 2-10% (equivalent to around 1-2 repetitions) implemented before load is increased (Kraemer et al. 2002).

3.3 Participants

3.3.1 Recruitment

It is important to differentiate the benefits of group exercise which are specific to exercise as opposed to the psychosocial benefits due to the social interaction that occurs within the group. The LMHDT provides an ideal solution to this. Participants are referred into this program by psychiatrists at Lakeridge Health with a DSM-V axis I diagnosis of depression and sometimes concomitant anxiety. Upon referral all participants are screened to determine if there is a history
of substance abuse, internal mental distress, behaviour complexity or crime and violence using the GAIN-SS (Dennis et al. 2006), a validated tool designed to identify individuals who are likely to have a mental health and/or substance use disorder and who should be referred for further assessment or treatment. Participants with concomitant substance abuse disorders were not included in this feasibility study and will not be included in either arm of the pilot study. Participants will also undergo the SCID-I to confirm the clinical diagnosis of major depression. This will be administered by either the referring psychiatrist or the clinical psychologist. The SCID-I has excellent inter-rater and longitudinal reliability (Zanarini and Frankenburg 2001).

The LMHDT is a 12 week program which includes a four week transition phase where participants meet twice per week, followed by six weeks of intensive group work focused on interpersonal relationships, depression, anxiety and stress management, relaxation, self-esteem building, communication skills, symptom management, goal setting / problem solving, mental health and substance use and community linkage. Participants then have a further two week transition out of the program where they meet once or twice per week.

Participants in this program will be offered the opportunity to participate in a structured 12 week exercise program in addition to the LMHDT and their results will be compared to a control group who has undergone the LMHDT but not exercised. The exercise cohort will be recruited in the first half of the study so that the study may age and gender match the control group in the second half of the study. This design also maintains the integrity of the LMHDT in that participants won’t feel that other people in their therapeutic group are getting something that they aren’t. Matched control participants will also be recruited from UOIT and Durham college for the non-depressed exercise group.
An objective for this feasibility study was to develop a recruitment process that minimizes the number of steps required for both Lakeridge staff and potential participants. Following an expression of interest, potential participants underwent a Pre-screening questionnaire (see Appendix 7) administered by Lakeridge staff. Those who were still eligible at this stage were given an Information Session Invitation (see Appendix 1) and their contact information was forwarded to the RC for further screening. Additional screening of participants was conducted over the telephone by the RC which consisted of the Baycrest Screening Form, and Par-Q. All eligible participants were then invited to a face-to-face screening interview and study orientation with the RC to ascertain their eligibility for the study. This included reviewing and signing Baycrest Screening Form and PAR-Q. Based on the official recommendations of the Canadian Society for Exercise Physiology (CSEP) and Health Canada if participants answer yes to any questions on the PAR-Q, they will be given a letter addressed to their physician (see Appendix 12) explaining the study along with the PARmed-X (see Appendix 13) and they must receive clearance by their physician to enrol in the study. Participants satisfying all criteria provided informed consent and were enrolled in the study. See Figure 3.3 for recruitment process.
Lakeridge staff administer the following measures to interested and eligible LHDT participants:
1. BDI
2. SCID
3. Pre screening questionnaire
4. GAIN-SS

Eligible participants are given Study Information Invitation and their contact information is forwarded to RC

RC telephones eligible participants to perform further screening:
1. Telephone Screening Questionnaire
2. Par-Q
2. Baycrest Safety Screening Form

Eligible participants meet RC at UOIT Flex Center for a study orientation session.
1. Powerpoint presentation
2. Tour of the gym facility

PARTICIPANT SIGNS CONSENT FORM

Figure 3.3: Participant recruitment process
3.3.2 Inclusion/exclusion criteria

Inclusion criteria for depressed group

- Male or female, age 18-50
- DSM-V diagnosis of major depression confirmed by the SCID-I interview
- BDI score $\geq 20$
- Depression symptoms minimum 6 months
- Attending LHDT program
- Concomitant pharmacological treatment must have been stabilized four weeks prior to study enrolment
- Currently sedentary (exercise less than 20 minutes, three times weekly)

Exclusion criteria for depressed group

- Medical contraindications to exercise, without relevant medical clearance
- Co-existing DSM-V Axis I apart from anxiety (APA, 1994)
- Participants who screened positive for substance abuse
- Religious or cultural beliefs that prevent the collection of bodily fluids
- Personal decision to withdraw

Inclusion criteria for non-depressed group

- Male or female, age 18-50
- Currently sedentary (exercise less than 20 minutes, three times weekly)

Exclusion criteria for non-depressed group

- Any potentially confounding medical conditions (including, but not limited to, diabetes, chronic fatigue, any DSM-IV Axis I and II disorders)
• Evidence of depressive symptoms (BDI score >13), or anxiety (HADS anxiety subscale score >7)

3.3.3 Informed consent

This study was approved by three ethics committees: University of Ontario Institute of Technology, Lakeridge Health and The Rotman Brain Research Institute/Baycrest. All three REB committees approved research ethics for the duration of one year with the option to renew in the subsequent year. Written consent (Appendix 2) was obtained from the participant at the study orientation session. They were assured they would not be identifiable from their individual data, and advised of their right to withdraw at any stage, without giving a reason.

3.4 Procedure

All measures (excluding fMRI and memory encoding and retrieval task) were conducted at UOIT. Psychometric assessments were administered by RC in the Flex Centre boardroom. Blood collection was performed in the UOIT laboratory by a Medical Lab Technician. Fitness assessment was conducted by a Certified Personal Trainer in the UOIT Kinesiology lab. A polystyrene bin with two saliva collection devices and saliva collection instructions (see Appendix 9) was given to participants to perform on the subsequent Wednesday morning immediately upon wakening. fMRI and memory tasks were performed at Baycrest Hospital. For data collection process (see Figure 3.4)
Figure 3.4: Data collection process

PSYCHOLOGICAL MEASURES
RC meets study participant at UOIT Flex Center to administer:
1. HADS
2. PSQI
3. Exercise Barriers and Self-Efficacy
4. MoCA

CORTISOL
Participant is given two labeled SOS devices and cooler pack. Swabs are returned to RC at first exercise session.

BIOMARKERS
Participant is taken to UOIT medical laboratory for blood collection

FITNESS ASSESSMENT
Participant is taken to UOIT Kinesiology lab located for Astrand-Rhyming Cycle Ergometer test

BRAIN IMAGING AND MEMORY TASK
Participant meets RC at Baycrest Hospital for fMRI scan and associative memory encoding and retrieval task
3.4.1 Testing

*Psychometric measures*

Questionnaires and neurocognitive assessment were administered by the RC in the UOIT Flex Centre boardroom. Each form was explained in detail by the RC. The entire process took approximately 30 minutes.

*Salivary cortisol*

Saliva samples were procured with an inert polymer non-citric acid collection device (SOS: Salimetrics®, State College, Pennsylvania). Participants received a polystyrene bin and a set of two SOS tubes. The SOS tubes were labelled ‘waking’ and ‘30 min’ to indicate sampling times, which were immediately upon awakening and 30 minutes after awakening. Instructions were given to place the cotton swab under the tongue and salivate for two minutes, replace the lid, and put straight into the freezer. Participants were instructed to follow standard sampling protocol (Clow et al. 2004; Salimetrics and Europe 2011): nil by mouth, except water, and no cleaning teeth, steroid inhalers or smoking between the two morning samples. This is all detailed in written instructions which was provided to participants (Appendix 9). Sampling took place on the Wednesday following the orientation session. Completed samples were returned in the polystyrene bin at a subsequent exercise session. Samples were immediately transported to the UOIT laboratory and stored in the in a -80°C freezer in the UOIT laboratory.

*Blood collection*

Peripheral venous blood was drawn in the UOIT laboratory by a medical lab technician. Collection times and other information that could affect biomarker levels such as illness or
infection were logged by the technician (see Appendix 14). A total of 35 ml of blood was collected from each participant by venipuncture into ethylenediaminetetraacetic acid (EDTA) tubes. Blood samples were prepared within 30 minutes by centrifugation (3000g for 5 minutes), and the fibrinogen containing plasma supernatant was aliquot into thirty 0.5 mL labeled tubes and stored at -85°C until assayed. A contingency plan using two freezers for aliquot storage was followed in the event of a power outage or freezer malfunction.

**Biomarker analysis**

On the day of analysis, plasma and saliva were thawed and brought to room temperature. Plasma samples were vortexed and saliva samples were centrifuged at room temperature 2500 rpm for 15 minutes. All assays were conducted according to the manufacturer’s protocols. The antigen levels of IL-6 and VEGF were measured using sandwich ELISA kits (Quantikine®HS, R&D Systems Inc., Minneapolis, Minn., USA). Salivary cortisol was measured using Salimetrics Expanded Range High Sensitivity Salivary Cortisol Enzyme Immunoassay kit (Salimetrics LLC, Philadelphia, PA). Briefly, standards, controls, and samples were pipetted into a 96-well microtiter plate coated with unconjugated antibodies to human IL-6, VEGF and cortisol. Plasma assays were incubated at room temperature then washed. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for each of these components was added to the wells, incubated at room temperature and washed again accordingly. Since the cortisol assay utilizes a competitive reaction, a horseradish peroxidase-conjugated cortisol was immediately added, incubated at room temperature and washed. Following a wash to remove unbound antibody-enzyme reagents, a substrate solution was added to the wells. Colour development for all the assays was stopped by a sulfuric acid and the intensity of the colour was measured by a microtiter plate reader within 10 minutes. Linear regression was performed on
plots of corrected absorbance at 450 nm for IL-6, VEGF and cortisol. The concentration of antigens in patient plasma and enzyme-linked cortisol was then quantified by interpolation from the standard curves. All assays were performed in duplicate and the average was reported.

*fMRI and memory encoding task*

MRI suite procedures were followed according to the Baycrest MRI suite procedures. A unique participant ID was assigned by Baycrest Subject Coordinator for each participant and scan time was reserved online through the Baycrest Resource Scheduler. Immediately upon arrival, participants were given a Baycrest parking pass and 25 dollar gas voucher from the RC. Participants arrived at the MR Suite 15 minutes prior to their scheduled scan time accompanied by the RC. The MRI Screening Form with participant ID number was filled in and reviewed by the MR Technologist. Participants were required to remove all makeup, jewellery, metallic and electronic items and all clothing except for underwear and socks. A hospital gown tied at the back and a pair of trousers was provided for participants to change into. The MR technologist escorted participants into the magnet room and the RC in the control area from the testing room. The MR Technologist gave the participant a brief orientation of what to expect in the scanner. Participants were given a panic button to press in case they needed to be removed from the scanner for any reason. During the resting state scan, participants were instructed to close their eyes but remain awake. During the memory encoding task (see Figure 3.2) participants were instructed to use their index finger to press the first button if the name suited the face and their middle finger to press the second response button to indicate if the name did not suit the face. All instructions were given by the RC and MR Technologist through a microphone/intercom system. Once the scan was complete the MR Technologist removed the participant from the scanner and relinquish them to the RC to get changed.
Memory retrieval

Immediately following the scan, participants were taken to a Rotman Research Institute (RRI) testing room located in Baycrest Hospital to perform the retrieval task on a laptop computer provided by the RC. (see Figure 3.2).
Figure 3.4.1: fMRI and associative memory task process
Astrand-Ryhming fitness test

The cycle seat height was adjusted to allow minimal knee flexion (approximately 10°) at the base of the pedal phase. Participants cycled for two minutes until their heart rate reached approximately 120 bpm, when the test was then initiated. Pedal speed between 50-70 RPM was required and workload (watts) was selected based on age and gender recommendations (Table 3.4). HR and rating of perceived exertion (RPE) was measured in the final 10 seconds of every minute. This workload was maintained for at least six minutes, until two consecutively comparable HR were obtained with a difference less than 5bpm. Final HR was used to estimate VO2max from a specifically-devised nomogram, using age correction factors.

Table 3.4: Recommended workloads for Astrand-Ryhming cycle protocol (modified from Whaley 2006)

<table>
<thead>
<tr>
<th>Physical activity level</th>
<th>Male/female</th>
<th>Age</th>
<th>Workload (watts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedentary</td>
<td>Female</td>
<td>&lt;40 years</td>
<td>25 – 50</td>
</tr>
<tr>
<td>Sedentary</td>
<td>Female</td>
<td>&gt;40 years</td>
<td>25</td>
</tr>
<tr>
<td>Active</td>
<td>Female</td>
<td>&lt;40 years</td>
<td>75 – 100</td>
</tr>
<tr>
<td>Active</td>
<td>Female</td>
<td>&gt;40 years</td>
<td>50 – 75</td>
</tr>
<tr>
<td>Sedentary</td>
<td>Male</td>
<td>&lt;40 years</td>
<td>50 – 100</td>
</tr>
<tr>
<td>Sedentary</td>
<td>Male</td>
<td>&gt;40 years</td>
<td>25 – 50</td>
</tr>
<tr>
<td>Active</td>
<td>Male</td>
<td>&lt;40 years</td>
<td>100 – 150</td>
</tr>
<tr>
<td>Active</td>
<td>Male</td>
<td>&gt;40 years</td>
<td>100</td>
</tr>
</tbody>
</table>
3.4.2 Intervention

Based on the general consensus from studies that report an aerobic intensity of 60–80% of maximum heart rate and an exercise frequency of three 30-minute sessions per week for 8 weeks, for a significant improvement in depressive symptoms, the intervention consisted of three sessions per week of aerobic and resistance exercises over a 12-week period, for a total of 36 sessions. Participants were eligible to be included in analysis if they attended at least 75% of these sessions. One of the three sessions was aerobic exercise only, and the remaining two were resistance exercise followed by a shorter aerobic bout. The latter were performed at least 24 hours apart. Participants attended on an individual basis. All sessions began with a 5-10 minute aerobic warm-up, and were supervised by a Certified Personal Trainer. Participants were advised to bring a drink bottle and keep well hydrated. Opportunities were provided to make up missed sessions.

Based on the participant’s experience and ability, one resistance exercise was selected from each of the six categories – horizontal push, anterior lower body, vertical pull, posterior lower body, horizontal pull, and vertical push (Table 3.4.2) – in order to establish a balanced, whole-body prescription (see photos, Appendix 15).

These exercises were performed as two or three paired supersets, in order to reduce the workout duration while still promoting adequate rest periods. The sessions utilised an 8-10 repetition range over three sets. To facilitate progression, participants were encouraged to increase their weights once they could perform three sets of 10 comfortably, reverting back to eight repetitions at the higher weight. Exercises were changed after four weeks, to avoid adaptation. The aerobic bout following resistance sessions was 20 minutes in the first week, and 30 minutes in subsequent weeks.
<table>
<thead>
<tr>
<th>Category</th>
<th>Exercise options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Horizontal push</td>
<td>Machine bench press</td>
</tr>
<tr>
<td></td>
<td>DB bench press</td>
</tr>
<tr>
<td></td>
<td>BB bench press</td>
</tr>
<tr>
<td>Anterior lower body</td>
<td>Machine leg press</td>
</tr>
<tr>
<td></td>
<td>DB split squat</td>
</tr>
<tr>
<td>Vertical pull</td>
<td>Underhand pull down</td>
</tr>
<tr>
<td></td>
<td>Overhand wide-grip pull down</td>
</tr>
<tr>
<td></td>
<td>Overhand close-grip pull up</td>
</tr>
<tr>
<td></td>
<td>Cable tricep extension</td>
</tr>
<tr>
<td>Posterior lower body</td>
<td>Machine leg curl</td>
</tr>
<tr>
<td></td>
<td>One-leg calf raise</td>
</tr>
<tr>
<td></td>
<td>Machine calf raise</td>
</tr>
<tr>
<td>Horizontal pull</td>
<td>Machine seated row</td>
</tr>
<tr>
<td></td>
<td>DB row</td>
</tr>
<tr>
<td></td>
<td>Machine preacher curl</td>
</tr>
<tr>
<td></td>
<td>BB biceps curl</td>
</tr>
<tr>
<td></td>
<td>DB jack-hammer curls</td>
</tr>
<tr>
<td>Vertical push</td>
<td>DB shoulder press</td>
</tr>
</tbody>
</table>
All aerobic exercises were performed on either the cycle or treadmill. Workloads were determined by HR response, which was prescribed as 70-85% max. The full aerobic sessions was initially 30 minutes, and progressed in five-minute increments over the 12 weeks, up to 60 minutes. Individuals could also progress their target HR within the prescribed range.

At every session, information was recorded for each participant on average and maximum HR obtained, exercise duration, workload (watts, for the cycle, or speed and incline for the treadmill), weights, sets, and repetitions.
3.5 Analysis

Statistical evaluation of the results for the psychometric measures, biomarkers and fitness assessment are presented as means, standard deviations (SD), ranges and percent change.

3.5.1 fMRI analysis

Data analysis procedure from Fairhall et al. (2010) was followed accordingly using SPM5 software (www.fil.ion.ucl.ac.uk/spm/). All functional volumes were slice time corrected, realigned, smoothed (5mm kernel), high-pass (128 s) filtered and normalised to standard stereotactic (MNI) space (using the segmented grey matter).

The analysis was based on a conventional general linear model (Friston et al. 1995). Three condition types were retrospectively nominated based upon whether the stimulus was matched to the correct name outside the scanner: with high confidence (HC correct), with low confidence (LC correct) or incorrectly. As the LC correct condition was uninformative, containing both truly correct responses and a high number of lucky guesses (chance = 50%), only HC correct and incorrect responses were taken to a second level factorial random effects design [group by encoding success] to permit inference at the population level.

Chapter 4 Preliminary results

4.1 Sample

Table 4.1 provides the number of cases (N), means (M), standard deviations (SD) and ranges for the variables of interest. Five (N=5) LMHDT patients (one male and four females) with a clinical
diagnoses of MDD, confirmed by the SCID-I, and no other co-existing DSM-IV Axis I disorders, have enrolled in this research study thus far. The mean age was 37.4 years \((SD=10.2)\) with a range of 28 to 49 years. Attrition rate was 60% however since one participant dropped out at nine weeks it was decided to collect their post exercise measures.

Of these five participants, three were medicated with a selective serotonin reuptake inhibitor (SSRI) and two were taking a serotonin-norepinephrine reuptake inhibitor (SNRI). In addition to antidepressant medications one participant was taking anti-inflammatory and immunosuppressant medications and one participant was taking psychostimulant and anticonvulsant medications. The mean depressive episode was 11.6 months \((SD=10.6)\) however four participants reported suffering from depression for several years. The data set did contain missing data. Of the biomarker variables, one participant failed to provide a waking saliva sample and one baseline IL-6 data was excluded due to an elevation from a confounding case of acute otitis media.

### 4.1.1 Psychometric evaluation

The mean baseline BDI score \((M=36, SD=2)\) indicates severe depression, the HADS-D \((M=11, SD=3.16)\) indicates definite depression, the HADS-A \((M=15.80, SD=2.28)\) indicates definite anxiety, the PSQI \((M=11, SD=5.53)\) indicates poor sleep quality, and the MoCA \((M=23.6, SD=2.10)\) indicates mild cognitive impairment.

### 4.1.2 Biomarker data

The mean waking salivary cortisol concentration \((M=10.73, SD=9.75)\), the 30 minute post awakening \((M=19.96, SD=13.82)\) and CAR \((M=133.10, SD=164.50)\) are within the normal healthy range. Unfortunately, the mean group value is misleading and does not translate the
abnormal levels and CAR occurring within the sample. Figure 4.1 depicts the waking, 30 minutes post awakening cortisol concentrations as well as the CAR for each participant compared to normal healthy values. Compared to normal values, no participant’s cortisol profile was within in the healthy range.

The mean IL-6 plasma concentration ($M=8.32$, $SD=5.07$) indicates higher than normal values suggesting an inflammatory state. Contrary to our hypothesis the mean VEGF concentration ($M=58.67$, $SD=15.34$) is higher than the normal value.

![Graph showing cortisol levels and CAR of the depressed group versus normal non-depressed values](image)

**Figure 4.1:** Baseline cortisol levels and CAR of the depressed group versus normal non-depressed values
4.1.3 Fitness scores

Individual fitness scores are allocated based on age and sex. Therefore a mean group score does not indicate an overall group fitness level. This measure will be used at 12 weeks following the exercise program to determine the relationship between changes in estimated relative VO$_{2\text{max}}$ with other variables.
Table 4.1: Baseline characteristics of the depressed group versus normal non-depressed values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depressed</th>
<th>Normal values</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N M SD</td>
<td>range</td>
<td>N M SD</td>
</tr>
<tr>
<td>Age (y)</td>
<td>5 37.40</td>
<td>10.20</td>
<td>28-49</td>
</tr>
<tr>
<td>BMI (kg·m⁻²)</td>
<td>5 27.38</td>
<td>6.90</td>
<td>21.30-36.50</td>
</tr>
<tr>
<td>Anti-depressant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRI</td>
<td>3 - -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SNRI</td>
<td>2 - -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Duration of depression (months)</td>
<td>5 11.20</td>
<td>10.60</td>
<td>6-300</td>
</tr>
<tr>
<td>Psychometric measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI depression</td>
<td>5 36.00</td>
<td>2.00</td>
<td>34-38</td>
</tr>
<tr>
<td>HADS-D depression</td>
<td>5 11.00</td>
<td>3.16</td>
<td>8-16</td>
</tr>
<tr>
<td>HADS-A anxiety</td>
<td>5 15.80</td>
<td>2.28</td>
<td>12-18</td>
</tr>
<tr>
<td>PSQI sleep rating</td>
<td>5 11.00</td>
<td>5.53</td>
<td>2-15</td>
</tr>
<tr>
<td>MOCA cognition</td>
<td>5 23.60</td>
<td>2.19</td>
<td>20-26</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol waking (nmol/L)</td>
<td>5 10.73</td>
<td>9.25</td>
<td>2.46-23.73</td>
</tr>
<tr>
<td>Cortisol 30 min (nmol/L)</td>
<td>4 19.96</td>
<td>13.82</td>
<td>4.93-38.08</td>
</tr>
<tr>
<td>CAR percent increase (%)</td>
<td>4 133.10</td>
<td>164.50</td>
<td>0.04-372.00</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>5 8.32</td>
<td>5.07</td>
<td>4.05-8.71</td>
</tr>
<tr>
<td>VEGF (pg/ml)</td>
<td>5 58.67</td>
<td>15.34</td>
<td>41.36-76.07</td>
</tr>
<tr>
<td>Face recognition task</td>
<td>5 - -</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>HC-correct (%)</td>
<td>5 60.20</td>
<td>17.20</td>
<td>44.78-80.00</td>
</tr>
<tr>
<td>Estimated VO₂max (mL·kg⁻¹·min⁻¹)</td>
<td>5 31.06</td>
<td>9.12</td>
<td>20.00-42.17</td>
</tr>
</tbody>
</table>
4.2 Change – Participant one

See Table 4.2.

4.2.1 Psychometric changes

The BDI score decreased from 34 at baseline to 17 at week 12, a change of 51.4% (see Figure 4.2.1). The HADS depression subscale score decreased from 12 to 5, a change of 58.3%. The HADS anxiety subscale score decreased from 16 to 14, a change of 12.5%. The HADS depression subscale score decreased from 1.6 to 0.9, a change of 3.3%. The PSQI score decreased from 10 to 9, a change of 10%. The MOCA score increased from 24 to 27, a change of 12.5%.

![Figure 4.2.1: Participant one change in depression scores following 12 week exercise intervention](image)

4.2.2 Biomarker changes

The waking cortisol decreased from 23.7nmol/L at baseline to 5.7nmol/L at 12 weeks, a change of 76%. Cortisol levels post 30 minute awakening decreased from 38.1nmol/L to 10.3nmol/L, a
change of 73% (see Figure 4.2.2). The CAR increased from 60.5 to 80.7, a change of 33.5%. IL-6 decreased from 7.82 µg /ml at baseline to 6.12 µg/ml at 12 weeks, a change of 21.76%. VEGF decreased from 41.36 µg /ml at baseline to 33.93 µg /ml at 12 weeks, a change of 13.76%.

![Cortisol Graph](image)

**Figure 4.2.2: Participant one change in cortisol following 12 week exercise intervention vs. mean normal values**

### 4.2.3 Fitness change

The estimated VO2max increased from 23.69 (mL·kg⁻¹·min⁻¹) at baseline to 50.76 (mL·kg⁻¹·min⁻¹), a change of 114.29% (see Table 4.2). Based on age, sex and BMI these results indicate a maximal fitness change from the classification of needs improvement to the excellent health benefit zone as determined by The Canadian Physical Activity, Fitness & Lifestyle Approach Protocol (CPAFLA).
Table 4.2: Participant one results at baseline vs 12 weeks following exercise intervention.

<table>
<thead>
<tr>
<th>DV</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>22.3</td>
<td>22.3</td>
<td>0</td>
</tr>
<tr>
<td>Psychometric measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BDI</td>
<td>34</td>
<td>17</td>
<td>-51.43</td>
</tr>
<tr>
<td>HAD-D</td>
<td>12</td>
<td>5</td>
<td>-58.33</td>
</tr>
<tr>
<td>HADS-A</td>
<td>16</td>
<td>14</td>
<td>-12.50</td>
</tr>
<tr>
<td>PSQI</td>
<td>10</td>
<td>9</td>
<td>-10.00</td>
</tr>
<tr>
<td>MOCA</td>
<td>24</td>
<td>27</td>
<td>12.50</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol waking (nmol/L)</td>
<td>23.7</td>
<td>5.7</td>
<td>-75.98</td>
</tr>
<tr>
<td>Cortisol 30 min (nmol/L)</td>
<td>38.1</td>
<td>10.3</td>
<td>-72.95</td>
</tr>
<tr>
<td>CAR percent increase (%)</td>
<td>60.5</td>
<td>80.7</td>
<td>33.50</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>7.82</td>
<td>6.12</td>
<td>-21.76</td>
</tr>
<tr>
<td>VEGF (pg/ml)</td>
<td>41.36</td>
<td>33.93</td>
<td>-13.76</td>
</tr>
<tr>
<td>Face recognition task</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HC-correct (%)</td>
<td>77</td>
<td>82</td>
<td>6.50</td>
</tr>
<tr>
<td>Estimated VO_{2max} (mL·kg^{-1}·min^{-1})</td>
<td>23.69</td>
<td>50.76</td>
<td>114.29</td>
</tr>
</tbody>
</table>

4.2.4 fMRI analysis

Recently, Fairhall et al. (2010) identified the network of brain regions involved in attempted encoding from the activation during an encoding task compared to baseline (fixation-events). Bilaterally, elements of the fronto-parietal attention networks and the ventral visual stream and, importantly, medial temporal lobe structures were activated (see Figure 2.2.4 A). In participant
one (Figure 4.2.4 C) a similar activation pattern in the medial temporal lobe structures, weighted towards the hippocampal complex rather than the parahippocampal gyrus, indicates that this task mainly recruited hippocampal structures. Activation has been colour coded into cortical (orange), hippocampal (red), parahippocampal (blue) and amygdalic regions (green) using anatomical templates (Tzourio-Mazoyer et al. 2002). All activations are thresholded at p < .001 and corrected for multiple comparisons at the cluster level. The yellow dot in the hippocampus represents the region extracted for further analysis (see Fig. 4.2.4 A).

Previous pilot data (Fairhall et al. 2010) formally demonstrates that the strong relationship between hippocampal activation and encoding success present in normal subjects is absent in individuals experiencing MDD (Fairhall et al. 2010). Figure 4.2.4 (B) shows a significant group by group (Controls vs MDD) interaction within the bilateral anterior hippocampus. This interaction was driven by a positive association between hippocampal activity and successful encoding in non-depressed controls (left: t(7) = 2.83, p < .05; right: t(7) = 3.00, p < .05) that was not present in individuals with MDD (left: t(7) =−0.46, ns; right: t(7) =−0.44, ns.). To measure the difference in the relationship between encoding success and bilateral hippocampal activation in control and MDD groups, Cohen’s d was calculated separately for each group. A large effect size (d= 1.11) was found for controls while depressed individuals showed no relationship between anterior hippocampus activity and stimulus encoding success (d=−0.19).

For this feasibility study, a region-of-interest (ROI) approach was adopted from previous pilot work by Fairhall and colleagues. The peak voxel in left and right anterior hippocampi were selected from the contrast of task versus fixation-events irrespective of encoding success (see Figure 4.2.4 C). This comparison to the loose fixation-baseline allowed for the identification of eloquent-voxels in a way orthogonal to the effects of interest (i.e. condition, group). Results also
show that we were able to detect differences pre/post intervention with the data set from participant one. Figure 4.2.4 D illustrates a baseline result similar to the ‘MDD response’ found in Fairhall et al. (2010) and the predicted pattern of increased activation in the anterior hippocampus during the associative encoding of stimuli that are later remembered with confidence following the 12 week exercise program.

Figure 4.2.4: A comparison of fMRI results from Fairhall et al. (2010) and participant one.
Chapter 5  Discussion

Despite the attempts of several theoretical models delineating the causes of depression, the pathogenesis remains elusive preventing the availability of treatments that target the causal factors. It has been well established that exercise is an effective treatment for depression however it is not clear on exactly how and why it works. The overall goal of this research is to investigate whether the mechanism by which exercise may improve depression is related to improving hippocampal function and if a supervised 12 week exercise program can promote changes in hippocampal function and improve memory in people living with depression. The purpose of this feasibility study was to develop comprehensive methods and validation of protocols to conduct our future pilot study. These included: 1) MDD participant recruitment from the LMHDT program; 2) fMRI protocol; 3) specimen collection and storage; 4) biomarker assays; and 5) an effective exercise program capable of improving depressive symptomatology.

A preliminary results section was also generated based on data collected thus far. Although the sample size is too small to infer meaningful statistical results, our preliminary findings have raised several methodological concerns that will be discussed.

Recruitment procedure

To ensure that the sample population is a true representation of the MDD population, all participants recruited were diagnosed as clinically depressed based on DSM-V criteria confirmed by the SCID-I. Our partners at the LMHDT program ensured that recruitment staff have been properly trained to administer the SCID-I. Additionally, to avoid unnecessary meetings between participants and RC, Lakeridge staff administered a pre-screening questionnaire provided by the RC to identify eligible sedentary, MRI safe participants. In support of these procedures, all five
participants recruited by Lakeridge staff have qualified for the study as confirmed by the additional screening measures and depression inventories administered by RC.

Methods for specimen collection and immunoassays

Well defined methods for specimen collection, processing and storage were established in accordance with laboratory procedures. The SOS was an effective device for obtaining copious saliva for cortisol analysis. Participants followed the saliva collection instructions provided to them and all samples were returned frozen and packed in their corresponding polystyrene bin. Given that immunoassays require very small samples volumes, plasma samples were divided into several small volume aliquots so that each aliquot could be assayed independently. This procedure proved to be very effective in minimizing plasma waste and avoiding the need for repeated freeze-thaw cycles. Additionally, the availability of several replicate aliquots will allow for further biomarker analysis and also increase reliability of assays by providing additional control samples to test inter- and intra-assay precision. All immunoassays were performed according to the manufacturers’ protocols. Standard curves generated from each biomarker corresponded with the manufacturer values. Optical density values from each standard curve were also sent to the manufacturers for further verification.

fMRI protocol validation

Four fMRI pilot scans were performed to successfully validate the fMRI protocol previously piloted in New Zealand on a 1.5 Tesla General Electric MRI scanner using the 3.0 Tesla Siemans MRI scanner at the Rotman Baycrest hospital. Ideally this experimental paradigm will produce robust modulation of hippocampal activity with encoding success, separation of true encoding success from chance success and the selection of a specific brain region-of-interest. Baseline results from participant one indicates hippocampal dysregulation as data fails to show the
positive relationship between hippocampal activity and successful encoding as seen in the non-depressed controls from Fairhall et al., (2010). Encouragingly, following the 12 week exercise program a more normalized pattern of hippocampal activation associated with successful memory encoding was observed. Taken together, these findings support the use of this experimental paradigm for future pilot work and also suggest that exercise may normalize hippocampal functioning in depressed individuals. If the study is able to show significant pilot results this may eventually lead to a potential in vivo biomarker for the functional integrity of the hippocampus in MDD to explore the relationships between 1) hippocampal dysregulation and clinical presentation, 2) hippocampal dysregulation and biomarker status and 3) the neurogenic effects of anti-depressant treatments such as pharmaceutical agents or exercise and the regulation of abnormal hippocampal function (Fairhall et al. 2010).

Preliminary results
Baseline psychometric data indicates that all participants were experiencing severe depression, anxiety, mild cognitive impairment and sleep disturbance. However 12 week results from participant one revealed the following improvements: severe depression to mild depression, mild cognitive impairment to normal cognitive functioning, and minimal improvements in anxiety score and sleep disturbance.

The cortisol analysis yielded variable results across the group and no individual cortisol profile resided in the healthy normal range. Observations ranged from below normal to above normal levels and an absent CAR to an above normal CAR of 372%. Although these findings do not support our hypothesis that cortisol would be elevated in MDD, they indicate that depression is associated with a dysregulation in cortisol secretion. Nonetheless, normal cortisol values were established in participant one following the 12 week exercise program.
Consistent with the literature the results show that depressed participants expressed higher plasma IL-6 concentrations compared with normal controls suggesting an inflammatory state. In support of our hypothesis, 12 week results from participant one show a decrease in IL-6 concentration following the exercise program. An additional observation was that the participant with the highest depression score revealed the highest IL-6 concentration. Although it remains unknown whether exercise specifically targets pro-inflammatory cytokines, exercise may actually dampen the inflammatory processes through its immuno-regulatory/anti-inflammatory effects. An important issue that needs further evaluation may be the absence of counter-balancing, immunoregulatory relationship between pro- and anti-inflammatory cytokines (Dhabhar et al. 2009). The future pilot study will include further analysis of additional pro-inflammatory cytokines (IFN-γ and TNF-α) and the anti-inflammatory cytokine IL-10 to seek these relationships.

Compared with normal healthy individuals, VEGF concentrations were increased in depressed individuals. Results from participant one showed a decrease in VEGF following the 12 week exercise program. These findings do not support the hypothesis or the neurogenic/neurotrophic hypothesis of depression which suggests that depression results partly from decreased neurotrophic growth factors. However the findings correspond with recent research findings that VEGF levels are higher in depression (Takebayashi et al. 2010) and depression comorbid with borderline personality disorder (Kahl et al. 2009) when compared to normal healthy controls. Other studies report no significant difference in plasma VEGF concentration were been found between medication-free MDD patients and controls (Ventriglia et al., 2009), and no alteration in VEGF plasma levels in medicated depressed patients during the courses of recovery (Dome et al., 2011). Studies have also found correlations with hormones and have reported higher levels of
VEGF in the follicular phase (Heer et al. 1998), the luteal phase (Agrawal et al. 1999), and significantly higher levels have been reported in postmenopausal compared with premenopausal women (Heer et al. 1998; Kim 1998). Interestingly, the older female participants experiencing menopause in this study were found to have the highest VEGF levels ($M=71.01$) compared to those who were premenopausal ($M=41.36$). These findings highlight the critical gap in research that peripheral VEGF levels and brain VEGF levels have not been quantified in parallel in any psychiatric population. To shed some light, an animal model investigating the possible correlation of peripheral and central VEGF levels using a genetic rat model of depression, found that VEGF levels were identical in serum, corpus striatum, and hypothalamus whereas in the hippocampus and frontal cortex, the VEGF levels were significantly decreased in the depressed rats compared to the non-depressed rats (Elfving et al. 2010). The authors considered these findings to be salient since the frontal cortex and hippocampus are considered to be core brain regions involved in depression (Elfving et al. 2010).

To further explore the relationship between exercise, neurotrophic factors and depression, the future pilot study will include additional growth factors (BDNF, IGF) known to be implicated in depression while eliminating VEGF for the reason that peripheral VEGF concentrations are influenced by several variables not associated with depression and do not correspond to VEGF levels in the CNS.

*Methodological confounds*

The high attrition rate of 60% indicates that the 12 week exercise program was difficult to adhere to for most participants. Two participants dropped out at seven weeks and one participant dropped out at nine weeks. A primary reason for withdrawal was that the LMHDT program ended two weeks prior to the exercise study and participants were returning to work. Since
research has shown that the benefits of exercise are reaped as early as eight weeks, it is recommended that the exercise program be reduced to 10 weeks. This will increased the probability of more participants completing the program.

Disturbingly, a major barrier confronted while conducting this study was obtaining sound comparative normal and depressed biomarker data due to the extreme variability reported between studies. This warrants the need to standardize methods of biological sample collection and assays, otherwise using what is reported in the literature will be equivocal.

Depression is a clinically and biochemically heterogeneous disorder. However, the majority of research examining the pathophysiology of depression have classified depression dichotomously either as yes/no or restricted the analyses to MDD when in fact there are several subtypes of depression which are based on the symptomatology (Baune et al. 2012). Subtypes of depression include dysthymia (a chronic, low-grade form of depression), melancholic MD (MMD) and MD with typical or atypical features (American Psychiatric Association 1994). Melancholic depression is characterized by anhedonia, lack of reactivity to pleasurable stimuli, reduced appetite, insomnia, and depression that is worse in the morning. In contrast, atypical depression is defined by appetite and weight increase, hypersomnia, fatigue and mood reactivity for positive events (Gold and Chrousos 2002). To further distinguish between subtypes of depression research has found that the principal arousal producing mediators of the stress response, such as CRH, are hyperactive in melancholic depression but not in non-melancholic depression (Gold and Chrousos 2002). Conversely, atypical depression and dysthymia (characterized by lethargy, fatigue, hypersomnia and hyperphagia) and have been associated with down regulated HPA activity and decreased cortisol levels (Griffiths et al. 2000; Hayley et al. 2005; Kaestner et al. 2012).
2005). Furthermore, increased inflammation has been found in non-melancholia depression and dysthymia but not in melancholic depression (Griffiths et al. 2000; Kaestner et al. 2005).

In short, the majority of antidepressant medications target monoamine systems and have ultimately fallen short in successfully treating depression. There is now sufficient evidence in the literature to support the exploration of alternative therapeutic areas to target mechanisms associated with depression such as neuroendocrine function, immune regulation and neurotrophic factors (Berton and Nestler 2006; Kennedy and Rizvi 2009). In order to delineate specific mechanisms, biomarker or combination of biomarkers, several challenges in this field the following must be addressed: 1) the clinical variability within the syndrome of MDD; 3) the need to standardize methods of biological sample collection and assay; 4) longitudinal studies to better illustrate the relationships between depressive symptoms, neuroendocrine, inflammatory and neurotrophic markers. (Maes et al. 2009; Loftis et al. 2010; Blume et al. 2011).

**Personal observations**

Overall, participant compliance was excellent for all data collection methods. Participant feedback from the study was very positive indicating that saliva collection instructions were easy to follow and no barriers (lack of transportation) were associated with commuting to the Rotman Baycrest hospital for the fMRI scans. On the other hand, participant compliance was poor for exercise attendance due to frequent tardiness for appointments and last minute cancellations and rescheduling which led to reduced trainer availability. Exercise attendance is a critical aspect of this study and trainer availability is essential. Therefore, a larger trainer pool is required for future pilot work to ensure trainer availability in the event of an inevitable schedule change.
Although participants were eager to participate in the study in hopes of curing their depression, participant anxiety was experienced during the initial exercise sessions. Feelings reported were poor body image and low self-efficacy for their exercise capabilities. To alleviate these anxiety provoking feelings associated with the initial exercise sessions, special attention must be given towards scheduling initial training sessions during the non-busy gym times or conducting initial training sessions in a private fitness room with only the participant and trainer.

Finally, each personal trainer was assigned a participant for the entire exercise program. Consequently, it was noted that participant-trainer attachment bonds were formed by the participant during the 12 weeks. To prevent the formation of bonds and separation anxiety experienced by the participants following study completion, future pilot work must assign and rotate several trainers to each participant throughout the 12 week exercise program.

5.1 Conclusion and recommendations

Depression is a multifaceted, biochemically and clinically heterogeneous disorder that may account for some of the variability and unpredictability associated with treatments. The future of successful treatments for MDD is contingent on the ability to produce a ‘personalized medicine’ paradigm (Kennedy and Rizvi 2009). Research must generate an integrative model illustrating how all the various targets interact. This will allow for a more precise exploration of neurobiological indicators of dysfunction and ultimately enable clinicians to identify and treat patients with specific dysfunctions based on their biochemical signature and clinical profile (Kennedy and Rizvi 2009).
Contrary to antidepressant medications, exercise is a treatment option that is linked to a myriad of therapeutic indications. Exercise sets into action an interactive cascade of biochemical reactions that has an overall net effect of stimulating neuroplasticity, enhancing cognitive function, normalizing HPA functioning, stimulating neurogenesis, improving cerebrovascular perfusion and improving immune function (Cotman et al. 2007). For researchers, this provides an optimal research setting to explore the broad assortment of biomarkers associated with the biological systems known to be altered in depression. However, before any relationship findings can be inferred, methodological limitations must be addressed.

First and foremost, the need to standardize methods of biological sample collection and assays must be established to minimize the variability between studies so that definite conclusions can be made. To increase assay reliability, it is recommended to prepare a normal human plasma bank from 15 normal healthy volunteers to create high volume plasma pools that can be used to test intra- and inter-assay precision. To ensure reproducibility between labs it is recommended that a plasma sample of known concentration be obtained from another institution using the same ELISA kits.

As a final point, symptoms of depression differ markedly across individuals and subtypes of depression exist that may implicate different neurochemical substrates. Future studies must consider these differences and recruit individuals with a specific subtype and/or assign participants into homogeneous groups based on specific criteria. Indubitably, future pilot work must categorize participants into depression subtypes and consider these subtypes during the hypotheses formulation and data interpretation. Otherwise specific relationships and significant findings will be lost in the compilation of heterogeneous results.
List of References


Foley, L. (2006). The effect of an eight week exercise program on depression intensity, self-efficacy and cortisol secretion in a clinically depressed individual and an examination of the salivary cortisol method. Sportsci 702 project. Auckland, University of Auckland.


Sharma, S. (2007). The development of a paradigm to test episodic memory that would reliably activate the hippocampus. Faculty of Science, Auckland, University of Auckland.


Appendix 1: Participant Information Sheet

EXERCISE AND DEPRESSION STUDY

Information Session Invitation

Hello,

We would like to invite you to come and hear more about a study that is being run by researchers in the Faculty of Health Sciences at UOIT and the Lakeridge Mental Health Day Treatment program.

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 12 week structured, supervised exercise program, in addition to the treatment you already receiving as part of the Lakeridge Mental Health Day Treatment program. The study will also involve two visits to a special MRI scanner at the Rotman Baycrest hospital.

In order to be eligible for this study you must be a man or woman aged 18 to 50 years. You must also currently be sedentary i.e you exercise less than 3 times weekly for less than 20 minutes at a time.

At the end of the information session, if you are interested in participating, we will get you to fill in some screening questionnaires to make sure that it is safe for you to exercise and that that you meet all the criteria to participate in this study.

If you are interested in hearing more, please fill in your contact details and the researchers will get in touch with you.

CONTACT INFORMATION

What is your preferred way to be contacted? ☐ Mobile ☐ Home Phone ☐ Email

Name ........................................................................................................................................................................

Home Phone .............................................................. Mobile Phone .............................................................

Email ........................................................................................................................................................................
Appendix 2: Consent Form

Professor Bernadette Murphy
University of Ontario Institute of Technology
Faculty of Health Sciences
2000 Simcoe St. North
Oshawa, Ontario
CANADA L0B 1J0
Email: Bernadette.Murphy@uoit.ca
Phone: (905) 721-8668  Fax: (905) 721-3179

The role of exercise in improving brain function: Part A: Exercise MHDP 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 July 6, 2011. 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 Yielder, Professor, Director-Bachelor of Health Sciences, Faculty of Health Sciences, University of Ontario Institute of Technology, Phone: (905) 721-8668 ext 2768, email: Paul.Yielder@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
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 12 week structured, supervised exercise programme, in addition to the treatment you already receiving as part of the Lakeridge Mental Health Day Treatment Programme. Once this phase of the study is complete we will be recruiting a group of patients in the Mental Health Day Treatment Programme who are of a similar age and gender to investigate the effects of the Day Treatment Programme 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 programme, participants may receive additional relief from their depression. This study offers a structured exercise programme 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 Programme 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 programme 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: 1) Questionnaire completion (page 3), 2) Saliva samples (page 3), 3) Bloodwork (see page 4), 4) Brainscan (see page 5) 5) Exercise (see page 6)
You will also be loaned a special activity monitor to wear for the duration of the study in order to monitor your background activity levels. The monitor straps on to your waist band and the research assistant will show you how to use it.
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 three Questionnaires, called the Beck Depression Inventory II (BDI-II) and the Hospital Anxiety and Depression Scale (HADS) and the Coping Self-Efficacy Scale.

2. Timeline
   Questionnaires will be given at:
   i. Week 0 (prior to the exercise programme)
   ii. Week 12 (after completion of the exercise programme).

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. 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 Programme. 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 12: after completion of the exercise programme (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.

C. 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 programme)
   ii. Week 12 (after completion of the exercise programme).

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, warfarin)
   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:
   i. Excessive bleeding at site of puncture
   ii. Bruising
   iii. Feeling light-headed, fainting
   iv. 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.
D. BRAIN SCAN (functional MRI)

1. Purpose

Prior to commencing your programme, 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 programme (12 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 programme)
   ii. Week 12 (after completion of the exercise programme).

3. Exclusion Criteria (please check box if you have any of the following)
   i. Phobia of small confined spaces
   ii. Metal Implants, pieces of shrapnel, aneurysm clips, or wires in your head. etc.
   iii. Implanted Pace Maker
   iv. Pregnant
   v. 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.

E. EXERCISE PROGRAMME

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 12 week exercise programme as part of the Mental Health Treatment Programme. The exercise sessions will take place at the Durham Family YMCA, located just down the road from the Lakeridge Health Day Programme. 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. In order to provide a transition out of the exercise programme, in weeks 9 and 12, participants will have one supervised session per week.

2. **Timeframe**
   i. 3 one hour sessions per week for 12 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 programme; however, the kinesiologists involved are trained in modifying exercise programmes 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 and coping self-efficacy, 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 programme 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):

1) Questionnaire completion □
2) Blood samples □
3) Saliva samples □
4) fMRI □
5) 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 a 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 than 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 Yielder to discuss.

Please advise us of your preferable format for communication (check one and provide details in the space provided):
Please indicate 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)
Appendix 3: PAR-Q & You

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.

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.

If you answered NO to all 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.

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.

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

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.
Appendix 4: Baycrest screening form

![Baycrest Logo]

**RESEARCH 3.0T MR**  
**PRE - PROCEDURE**  
**PARTICIPANT SCREENING FORM**

Romaan Research Institute  
Baycrest Centre for Geriatric Care  
2300 Bayview Avenue, Toronto, ON M4A 3K1  
Phone: (416) 785-2500 Ext. 3320, Fax: (416) 785-4299

**Participant ID:** [Redacted]  
**fMRI Project Study #:** [Redacted]

**Date:** / / **DD/MM/YY**

**Name:**  
**First Name:** [Redacted]  
**MI:** [Redacted]  
**Last Name:** [Redacted]  
**Height:** [Redacted]  
**Weight:** [Redacted]

**Birth Date:** / / **DD/MM/YY**

---

1. Have you ever worked as a machinist, metalworker, or in any profession or hobby grinding metal?  
   - [ ] Yes  
   - [ ] No

2. Have you ever had an injury to the eye involving a metallic object (e.g., metallic slivers, shards, or foreign body)?  
   - [ ] Yes  
   - [ ] No

3. Have you ever been injured by a metallic object or foreign body (e.g., BB, bullet, buckshot, shrapnel, etc.)?  
   - [ ] Yes  
   - [ ] No

4. Are you pregnant, experiencing a late menstrual period, or having fertility treatments?  
   - [ ] Yes  
   - [ ] No

5. Are you currently taking or have recently taken any medication?  
   - [ ] Yes  
   - [ ] No

6. Do you have drug allergies or have you had an allergic reaction?  
   - [ ] Yes  
   - [ ] No

---

Some of the following items may be hazardous to your safety and some can interfere with the MRI examination. Please check the correct answer for each of the following:

- [ ] Yes  
- [ ] No

- [ ] Cardiac pacemaker  
- [ ] No Aneurysm clip or brain clip  
- [ ] Yes Cochlear, endotracheal, or ear implant

- [ ] Yes Neurostimulator  
- [ ] Yes Implanted cardiac defibrillator

- [ ] Yes Insulin or infusion pump  
- [ ] Yes Implanted drug infusion device

- [ ] Yes Spinal or bone fusion stimulator

- [ ] Yes Carotid artery vascular clamp

- [ ] Yes Tissue expander (breast)

- [ ] Yes Prosthesis (eye, oral, or nasal prosthesis)

- [ ] Yes Heart valve graft

- [ ] Yes Artificial limb or joint

- [ ] Yes Other implants in body or head (radiation seeds)

- [ ] Yes Internal pacing wires

- [ ] Yes Intravascular stents, filters, or coils

- [ ] Yes Slant (spinal or intracranial)

- [ ] Yes Vascular access port or catheters

- [ ] Yes Swan-Ganz or thermistor catheter

- [ ] Yes Tattoos, permanent makeup

- [ ] Yes Claustraphobia  
- [ ] Yes IUD or diaphragm

- [ ] Yes Pessary or bladder ring

- [ ] Yes Medication patch (remove before scan)

- [ ] Yes Body piercing(s) (remove before scan)

- [ ] Yes Metal fragments (eye, head, ear, skin)

- [ ] Yes Facelift or other cosmetic surgery on body

- [ ] Yes Electrodes (on body, head, or brain)

- [ ] Yes Arterial clips

- [ ] Yes Venous umbilical

- [ ] Yes Metal or wire mesh implants, Retainers/Braces

- [ ] Yes Wire sutures or surgical staples, clips

- [ ] Yes Harrington rods (spine)

- [ ] Yes Metal rods in bones, joint replacements

- [ ] Yes Bone joint pin, screw, nail, wire, plate

- [ ] Yes Wig, toupee, or hair implants

- [ ] Yes Hearing aid (remove before scan)

- [ ] Yes Dentures (remove before scan)

- [ ] Yes Adam’s or breathing disorders

- [ ] Yes Seizures or motion disorders

- [ ] Yes Other implant

---

Please remove all metallic objects prior to your MR examination including: keys, hair pins, barrettes, jewelry, watch, safety pins, paperclips, money clip, credit cards, pens, pens, belt, metal buttons, pocket knife, cell phone and beeper.

You will be required to change for your MR examination. Non-metallic, cotton attire will be provided.

Earplugs and/or headphones are required during the MR examination.

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

**Signature of Person Completing Form:** __________________________  
**Date:** / / **DD/MM/YY**

**Form Completed By:**  
- [ ] Volunteer  
- [ ] Relative  
**Print Name:** [Redacted]  
**Relationship to Volunteer:** [Redacted]

**Form Information Reviewed By:**  
**Print Name:** [Redacted]  
**Signature:** [Redacted]

- [ ] MR Technologist  
- [ ] Other

**Revised:** April 14th, 2003 EEW

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Appendix 5: 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.
<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.</td>
<td>I am no more irritated by things than I ever was.</td>
</tr>
<tr>
<td>12.</td>
<td>I am slightly more irritated now than usual.</td>
</tr>
<tr>
<td>13.</td>
<td>I have not lost interest in other people.</td>
</tr>
<tr>
<td>14.</td>
<td>I am quite annoyed or irritated a good deal of the time.</td>
</tr>
<tr>
<td>15.</td>
<td>I feel irritated all the time.</td>
</tr>
<tr>
<td>16.</td>
<td>I have not lost interest in other people than I used to.</td>
</tr>
<tr>
<td>17.</td>
<td>I have lost most of my interest in other people.</td>
</tr>
<tr>
<td>18.</td>
<td>I have lost all of my interest in other people.</td>
</tr>
<tr>
<td>19.</td>
<td>I make decisions about as well as I ever could.</td>
</tr>
<tr>
<td>20.</td>
<td>I put off making decisions more than I used to.</td>
</tr>
<tr>
<td>21.</td>
<td>I have greater difficulty in making decisions more than I used to.</td>
</tr>
<tr>
<td>22.</td>
<td>I can't make decisions at all anymore.</td>
</tr>
<tr>
<td>23.</td>
<td>I don't feel that I look any worse than I used to.</td>
</tr>
<tr>
<td>24.</td>
<td>I am worried that I am looking old or unattractive.</td>
</tr>
<tr>
<td>25.</td>
<td>I feel there are permanent changes in my appearance that make me look</td>
</tr>
<tr>
<td>26.</td>
<td>unattractive</td>
</tr>
<tr>
<td>27.</td>
<td>I believe that I look ugly.</td>
</tr>
<tr>
<td>28.</td>
<td>I can work about as well as before.</td>
</tr>
<tr>
<td>29.</td>
<td>It takes an extra effort to get started at doing something.</td>
</tr>
<tr>
<td>30.</td>
<td>I have to push myself very hard to do anything.</td>
</tr>
<tr>
<td>31.</td>
<td>I can't do any work at all.</td>
</tr>
<tr>
<td>32.</td>
<td>I can sleep as well as usual.</td>
</tr>
<tr>
<td>33.</td>
<td>I don't sleep as well as I used to.</td>
</tr>
<tr>
<td>34.</td>
<td>I wake up 1-2 hours earlier than usual and find it hard to get back to</td>
</tr>
<tr>
<td>35.</td>
<td>sleep.</td>
</tr>
<tr>
<td>36.</td>
<td>I wake up several hours earlier than I used to and cannot get back to</td>
</tr>
<tr>
<td>37.</td>
<td>sleep.</td>
</tr>
<tr>
<td>38.</td>
<td>I don't get more tired than usual.</td>
</tr>
<tr>
<td>39.</td>
<td>I get tired more easily than I used to.</td>
</tr>
<tr>
<td>40.</td>
<td>I get tired from doing almost anything.</td>
</tr>
<tr>
<td>41.</td>
<td>I am too tired to do anything.</td>
</tr>
<tr>
<td>42.</td>
<td>My appetite is no worse than usual.</td>
</tr>
<tr>
<td>43.</td>
<td>My appetite is not as good as it used to.</td>
</tr>
<tr>
<td>44.</td>
<td>My appetite is much worse now.</td>
</tr>
<tr>
<td>45.</td>
<td>I have no appetite at all anymore.</td>
</tr>
<tr>
<td>46.</td>
<td>I haven't lost much weight, if any, lately.</td>
</tr>
<tr>
<td>47.</td>
<td>I have lost more than five pounds.</td>
</tr>
<tr>
<td>48.</td>
<td>I have lost more than ten pounds.</td>
</tr>
<tr>
<td>49.</td>
<td>I have lost more than fifteen pounds.</td>
</tr>
</tbody>
</table>
20.  
0  I am no more worried about my health than usual.
1  I am worried about physical problems like aches, pains, upset stomach, or constipation.
2  I am very worried about physical problems and it's hard to think of much else.
3  I am so worried about my physical problems that I cannot think of anything else.

21.  
0  I have not noticed any recent change in my interest in sex.
1  I am less interested in sex than I used to be.
2  I have almost no interest in sex.
3  I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible score for the test would be zero. This would mean you circles zero on each question. You can evaluate your depression according to the Table below.

Total Score__________________Levels of Depression

1-10____________________These ups and downs are considered normal
11-16____________________Mild mood disturbance
17-20____________________Borderline clinical depression
21-30____________________Moderate depression
31-40____________________Severe depression
over 40____________________Extreme depression

A PERSISTENT SCORE OF 17 OR ABOVE INDICATES THAT YOU MAY NEED MEDICAL TREATMENT. IF YOU HAVE ANY CARDIAC CONCERNS, PLEASE CONTACT CARDIOVASCULAR INTERVENTIONS, P.A. at 407-894-4880
Appendix 6: 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.

<table>
<thead>
<tr>
<th>I feel tense or ‘wound up’:</th>
<th>I still enjoy the things I used to enjoy:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Most of the time</td>
<td>o Definitely as much</td>
</tr>
<tr>
<td>o A lot of the time</td>
<td>o Not quite so much</td>
</tr>
<tr>
<td>o From time to time, occasionally</td>
<td>o Only a little bit</td>
</tr>
<tr>
<td>o Not at all</td>
<td>o Hardly at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I get a sort of frightened feeling as if something awful is about to happen:</th>
<th>I can laugh and see the funny side of things:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very definitely and quite badly</td>
<td>o As much as I always could</td>
</tr>
<tr>
<td>o Yes, but not too badly</td>
<td>o Not quite so much now</td>
</tr>
<tr>
<td>o A little, but it doesn’t worry me</td>
<td>o Definitely not so much now</td>
</tr>
<tr>
<td>o Not at all</td>
<td>o Not at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Worrying thoughts go through my mind:</th>
<th>I feel cheerful:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o A great deal of the time</td>
<td>o Not at all</td>
</tr>
<tr>
<td>o A lot of the time</td>
<td>o Not often</td>
</tr>
<tr>
<td>o From time to time, but not too often</td>
<td>o Sometimes</td>
</tr>
<tr>
<td>o Only occasionally</td>
<td>o Most of the time</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I can sit at ease and feel relaxed:</th>
<th>I feel as if I am slowed down:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Definitely</td>
<td>o Nearly all the time</td>
</tr>
<tr>
<td>o Usually</td>
<td>o Very often</td>
</tr>
<tr>
<td>o Not often</td>
<td>o Sometimes</td>
</tr>
<tr>
<td>o Not at all</td>
<td>o Not at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I get a sort of frightened feeling like ‘butterflies’ in the stomach:</th>
<th>I have lost interest in my appearance:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Not at all</td>
<td>o Definitely</td>
</tr>
<tr>
<td>o Occasionally</td>
<td>o I don’t take as much care as I should</td>
</tr>
<tr>
<td>o Quite often</td>
<td>o I may not take quite as much care</td>
</tr>
<tr>
<td>o Very often</td>
<td>o I take just as much care as ever</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I feel restless as I have to be on the move:</th>
<th>I look forward with enjoyment to things:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very much indeed</td>
<td>o As much as I ever did</td>
</tr>
<tr>
<td>o Quite a lot</td>
<td>o Rather less than I used to</td>
</tr>
<tr>
<td>o Not very much</td>
<td>o Definitely less than I used to</td>
</tr>
<tr>
<td>o Not at all</td>
<td>o Hardly at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>I get sudden feelings of panic:</th>
<th>I can enjoy a good book or radio or TV programme:</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Very often indeed</td>
<td>o Often</td>
</tr>
<tr>
<td>o Quite often</td>
<td>o Sometimes</td>
</tr>
<tr>
<td>o Not very often</td>
<td>o Not often</td>
</tr>
<tr>
<td>o Not at all</td>
<td>o Very seldom</td>
</tr>
</tbody>
</table>

(Modified from Zigmond & Snaith, 1983)
Appendix 9: MoCA

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

VISUOSPATIAL / EXECUTIVE

Copy cube
Draw CLOCK (Ten past eleven) (3 points)

POINTS

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

VISUOSPATIAL / EXECUTIVE

End

Begin

Copy cube

Points

5

E

A

B

D

C

1

2

3

4

End

Draw CLOCK (Ten past eleven) (3 points)

Contour Numbers Hands

5/5

NAMING

Rhino

Camel

[ ]

FACE  VELVET  CHURCH  DAISY  RED

1st trial

2nd trial

MEMORY

Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

ATTENTION

Read list of digits (1 digit/sec.). Subject has to repeat them in the forward order. Subject has to repeat them in the backward order.

1st trial

2nd trial

Read list of letters. The subject must tap with his hand at each letter. No points if ≥ 2 errors.

Serial 7 subtraction starting at 100

4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt

LANGUAGE

Repeat: I only know that John is the one to help today. The cat always hid under the couch when dogs were in the room.

Fluency / Name maximum number of words in one minute that begin with the letter F

ABSTRACTION

Similarity between e.g. banana - orange = fruit

[ ] train - bicycle

[ ] watch - ruler

DELAYED RECALL

Has to recall words with no cue

FAC  VELVET  CHURCH  DAISY  RED

Points for uncued recall only

Optional

Category cue

Multiple choice cue

ORIENTATION

Date

Month

Year

Day

Place

City

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Administered by:__________________________

Normal ≥ 26 / 30

TOTAL

Add 1 point if ≤ 12 yr edu

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# Appendix 7: Pre-screening form

## Exercise and Depression Screening Form

Please check the appropriate response

<table>
<thead>
<tr>
<th>SECTION A</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Does the participant have only one Axis One disorder, i.e. Major</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive Disorder (MDD)? **Anxiety is the one allowable secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diagnosis for inclusion. <strong>If YES go to question 2</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. “We currently have a free three month exercise study running as part</td>
<td></td>
<td></td>
</tr>
<tr>
<td>of the Day Treatment program. Is this something you might be interested</td>
<td></td>
<td></td>
</tr>
<tr>
<td>in?” <strong>If YES go to question 3</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Does the participant have any current substance abuse?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If NO go to question 4</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. “Are you between the ages of 18 to 50?”</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If YES go to question 5</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. “Are you currently sedentary (i.e. do you do less than 20 minutes of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>exercise a day, less than 3 times per week)? **If YES, go to question 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Does the participant have any inflammatory disease (i.e. rheumatoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>arthritis, lupus or other autoimmune conditions)?</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If NO, go to question 7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Will the pharmacological treatment be stabilized 4 weeks prior to</td>
<td></td>
<td></td>
</tr>
<tr>
<td>enrolment (if not how long have they been on their treatment)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>................................................................. <strong>Please proceed to Section B</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SECTION B</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>“As part of this study you get a free MRI scan of your brain at the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>beginning and end of the study. I just need to ask a few quick</td>
<td></td>
<td></td>
</tr>
<tr>
<td>screening questions to make sure that it is safe for you to go in the</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scanner.”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Do you have a cardiac pacemaker?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Do you have an aneurysm clip?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Do you have a cochlear implant?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Have you had any injury that might have left a metal fragment in your</td>
<td></td>
<td></td>
</tr>
<tr>
<td>eye?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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: 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……………….

<table>
<thead>
<tr>
<th>Reason</th>
<th>Not during the past 2 weeks</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannot get to sleep within 30 minutes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wake up in the middle of the night or early morning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have to get up to use the bathroom</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannot breathe comfortably</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough or snore loudly</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel too cold</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feel too hot</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had bad dreams</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other reason(s) please describe__________</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 past 2 weeks  Less than once a week  Once or twice a week  Three or more 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 past 2 weeks  Less than once a week  Once or twice a week  Three or more 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 slight problem  Somewhat of a problem  A very 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….

<table>
<thead>
<tr>
<th></th>
<th>Not during the past 2 weeks</th>
<th>Less than once a week</th>
<th>Once or twice a week</th>
<th>Three or more times a week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loud snoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long pauses between breaths while asleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legs twitching or jerking while you sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Episodes of disorientation or confusion during sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other restlessness while you sleep (please describe)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Modified from (Buysse et al. 1989))
Appendix 9: 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.

Week 0 and Week 12

- 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 10: 11-item exercise self-efficacy

Barriers Efficacy Scale

The items below reflect common reasons preventing people from participating in exercise sessions or in some cases, dropping out or quitting exercise altogether. Using the scale below please indicate how confident you are that you could exercise in the event that any of the following circumstances were to occur.

No confidence at all  Somewhat confident  Completely confident

For example, if you have complete confidence that you can continue to exercise, even if you are bored by the activity, you should circle 100%. However, if you are absolutely sure that you could not exercise if you failed to make or continue to make progress you would circle 0% (No confidence at all).

I believe I can exercise 3 times per week if:

- The weather is very bad (hot, humid, rainy, snow, cold).
- I was bored by the program or activity.
- I was on vacation.
- I felt pain or discomfort when exercising.
- I had to exercise alone.

0%  10%  20%  30%  40%  50%  60%  70%  80%  90%  100%
No confidence at all  Somewhat confident  Completely confident
- Exercise was not enjoyable or fun.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- It became difficult to get to the exercise location.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- I didn’t like the particular activity program that I was involved in.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- My work schedule conflicted with my exercise session.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- I felt self-conscious about my appearance when I exercised.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- The instructor did not offer me any encouragement.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident

- I was under personal stress of some kind.
  0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
  No confidence at all  Somewhat confident  Completely confident
Appendix 11: 6-item exercise self-efficacy

SELF EFFICACY FOR EXERCISE SCALE

The following questions regard how confident you are that you could perform exercise three times per week for the next four weeks without quitting and accurately completing the prescribed workload (40 minutes, 3 times per week). You would indicate 100% if you are confident you can continuously exercise for at least 40 minutes involving aerobic and weights training, three times per week.

1. I am able to continue to exercise three times per week performing all prescribed repetitions, for 40+ minutes without quitting for the NEXT WEEK

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

2. I am able to continue to exercise three times per week performing all prescribed repetitions, for 40+ minutes without quitting for the NEXT TWO WEEKS

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

3. I am able to continue to exercise three times per week performing all prescribed repetitions, for 40+ minutes without quitting for the NEXT THREE WEEKS

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

4. I am able to continue to exercise three times per week performing all prescribed repetitions, for 40+ minutes without quitting for the NEXT FOUR WEEKS

   0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

(Modified from McAuley, 1993)
Appendix 12: Letter to go with PARmed-X

Professor Bernadette Murphy  
Head Kinesiology Specialization and Director of Health Sciences  
Faculty of Health Sciences  
University of Ontario Institute of Technology  
2000 Simcoe St North,  
Oshawa, Ontario.  
L1H 7K4  
Phone: (905) 721-8668 ext 2778  
email: Bernadette.Murphy@uoit.ca  
Fax: 905 721 3179  

April 26, 2012  

Dear Dr. ___________________________.  

Your patient, ___________________________, wishes to participate in  
a study entitled “Mechanisms by which exercise promotes hippocampal function in both  
depressed and non-depressed individuals” being run by UOIT Kinesiology in conjunction  
with the Lakeridge Mental Health Day Treatment program.  

This research study is being conducted to study the effect of exercise on 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 their brain functions during certain  
memory tasks. We are also interested in how exercise may affect the intensity of  
depression symptoms. These will be assessed over the course of a 12 week structured,  
supervised exercise program, in addition to the treatment they are already receiving as  
part of the Lakeridge Mental Health Day Treatment program. The study will also involve  
two visits to a special MRI scanner at the Rotman Baycrest hospital.  

In order to be eligible for this study participants can be a man or woman aged 18 to 50  
years. They must also currently be sedentary (i.e. exercising less than 3 times weekly for  
less than 20 minutes at a time). The 12 week exercise programe will be supervised by  
CSEP certified personal trainers, with heart rate monitoring for the aerobic component.  
Your patient answered yes to one or more questions on the PAR-Q which means that they  
need physician clearance prior to commencing exercise. We have attached a copy of the  
Par Med X which needs to be completed before your patient can join the study. In the  
interests of participant safety if they have any absolute or relative contraindications they  
are not eligible. However, we can certainly adjust the exercise prescription to  
accommodate those with minor musculoskeletal issues or individuals with well controlled  
hypertension as examples.  

If you have any additional questions, please contact the research co-ordinator, Joanne  
Gourgouvelis, by phone at 905-550-4055 or email: j.gourgouvelis@sympatico.ca.  

Kind regards,  

Bernadette Murphy, PhD
Appendix 13: PARmed-X

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.

A) PERSONAL INFORMATION:
- NAME
- ADDRESS
- TELEPHONE
- BIRTHDATE
- MEDICAL No.

B) PAR-Q: Please indicate the PAR-Q questions to which you answered YES
- Q. 1 Heart condition
- Q. 2 Chest pain during activity
- Q. 3 Chest pain at rest
- Q. 4 Loss of balance, dizziness
- Q. 5 Bone or joint problem
- Q. 6 Blood pressure or heart drugs
- Q. 7 Other reason:

C) RISK FACTORS FOR CARDIOVASCULAR DISEASE:
- Less than 30 minutes of moderate physical activity most days of the week
- Currently smoker (tobacco smoking 1 or more times per week)
- High blood pressure reported by physician after repeated measurements
- High cholesterol level reported by physician

D) PHYSICAL ACTIVITY INTENTIONS:
- What physical activity do you intend to do?

This section to be completed by the examining physician:

- Physical Exam:
  - Height
  - Weight
  - Blood Pressure
- Conditions limiting physical activity:
  - Cardiovascular
  - Respiratory
  - Musculoskeletal
  - Abdominal
- Tests required:
  - ECG
  - Exercise Test
  - X-Ray

- Physical Activity Readiness Conveyance/Referral:
  - Based upon a current review of health status, I recommend:
    - No physical activity
    - Only a medically-supervised exercise program until further medical clearance
    - Progressive physical activity:
      - with avoidance of:
      - with inclusion of:
    - Under the supervision of a CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™
    - Unrestricted physical activity—start slowly and build up gradually

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Health Canada
Santé Canada
### Absolute Contraindications
- Permanent restriction or temporary restriction until condition is treated, stable, and/or pain acute phase.

### Relative Contraindications
- Highly variable. Value of exercise testing and/or program may exceed risk. Activity may be restricted.
- Desirable to maximize control of condition.
- Direct or indirect medical experience of exercise program may be desirable.

### Special Prescriptive Conditions
- Individualized prescription advice generally appropriate:
  - Limitations imposed, and/or
  - Special exercises prescribed.
- May require medical monitoring and/or initial supervision in exercise program.

### Cardiovascular
- **Absolute**
  - angina pectoris (dysrhythmia)
  - atrial fibrillation
  - congestive heart failure
  - coronary artery disease
  - myocardial infarction (acute)
  - myocardial infarction (chronic)
- **Relative**
  - atrial fibrillation (onsus)
  - atrial fibrillation (chronic)
  - marked cardiac enlargement
  - preexisting untreated diabetes (controlled or high risk)
  - ventricular arrhythmia (supraventricular tachycardia or frequent)
  - ventricular arrhythmia (ventricular tachycardia)
- **Special**
  - atrial fibrillation (onsus)
  - atrial fibrillation (chronic)
  - preexisting untreated diabetes (controlled or high risk)
  - ventricular arrhythmia (ventricular tachycardia)

### Infections
- **Absolute**
  - acute infectious disease (regardless of site)
- **Relative**
  - subacute/chronic recurrent infectious diseases (e.g., malaria, others)
- **Special**
  - acute infectious disease (regardless of site)
  - subacute/chronic recurrent infectious diseases (e.g., malaria, others)

### Metabolic
- **Absolute**
  - uncontrolled metabolic disorders (diabetes mellitus, thyrotoxicosis, myxedema)
- **Relative**
  - renal, hepatic, or other metabolic insufficiency
- **Special**
  - uncontrolled metabolic disorders (diabetes mellitus, thyrotoxicosis, myxedema)
  - renal, hepatic, or other metabolic insufficiency

### Pregnancy
- **Absolute**
  - complicated pregnancy (e.g., toxemia, hemorrhage, incompetent cervix, etc.)
- **Relative**
  - advanced pregnancy (late third trimester)
- **Special**
  - complicated pregnancy (e.g., toxemia, hemorrhage, incompetent cervix, etc.)
  - advanced pregnancy (late third trimester)

### Advice
- Intermittent claudication: progressive exercise to tolerance
- Hypertension: systolic 160-180, diastolic 105+ progressive exercise; care with medications (serum electrolytes; post-exercise syncope; etc.)
- Other: exercise limited to significant activity limitations.

### References:

The PAR-Q and PARmed-X were developed by the British Columbia Ministry of Health. They have been reviewed by an Expert Advisory Committee of the Canadian Society for Exercise Physiology chaired by Dr. N. Gledhill (2002).

No changes permitted. You are encouraged to photocopy the PARmed-X, but only if you use the entire form.

Disponible en français sous le titre
"Evaluations médicales de l'aptitude à l'activité physique (X-AAP)"

Continued on page 3...
### Special Prescriptive Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung</strong></td>
<td></td>
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<tr>
<td>Chronic pulmonary disorders</td>
<td>Special relaxation and breathing exercises</td>
</tr>
<tr>
<td>Obstructive lung diseases</td>
<td>Breath control during endurance exercises to tolerance; avoid polluted air</td>
</tr>
<tr>
<td>Asthma</td>
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<tr>
<td>Exercise-induced bronchospasm</td>
<td>Avoid hyperventilation during exercise; avoid extremely cold conditions; warm up adequately; utilize appropriate medication</td>
</tr>
<tr>
<td><strong>Musculoskeletal</strong></td>
<td></td>
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<tr>
<td>Low back conditions (pathological, functional)</td>
<td>Avoid or minimize exercises that precipitate or exacerbate e.g., forced extreme flexion, extension, and violent twisting; correct posture, preprogrammed exercises</td>
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<tr>
<td>Arthritis – acute (infective, rheumatoid, gout)</td>
<td>Treatment; plus judicious blend of rest, splinting and gentle movement</td>
</tr>
<tr>
<td>Arthritis – subacute</td>
<td>Progressive increase of active exercise therapy</td>
</tr>
<tr>
<td>Arthritis – chronic (ostearthritis and disease conditions)</td>
<td>Maintenance of mobility and strength; non-weight-bearing exercises to minimize joint trauma (e.g., cycling, aquatic activity, etc.)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Highly variable and individualized</td>
</tr>
<tr>
<td>Tumors</td>
<td>Maintain strength and kinesthesia; strengthen abdominal muscles</td>
</tr>
<tr>
<td>Osteoporosis or low bone density</td>
<td>Avoid exercises with high risk for fractures such as pull-ups, pull-ups, vertical jump and trunk forward flexion; engage in low-impact weight-bearing activities and resistance training</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td></td>
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<tr>
<td>Concussive disorder not completely resolved by medication</td>
<td>Moderate or avoid exercise in hazardous environments and/or exercising alone (e.g., swimming, mountain climbing, etc.)</td>
</tr>
<tr>
<td>Recent concussion</td>
<td>Through examination if history of two concussions; review for discontinuation of contact sport if three concussions, depending on duration of unconsciousness, retrogade amnesia, persistent headaches, and other objective evidence of cerebral damage</td>
</tr>
<tr>
<td><strong>Blood</strong></td>
<td></td>
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<tr>
<td>Anemia – severe (&lt; 9 Gm/dl)</td>
<td>Control hemoglobin, exercise as tolerated</td>
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<tr>
<td>Electrolyte disturbances</td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td>Antihypertensive</td>
<td>Antiarrhythmic</td>
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<tr>
<td>Anticoagulant</td>
<td>Antiplatelet</td>
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<tr>
<td>Beta-blockers</td>
<td>Digitalis preparations</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Gangliergic blockers</td>
</tr>
<tr>
<td>Diuretic</td>
<td>Gangliergic blockers</td>
</tr>
<tr>
<td><strong>Other</strong></td>
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<tr>
<td>Post-exercise syncope</td>
<td>Moderate program</td>
</tr>
<tr>
<td>Heat intolerance</td>
<td>Prevent cool-down with light activities; avoid exercise in extreme heat</td>
</tr>
<tr>
<td>Temporaryilletness</td>
<td>Postpone until recovered</td>
</tr>
<tr>
<td>Cancer</td>
<td>If potential metastases, test by bone scan/scan; consider non-weight bearing exercises; exercise at lower end of prescriptive range (48-60% of heart rate reserve); depending on condition and recent treatment (radiation, chemotherapy); monitor hemoglobin and lymphocyte counts; add dynamic lifting exercises to strengthen muscles, using machines either than weights</td>
</tr>
</tbody>
</table>

*Refer to special publications for elaboration as required.*

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The following companion forms are available online: [http://www.csep.ca/forms.php](http://www.csep.ca/forms.php)

The Physical Activity Readiness Questionnaire (PAR-Q) - a questionnaire for people aged 15-69 to complete before becoming much more physically active.

The Physical Activity Readiness Medical Examination for Pregnancy (PAR-MED) - for PREGNANCY - to be used by physicians with pregnant patients who wish to become more physically active.

For more information, please contact the:

Canadian Society for Exercise Physiology
252 - 155 Somerset St. West
Ottawa, ON K1N 6E9
Tel: 1-877-651-3735 • FAX: 613-784-5650 • Online: [www.csep.ca](http://www.csep.ca)

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**Note to physical activity professionals...**

It is a prudent practice to retain the completed Physical Activity Readiness Conveyance/Referral Form in the participant's file.

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Physical Activity Readiness Medical Examination  

PARmed-X Physical Activity Readiness Conveyance/Referral Form

Based upon a current review of the health status of __________________________, I recommend:

- No physical activity
- Only a medically-supervised exercise program until further medical clearance
- Progressive physical activity
  - with avoidance of __________________________
  - with inclusion of __________________________
  - under the supervision of a CSEP-Professional Fitness & Lifestyle Consultant or CSEP-Exercise Therapist™
- Unrestricted physical activity — start slowly and build up gradually

________________________________________________________________________ 

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________

Physician’s signature: __________________________
M.D.

Date: __________________________

Further Information:
- Attached
- To be lowered
- Available on request

Physician’s note:

NOTE: This physical activity clearance is valid for a maximum of six months from the date it is completed and becomes invalid if your medical condition becomes worse.
Appendix 14: Blood collection log

EXERCISE AND DEPRESSION STUDY

Participant Name: ________________________________________________________________

Participant Number: ______________________________________________________________

<table>
<thead>
<tr>
<th>DATE</th>
<th>TIME OF COLLECTION</th>
<th>NO. OF TUBES</th>
<th>TIME OF CENTRIFUGE</th>
<th>TIME PLACE IN FREEZER</th>
<th>EMOTIONAL STATUS</th>
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NOTES:
______________________________________________________________________________
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Appendix 15: Resistance exercise options

Appendix 12: Resistance Exercise Options

Horizontal Push Exercises

- Dumbbell Bench Press
- Barbell Bench Press
- Machine Bench Press

Anterior Lower Body Exercises

- Machine Leg Press
Dumbbell Split Squat

Vertical Pull Exercises

Under-Hand Grip Pulldown

Over-Hand Wide-Grip Pulldown

Over-Hand Close-Grip Pullup
Posterior Lower Body Exercises

- Cable Triceps Extension
- Machine Leg Curl
- One-Legged Calf Raises
- Machine Calf Raises
Horizontal Pull Exercises

- Machine Row
- Dumbbell Row
- Machine Preacher Curl
- Barbell Biceps Curl