THE IMPACT OF EXERCISE ON MOOD, SOCIAL AND COGNITIVE OUTCOMES

THE IMPACT OF EXERCISE ON MOOD, SOCIAL AND COGNITIVE OUTCOMES

By LAURA ELIZABETH KEATING, B.A., M.SC.

A Thesis Submitted to the School of Graduate Studies in Partial Fulfilment of the Requirements for the Degree Doctor of Philosophy

McMaster University © Copyright by Laura Elizabeth Keating, June 2018

McMaster University DOCTOR OF PHILOSOPHY IN NEUROSCIENCE (2018)
Hamilton, Ontario (History)

TITLE: The Impact of Exercise on Mood, Social and Cognitive Outcomes

AUTHOR: Laura Elizabeth Keating, B.A., M.Sc. (McMaster University)

SUPERVISORS: Dr. Suzanna Becker and Dr. Margaret C. McKinnon

NUMBER OF PAGES: xii, 178

Lay abstract

This dissertation examines the impact of exercise across multiple indications of mental health and functioning including mood scores, stress, cognitive function, social function and health-related quality of life (HRQOL) in participants with and without mood disorders. Youth and adults engaged in 12-week group-based exercise interventions of running or yoga and completed comprehensive mental health and neurocognitive assessments. Results: Participation in a structured exercise program was associated with improved stress and depression, social functioning, physical and mental HRQOL domains and limited improvements in cognitive function. Results also support therapeutic benefits of structured high- and low-intensity exercise programs across multiple symptoms in patients with difficult-to-treat mood disorders, and further suggest that reduced stress and increased social functioning play key roles in the mental health benefits observed. These results represent a new standard for mood disorders research, to better understand the how lifestyle strategies are effective for the treatment of mental illness.

Abstract

While the physical health benefits of exercise are well established, mental health benefits remain unclear. The literature reports reduced stress and improved cognitive function in rodent exercise studies, and improved mood scores in humans. However, though mood disorders are characterized by poor response to treatment, studies rarely evaluate difficult-to-treat patients or functional outcomes. Therefore, we evaluated the impact of 12-week, group-based exercise programs (running or yoga) on mood and functional outcomes including health-related quality of life (HRQOL) and social and cognitive functioning. Methods: Study 1 was a retrospective review of mood and stress outcomes in participants with difficult-to-treat mood disorders. In Study 2, we measured functional outcomes before and after the running program in a subsample from Study 1. Improved friendship and high injury rates in the running group inspired Study 3, a randomized control trial to evaluate mood and functional outcomes in a non-clinical sample using yoga, a low-impact exercise program that included cognitive control. Results: In Study 1 ($n=46$), depression ($p<0.0001$) and stress ($p=0.01$) scores improved over time, and improved friendship levels were predictive of improved mood scores ($p<0.04$). In Study 2 ($n=18$), we found improved scores on several HRQOL subscales, including social functioning (p-values$\leq$0.01) and weak improvements in working memory and processing speed (p-values$\leq$0.04). In Study 3, yoga participants ($n=20$) had improved stress ($p=0.02$), loneliness ($p=0.002$), and HRQOL (p-values$\leq$0.03) scores, compared to wait-list controls ($n=8$). Yoga participants improved on tasks reflecting hippocampal memory (p-values$\leq$0.006) and attention and inhibitory control ($p=0.03$). Regression and mediation

analyses suggest that social support mediates the stress-reducing impact of yoga (p-values$\leq$0.0005). Discussion: Group-based exercise programs impart benefits across mental health and functional outcomes for participants with and without mood disorders. Exercise may be an effective adjunctive treatment for mood disorders, and more data is needed on how social support impacts clinical outcomes.

Acknowledgements

"In order for man to succeed in life, God provided him with two means, education and physical activity. Not separately, one for the soul and the other for the body, but for the two together. With these two means, man can attain perfection." –Plato

I would like to thank my supervisors Dr. Sue Becker and Dr. Margaret McKinnon for their guidance over the past five years. I could not have asked for more supportive supervisors to help me navigate this journey. I also thank my committee members, Dr. Benicio Frey and Dr. Roberto Sassi, for their thoughtful insight and guidance.

Thanks to my fellow McMaster graduate students in the Becker lab and Mood Disorders Program at St Joseph's Healthcare Hamilton for their help and support. Special thanks to Laura Garrick, for helping me navigate my way at SJHH, and to Katie McCabe and Jeff Whattam, for their support with the Running Group study.

I am grateful for the yoga teachers in my life, who have helped more than they know.

I am eternally grateful for the support of my tribe. Thank you to my street family Julie Bijl, Angela Camparone, Kristy Dickinson, Jennifer Houston and Bianca Kirk, and especially Jennifer Clark Douthwright for your tireless support. Thanks to my parents Sharon and Chris Scutt, for being there when I needed them, and to my sisters Janet Armstrong and Karen Clemens for their ongoing support. I am grateful to my daughters Julia, Jordan and Christie for always reminding me what is important. Finally, last but not least, my amazing husband, Tom, for too many things to mention, but mostly for just listening to me as I navigated this journey.

Table of Contents

Lay abstract iii
Abstract iv
Acknowledgements vi
Table of Contents vii
List of Illustrations, Charts and Tables x
List of Abbreviations and Symbols xi
Declaration of Academic Achievement xii

Chapter I: Introductions
I.A. Overview of current dissertation 1
I.B. Stress in society
I.B.i. The hypothalamus-pituitary adrenal (HPA) axis 2
I.B.ii. The impact of stress on rodents 4
I.B.iii. The impact of stress on humans 6
I.C. Stress and mental illness
I.C.i. Mood disorders: Prevalence, diagnosis and causes 8
I.C.ii. First-line treatments for mood disorders 9
I.C.iii. Adjunctive treatments for mood disorders 10
I.D. Physiological effects of exercise 12
I.E. Psychological effects of exercise 14
I.F. Exercise and social functioning 17
I.G. Exercise and health-related quality of life 19
I.H. Current dissertation: Hypotheses and overview of research 21

Chapter II: Effects of a 12-week running programme in youth and adults with complex mood disorders
Introduction to Chapter II 23
Abstract 25
Background 25
Methods 26
Results 27
Discussion 28
Conclusions 30
References 31

Chapter III: Impact of a structured, group-based running program on clinical, cognitive and social function in youth and adults with complex mood disorders
Introduction to Chapter III 32
III.A. Abstract 35
III.B. Introduction
III.B.i. Mood disorders: Prevalence and cost 37
III.B.ii. Mood disorders: Diagnosis and treatment 38

III.B.iii. Mood disorders: Evaluating Treatment Outcomes 39
III.B.iv. Mood disorders: Exercise as adjunctive treatment 39
III.B.v. Functional outcomes in mood disorders 40
III.B.vi. Study 2: Objectives 43
III.C. Methods
III.C.i. Study participants 45
III.C.ii. Clinical assessments 46
III.C.iii. Neurocognitive functioning assessments 47
III.C.iv. Running protocol 49
IIII.C.v. Statistical analyses 50
III.D. Results
III.D.i. Clinical and demographic results 51
III.D.ii. Pre- and post-intervention assessments 55
III.D.iii. Multiple linear regression and correlation analyses 59
III.D.iv. Secondary analyses: Mood symptoms 60
III.E. Discussion
III.E.i. Summary of results 62
III.E.ii. Comparison to the literature 63
III.E.iii. Limitations 68
III.E.iv. Future research 69
III.E.v. Overall conclusion 70
III.E.vi. Acknowledgements 70
III.E.vii. Funding 71

Chapter IV: Impact of yoga on stress reduction: Investigating multiple pathways via exercise, cognitive control and social interaction
Introduction to Chapter IV 74
IV.A. Abstract 77
IV.B. Introduction
IV.B.i. The benefits of voluntary exercise in rodents 79
IV.B.ii. The benefits of exercise in humans 80
IV.B.iii. Non-exercise interventions: Yoga and mindfulness 81
IV.B.iv. The positive impact of social support 83
IV.B.v. Study 3: Objectives 85
IV.C. Methods
IV.C.i. Study participants 87
IV.C.ii. Pre- and post-intervention assessments 88
IV.C.iii. Yoga intervention protocol 91
IV.C.iv. Statistical analyses 93
IV.D. Results
IV.D.i. Stress and mood outcomes 94
IV.D.ii. Social functioning outcomes 94
IV.D.iii. Health-related quality of life 95
IV.D.iv. Neurocognitive function 95

IV.D.v. Linear regression and mediation analyses 96

IV.E. Discussion
IV.E.i. Summary of results 105
IV.E.ii. Comparison to the literature 106
IV.E.iii. Implications for underlying systems 108
IV.E.iv. Limitations 109
IV.E.v. Future research 110
IV.E.vi. Overall conclusion 111
IV.E.vii. Acknowledgements 112
IV.E.viii. Funding 112

Chapter V: Overall Discussion
V.A. Overview 113
V.B. Summary of Research Results
V.B.i. Summary of study 1 115
V.B.ii. Summary of study 2 117
V.B.iii. Summary of study 3 119
V.B.iv. Study limitations 123
V.C. Implications of findings for mood disorders and stress management 124
V.D. Lifestyle factors and health management 127
V.E. Future research 128
V.F. Final conclusions 131

VI. References 133

List of Illustrations, Charts and Tables

TITLE **PAGE**

Chapter I:
Figure I.1. The Stress Response System: the hypothalamus-pituitary-adrenal axis 3

Chapter II:
Table 1: Characteristics of the running groups 26
Table 2: Remission rates of baseline compared with end-of-study depression and anxiety scores 28
Figure 1: Stress, anxiety and depression scores over time 28
Figure 2: Changes in scores for the BDI (2A), PSS (2B) and BAI (2C) for high and low attenders 29

Chapter III:
Table III.1: Sample demographics 53
Table III.2: Demographic characteristics of completers compared to dropouts 54
Table III.3: Health-related quality of life 56
Table III.4: Neurocognitive assessments 57
Figure III.1: Change in BDI scores plotted against change in health-related quality of life subscale scores from pre to post assessments 72

Chapter IV:
Table IV.1: Self-report measures of mental health and functioning 99
Table IV.2: Health-related quality of life 100
Table IV.3: Neurocognitive assessments 101
Figure IV.1: Changes in mood, social and neurocognitive functioning scores from pre to post assessment 103
Figure IV.2: Stress and social support change scores 104

List of Abbreviations and Symbols

ACTH: Adrenocorticotropic hormone
ACC: Anterior cingulate cortex
BD: Bipolar disorder
BAI: Beck Anxiety Inventory
BDI: Beck Depression Inventory
BDNF: Brain-derived neurotrophic factor
DLPFC: Dorsolateral prefrontal cortex
DMN: Default mode network
DMS: Delayed match to sample
GLM: General linear model
HIREB: Hamilton Integrated Research Ethics Board
HPA: Hypothalamus-pituitary-adrenal
HRQOL: Health-related quality of life
IPL: inferior parietal lobule
MDD: Major depressive disorder
mPFC: Medial prefrontal cortex
MST: Mnemonic similarity task
PAL: Paired associate learning task
PAR-Q and You®: Physical Activity Readiness Questionnaire
PCC: Posterior cingulate cortex
PFC: Prefrontal cortex
PSS: Perceived stress scale
RVP: Rapid visual processing task
SD: Standard deviation
SF-36: 36-Item Short Form health-related quality of life survey
SRM: Spatial recognition memory task
SSRI: Selective-serotonin reuptake inhibitors

Declaration of Academic Achievement

I, Laura Elizabeth Keating, declare the works included in this dissertation to be my own original research, with guidance and support from study team members, as described below.

Author contributions for Chapters 1 and 5: I was the sole author of the Introduction and Discussion sections. I received feedback and guidance from my supervisors, Dr. Sue Becker and Dr. Margaret McKinnon, and from my committee members, Drs. Benicio Frey and Roberto Sassi.

Author contributions for Chapter 2:
The concept for this study, to analyze data collected for qualitative assessment of the running program, was my own. I was responsible for the ethics application, data entry, analyses and interpretation. I was the primary author of the published manuscript (Keating et al., 2018). Drs Margaret McKinnon, Sue Becker, Benicio Frey and Roberto Sassi provided feedback for the study design, data analyses, interpretation and for the preparation of the manuscript. Dr. McKinnon was the Principal Investigator and additionally provided guidance for the collection and interpretation of the clinical diagnoses for the participants. Co-authors Katie McCabe, Jeff Whattam and Laura Garrick assisted with design of the running program, recruitment of participants and weekly data collection. All authors read and approved the final manuscript.

Author contributions for Chapter 3:
I was the primary author of the manuscript, performed the majority of the patient assessments and all of the data analyses. Co-authors Katie McCabe, Jeff Whattam and Laura Garrick oversaw the running program and assisted with recruitment. Dr. Sue Becker was involved in the design of the study, in particular surrounding cognitive assessments, and provided direction for analyses, interpretation of findings, and manuscript preparation. Dr. Benicio Frey was involved in the design of the study; he provided advice for data analyses and interpretation and on the paper. Dr. Roberto Sassi and Dr. Margaret McKinnon were co-Principal Investigators; they designed the study, provided guidance on data analyses and interpretation, and preparation of the manuscript. Dr. Margaret McKinnon also provided direction on confirming clinical diagnoses.

Author contributions for Chapter 4:
The idea for Chapter 4 was entirely my own, based on observations from the running group, and my personal experience with yoga. I wrote the proposal and obtained funding from Natural Sciences Engineering Research Council to support the study. I was the principal investigator at Humber College, and principal author of the manuscript. I oversaw the training of students, completion of assessments, data entry, analyses and interpretation. Drs. Sue Becker and Margaret McKinnon provided guidance on the protocol and grant application, manuscript and analyses. Drs. Benicio Frey and Roberto Sassi also provided guidance and support at all stages, including manuscript preparation.

I.A. OVERVIEW OF CURRENT DISSERTATION

In our North American society, the concept of stress seems to permeate everyday life, and there is increasing evidence that excessive or chronic stress can lead to serious health issues. The direct (e.g. absenteeism, healthcare) and indirect (e.g. dealing with friends and family with stress-related illness, decreased productivity) costs were an estimated $33 billion in Canada more than a decade ago (K. MacQueen, 2007). Yet, in spite of significant costs and media attention, effective ways to manage and optimize the human stress response system remain poorly understood. The physiological stress response plays a critical role in mammalian survival and well-being; as the stress response system confers certain biological advantages, experts believe that a healthy stress response system is an important part of normal development and functioning. It is chronic, excessive and/or uncontrolled stress that leads to physical and mental burdens, and resulting health issues. Given the considerable health, economic and social burdens associated with excessive levels of stress, it is not surprising that policy makers and healthcare providers are keen to better understand our stress response system, and to help Canadians manage real and perceived causes of stress and associated stress-related illness.

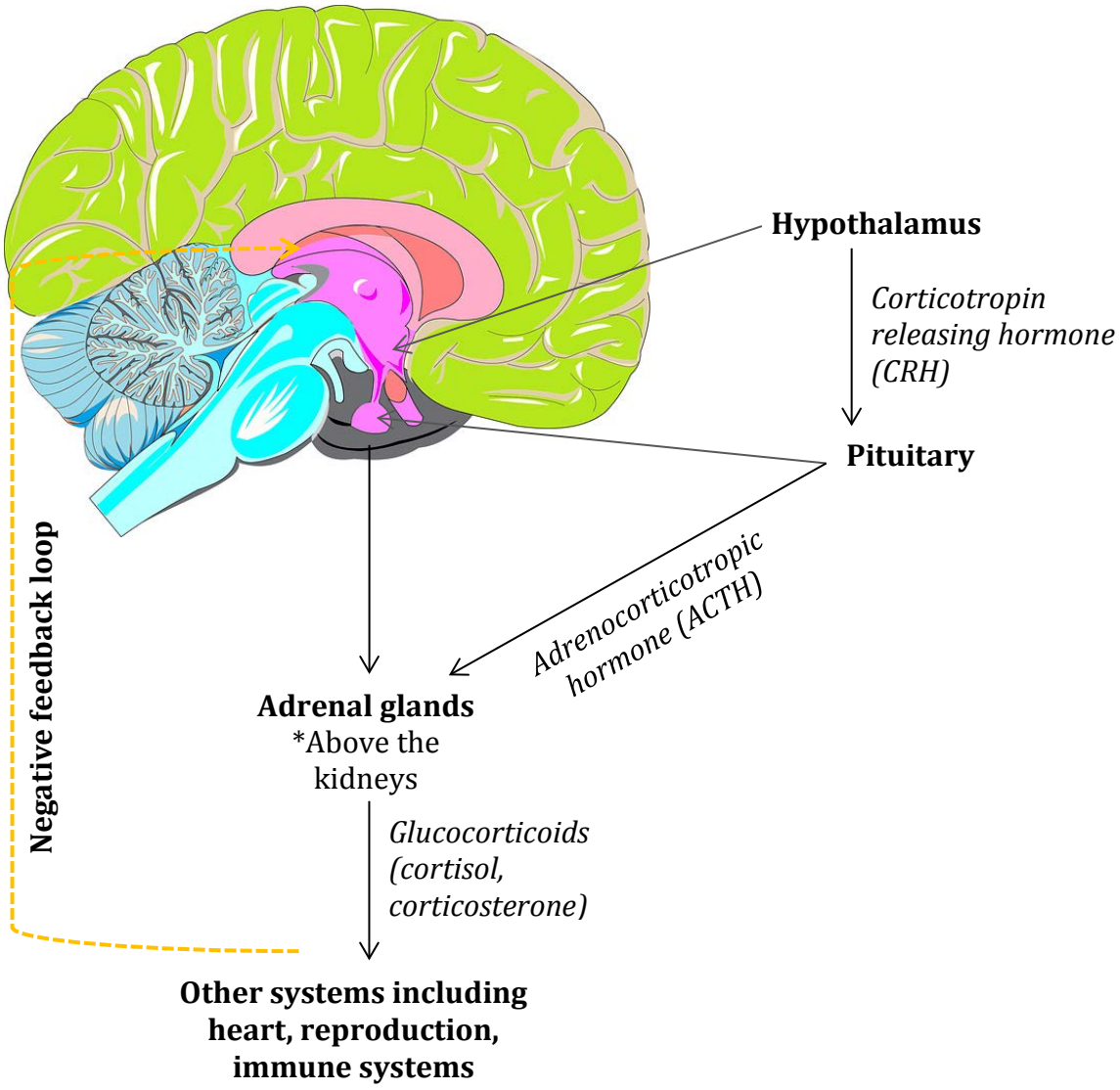
I.B. STRESS IN SOCIETY

I.B.i. THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS

The mammalian brain has evolved to quickly detect, assess and respond to stress – this system confers a distinct biological advantage to animals, and is highly conserved across vertebrate species (Denver, 2009). A stressor is identified when the brain perceives a stimulus that is categorized by the amygdala as potentially harmful. In response to this perceived threat, the sympathetic nervous system activates the hypothalamic-pituitary-adrenal (HPA) axis (Conrad, 2008): the hypothalamus responds with an instant release of corticotrophin-releasing factor, which triggers the pituitary gland and the release of adrenocorticotropic hormone (ACTH), which triggers the adrenal glands which are located just above the kidneys. The adrenal gland is responsible for the second, slower response, involving the release of glucocorticoids (cortisol in humans; corticosterone in non-human animals) and catecholamines including epinephrine (adrenaline) and norepinephrine. This response drives physiological changes that help mammals deal with an immediate threat: increased heart rate pushes blood to muscles, airways in the lung expand to allow for additional oxygen intake and stimulated appetite to encourage eating for additional energy. To compensate for these additional resources required, non-vital (e.g. immune, reproductive) systems are temporarily suppressed. When the perceived threat is over, the hippocampus stimulates a negative feedback loop on the HPA axis, which slows the release of glucocorticoids to normal levels e.g. restores homeostasis (Tafet & Nemeroff, 2016); see Figure I.a, below. This acute stress response is

biologically advantageous, and in addition to readying the body to fight or flee, the system can stimulate additional short-term benefits (McEwen, 2006), including enhanced hippocampal neurogenesis (Kirby et al., 2013) and social bonding (Muroy, Long, Kaufer, & Kirby, 2016). However, when the stress response system is not turned off, there can be long-term negative outcomes.

Figure I.1. The Stress Response System: the hypothalamus-pituitary-adrenal axis



I.B.ii. THE IMPACT OF STRESS ON RODENTS

Chronic stress has been widely studied in non-human animal models, with much data coming from rodent studies. Chronically elevated corticosterone levels are associated with multiple adverse health outcomes including cardiovascular dysfunction (Grippo, Beltz, & Johnson, 2003), cognitive impairment (Grippo et al., 2003; Henningsen et al., 2009) and depressive symptoms (Henningsen et al., 2009; Peng et al., 2012). In fact, chronic mild stress is often used to develop a model of depression in rodent studies (Grippo, Cushing, & Carter, 2007; Grippo, Gerena et al., 2007; Schweizer, Henniger, & Sillaber, 2009; Willner, Muscat, & Papp, 1992). It is likely that these negative effects of chronic stress arise from damage caused by excessive glucocorticoids at the cellular level.

Over the long-term, chronically elevated corticosterone levels are a cause of "allostatic load" (McEwen, 2006), and result in neuronal damage, including decreased dendritic branching and reduction in the number of new neurons (impaired neurogenesis) in the hippocampus (Gould & Tanapat, 1999; Li et al., 2008; Peng et al., 2012; Watanabe, Gould, & McEwen, 1992). Neurogenesis was originally identified in rats several decades ago by Altman & Das (Altman & Das, 1965), and was localized to the olfactory bulb and the dentate gyrus of the hippocampus. In humans, neurogenesis was not confirmed until 1998 (Eriksson et al., 1998), and, to date, has only been verified in the dentate gyrus.

Though the exact function of adult neurogenesis is not fully understood, a larger body of evidence supports a role for neurogenesis in mitigating cognitive interference. Pro-neurogenic factors lead to improved performance on high interference learning and memory tasks, including contextual fear conditioning, and discriminating similar spatial locations and contexts (Creer, Romberg, Saksida, van Praag, & Bussey, 2010; Nakashiba et al., 2012; Sahay et al., 2011; van Praag, Christie, Sejnowski, & Gage, 1999; van Praag, Shubert, Zhao, & Gage, 2005; Wojtowicz, Askew, & Winocur, 2008), while neurogenesis knockdown increases susceptibility to interference, for example, on tests of fine spatial discrimination (Clelland et al., 2009), contextual fear conditioning (Saxe et al., 2006) and retroactive and proactive interference (P. Luu et al., 2012; Winocur, Becker, Luu, Rosenzweig, & Wojtowicz, 2012) in rodents. While some have interpreted these data as supporting a role for neurogenesis in “pattern separation”, defined as generating less overlapping representations for overlapping or similar stimuli, other evidence indicates that neurogenesis contributes to overcoming interference while at the same time actually *increasing* pattern separation (Becker, 2017; Finnegan & Becker, 2015). Further complicating matters, under some circumstances elevated neurogenesis may actually increase interference between newly acquired and previously learned information (Akers et al., 2014). Notwithstanding these unresolved controversies, it is widely agreed that the high plasticity and neurogenic properties of the hippocampus render it one of the most sensitive and malleable brain areas, and hippocampal remodeling may reflect vulnerability to or protection against acute and chronic stress in humans (McEwen, 1999).

I.B.iii. THE IMPACT OF STRESS ON HUMANS

There is substantial evidence that chronic stress can have similarly deleterious effects on humans. Chronic stress has been linked with increased risk of physical health problems, including a suppressed immune system (Segerstrom & Miller, 2004; Selye, 1975) and increased risk of cardiovascular disease (Kivimäki & Steptoe, 2018; Kivimäki et al., 2006). Consistent with studies in rodents, elevated stress and depression scores are associated with impaired performance on tests of executive functioning (Evans & Schamberg, 2009; Öhman, Nordin, Bergdahl, Slunga Birgander, & Stigsdotter Neely, 2007), episodic memory (Öhman et al., 2007), and high interference memory tests (Becker, MacQueen, & Wojtowicz, 2009; Déry, Goldstein, & Becker, 2015; Déry et al., 2013; Goldstein, Déry, Pilgrim, Ioan, & Becker, 2016) in adults. Multiple lines of evidence also implicate chronic stress in the pathogenesis of mood disorders.

Stress is a well-known trigger for the onset of mood disorders, including major depressive disorder (Kendler, Karkowski, & Prescott, 1999; Kessler, 1997). Increased scores on measures of perceived stress (Cohen, Kamarck, & Mermelstein, 1983) and impaired cognitive function (Henningsen et al., 2009; G. M. MacQueen & Memedovich, 2017; McIntyre et al., 2013; Trivedi & Greer, 2014) are commonly reported in patients with MDD. Moreover, the impact of multiple episodes of major depressive disorder is cumulative, and leads to progressive loss of hippocampal volume (Campbell, Marriott, Nahmias, & MacQueen, 2004; McKinnon, Yucel, Nazarov, & MacQueen, 2009). Interestingly, there is some evidence that the efficacy of anti-depressant treatments,

including of selective-serotonin reuptake inhibitor (SSRI) medications, environmental enrichment and exercise, require adequate neurogenesis in rodent models (Bjørnebekk, Mathé, & Brené, 2005; S. Jha, Dong, & Sakata, 2011; Santarelli et al., 2003), while reduced neurogenesis increases the vulnerability to subsequent stress (Snyder, Soumier, Brewer, Pickel, & Cameron, 2011), suggesting a role for decreased neurogenesis in the pathogenesis of major depressive disorder (Jacobs, van Praag, & Gage, 2000; Kempermann, 2002). Taken together, these data suggest strategies that have a positive impact on stress and depression via their impact on neurogenesis may be helpful in the treatment of mood disorders, a prevalent illness with multiple health and functional consequences.

I.C. STRESS AND MENTAL ILLNESS

I.C.i. MOOD DISORDERS: PREVALENCE, DIAGNOSIS AND CAUSES

Mood disorders represent a cluster of diseases with differing, though overlapping, diagnostic criteria. Depressive disorders, including major depressive disorder (MDD) and bipolar disorder (BD), share the diagnostic features of mood dysfunction, and somatic, cognitive and social symptoms (American Psychiatric Association, 2013a) that are expressed by impaired school, occupational, social and/or cognitive functioning (Kessler et al., 2009; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015); refer to Chapters II (Keating et al., 2018) and III for more details. Chronic mood disorders are also associated with increased risk of other health issues (Whiteford et al., 2015) and higher rates of all-cause mortality, including suicide (Angst, Stassen, Clayton, & Angst, 2002; Kupfer, 2005; Walker, McGee, & Druss, 2015).

Mood disorders are common, affecting an estimated 350 million people worldwide (World Health Organization, 2008, 2017). In Canada, the reported prevalence for MDD is 6.5% (Public Health Agency of Canada, 2016), and U.S. data suggests a lifetime prevalence of 16-20% (Kessler et al., 2003; Kessler, Berglunds et al., 2005; Kessler, Chiu, Demler, & Walters, 2005) affecting twice as many women as men (Kessler, 2003). The prevalence of BD in Canada has been estimated to be 0.4 to 1.5% (McDonald et al., 2015; Pearson, Janz, & Ali, 2013), with estimates of 2.2% for lifetime prevalence (Schaffer, Cairney, Cheung, Veldhuizen, & Levitt, 2006). These figures may

underestimate true population rates, as people may have concerns about stigma or may not realize they have a medical condition, therefore may not seek treatment when needed (Kessler, Berglunds et al., 2005; Kessler, Chiu et al., 2005; Moffitt et al., 2010).

There is no single established cause of mood disorders. Though some cases are caused by medical treatment and/or chronic illness, the current thesis will focus on mood disorders as a primary diagnosis, with no known organic or medical cause. There is some evidence for genetic contributions: some rodent strains exhibit depressive behaviours (e.g. anhedonia inferred by decreased sucrose consumption) (Delgado y Palacios et al., 2011; El Yacoubi et al., 2003; Schweizer et al., 2009) while heritability rates from twin studies are estimated at 37-43% for MDD (Sullivan, Neale, & Kendler, 2000) and 60-85% for BD(Kendler, 1983; Smoller & Finn, 2003) (compared to a heritability of 100% for a diagnosis such as Huntington disease with a known genetic cause). Therefore, mood disorders are likely caused by a combination of genetic and environmental (e.g. stress) factors. This heterogeneity of causes and symptoms that characterize mood disorders may partly underlie the challenges associated with treatments for mood disorders.

I.C.ii. FIRST-LINE TREATMENTS FOR MOOD DISORDERS

In keeping with established guidelines, antidepressants, mood stabilizers and psychotherapy are considered first-line agents in the treatment of mood disorders (Lam, Kennedy et al., 2016; Yatham et al., 2013). In clinical settings, response to treatment is often defined as a 50% improvement on a standardized assessment tool score (Riedel et

al., 2010). Using this definition, the response rate to first-line treatment for MDD is only about 50-65% and is often associated with residual symptoms including depressed mood, decreased concentration and hopelessness (Iacoviello, Alloy, Abramson, & Choi, 2010; Kaya, Aydemir, & Selcuki, 2007), and increased risk of relapse (Keller et al., 1992; Nierenberg et al., 2010; Paykel et al., 1994). This pattern of poor response to treatment, high risk of relapse and ongoing residual symptoms has motivated clinicians and health care providers to seek alternative treatment options.

I.C.iii. ADJUNCTIVE TREATMENTS FOR MOOD DISORDERS

When first-line interventions are deemed ineffective, patients and/or their health care providers may seek to add alternative types of treatments for symptoms, including lifestyle strategies (Kennedy et al., 2016). Emerging evidence from studies in humans and rodents suggests that physical exercise is one non-pharmaceutical adjunctive approach that may offer therapeutic benefits over and above those associated with first-line strategies. There have been dozens of articles investigating the possible effects of exercise on symptoms of MDD, with variable methods, participants and results; see Chapters II (Keating et al., 2018) and III for more background information. One recent meta-analysis of randomized trials evaluating the impact of exercise on mood symptoms reported a significant positive effect of exercise across multiple exercise programs, including aerobic, stretching and mind-body (e.g. yoga) interventions (Josefsson, Lindwall, & Archer, 2014). Thus, research in humans and in non-human animal models

suggests that exercise could confer stress, mood and neurocognitive benefits via physiological changes within the brain.

I.D. PHYSIOLOGICAL EFFECTS OF EXERCISE

If stress is a trigger for depression, and exercise is associated with improved symptoms of depression, one would expect a positive impact of exercise on the stress response system. In fact, exercise does appear to mitigate the negative effects of the chronically active HPA system. In rodents, for example, voluntary exercise is associated with increased hippocampal neurogenesis (van Praag, Christie et al., 1999; van Praag, Kempermann, & Gage, 1999), improved cognitive function (Creer et al., 2010; Grace, Hescham, Kellaway, Bugarith, & Russell, 2009; van der Borght, Havekes, Bos, Eggen, & van der Zee, 2007; van Praag, Christie et al., 1999) and protection against the deleterious effects of chronic mild stress (Droste et al., 2003; Droste, Schweizer, Ulbricht, & Reul, 2006; Lalanza et al., 2015).

In addition to moderating the impact of the HPA system, exercise may additionally exert anti-depressant effects via its impact on monoamine neuromodulators. Dopamine, noradrenaline, and serotonin, are three major monoamines that are modulated by exercise (Clark et al., 2015; Lin & Kuo, 2013), while adequate levels of serotonin are required for adult neurogenesis (Klempin et al., 2013). In addition, most anti-depressant medications work by raising levels of dopamine, noradrenaline, and serotonin in the brain (Belmaker & Agam, 2008; Nestler & Carlezon Jr., 2006). These data collectively suggest that exercise-induced neurocognitive benefits may impart benefit and/or resilience to stress and depression, perhaps involving regulation of these neurotransmitters. Thus, exercise-

related benefits for symptoms of mental health may rely on neurological and/or neurochemical changes that impact mood, stress, cognitive and social outcomes.

I.E. PSYCHOLOGICAL EFFECTS OF EXERCISE

In addition to physiological changes, exercise promotes improved cognitive function, mitigates the adverse effects of stress, and reverses cognitive deficits in rodents. Importantly, running is inherently rewarding for rodents; most mice will freely use a running wheel if available (Novak, Burghardt, & Levine, 2012). Voluntary wheel running causes improvements in hippocampal-dependent tests of episodic (Castilla-Ortega et al., 2014), spatial (Patki et al., 2014) and high interference (Winocur et al., 2012) memory in rats. Interestingly, forced exercise is associated with elevated stress in rodents (Greenwood & Fleshner, 2008; Reul et al., 2015; Svensson et al., 2016) though improvements in learning and memory are still observable (Greenwood et al., 2013), suggesting the motivation for engaging in exercise might also affect neurocognitive outcomes.

The impact of exercise on cognitive function in humans is less consistent, possibly related to methodological variability. Sample characteristics represent one challenge: most of the research on cognitive function is focused on older adults who may have age-related cognitive deficits and thus more room for improvement. A second challenge is the assessment of learning and memory: some studies look at only one or two outcome tests, whereas different types of learning and memory are likely differentially impacted by the type of exercise, the extent to which the exercise stimulates cognitive demand, and other non-exercise factor, for example social support (see also Chapter IV). Ideally, a full

cognitive battery will include measures that tap into different brain structures and cognitive abilities, including hippocampally-dependent memory functions (e.g. associative, spatial and episodic memory), neurogenesis-dependent memory functions (e.g. the ability to distinguish between highly similar objects), and prefrontal cortex-mediated executive functions (e.g. working memory, attention, cognitive flexibility and inhibitory control); refer to Chapters III and IV for more information on neurocognitive assessments.

In healthy, older adults, aerobic exercise has been associated with enhanced performance on tests of executive functioning (Vasques, Moraes, Silveira, Deslandes, & Laks, 2011; Weinstein et al., 2012) and spatial memory (Erickson et al., 2011). In a study of middle-aged and older adults with MDD, improved executive functioning has been reported after a single 30-minute aerobic exercise session (Kubesch et al., 2003; Kubesch et al., 2009), while another study failed to detect significant differences in the exercise group after four months of intervention, compared to a placebo (Hoffman et al., 2008). In young and middle-aged adults, high-impact exercise has been associated with improvements on high interference memory tests (Déry et al., 2013; Heisz et al., 2017). Benefits have also been reported for low-impact exercise interventions: a recent meta-analysis reported moderate improvement across several measures of executive function associated with yoga practice (Gothe & McAuley, 2015); see Chapter IV for more details on yoga and neurocognitive outcomes.

Consistent with the rodent literature, multiple studies support a positive effect of exercise on symptoms of mood disorders (e.g. (Josefsson et al., 2014). However, there are many study limitations that preclude making a definitive statement that exercise is an effective treatment for stress and mood outcomes. Most studies employ only a single outcome variable – typically the change in score on a mood symptom scale – and attribute any change to the exercise intervention. Few if any studies investigate other predictor or outcome variables, even though the evidence suggests the relationship between stress, depression, cognitive function, social function and exercise appears to be rather complex. Further, though exercise is often investigated as a potential adjunctive therapy for mood disorders, there is almost no data evaluating exercise in difficult-to-treat, treatment-resistant and/or chronically ill samples of patients; see Chapters II (Keating et al., 2018) and III for more details. Therefore, though studies evaluating the impact of exercise on neurocognitive outcomes are promising, there is much that we still don't know. Moreover, a critical factor that differs significantly between protocols, and has not been explored in detail, is the level of social support in exercise paradigms, and the possible therapeutic effects of social support in outcomes of interest.

I.F. EXERCISE AND SOCIAL FUNCTIONING

Social species, including humans, have evolved to survive as an entity, and therefore, any research that investigates cellular, neural and/or behavioural paradigms should assess the biological foundations which underlie these systems (Cacioppo, Hawkley, Norman, & Berntson, 2011). Accordingly, evidence supports a relationship between social isolation and excessive stress in animals that evolved as social species.

At the cellular level, social isolation is associated with decreased hippocampal neurogenesis (Westenbroek, Den Boer, Veenhuis, & Ter Horst, 2004), as well as brain-derived neurotrophic factor (BDNF) (Murinova, Hlavacova, Chmelova, & Riecansky, 2017), a substance involved in the development and function of the mammalian brain, including neurogenesis (Lee, Duan, & Mattson, 2002; Rossi et al., 2006). Social isolation in a critical early period in mice has been associated with underdeveloped oligodendrocytes in the medial prefrontal cortex (Makinodan, Rosen, Ito, & Corfas, 2012) and decreased dendritic spine density in the medial prefrontal cortex and hippocampus (Silva-Gomez, Rojas, Juarez, & Flores, 2003). Conversely, social interaction has been linked to increased neurogenesis and improved mortality following ischemic brain injury in a mouse stroke model (Venna, Xu, Doran, Patrizz, & McCullogh, 2014).

In terms of neurocognitive and behavioural outcomes, social isolation can be employed in animal studies to generate behavioural (Grippo, Cushing et al., 2007; Zanier-Gomes et al., 2015) and physiological (Grippo, Gerena et al., 2007; Silva-Gomez et al., 2003; Stranahan, Khalil, & Gould, 2006) models of depression in rodents. In addition to cellular damage, social isolation in a critical early period in mice leads to abnormal social behavior and cognitive impairment (Makinodan et al., 2012). Social isolation in humans is associated with multiple health risks including increased rates of coronary heart disease (Valtorta, Kanaan, Gilbody, Ronzi, & Hanratty, 2016) and all-cause mortality (Holt-Lundstad, Smith, & Layton, 2010; House, Landis, & Umberson, 1988). On the other hand, resilience to stress and depression may be enhanced by strong social relationships in non-human (Grippo, Cushing et al., 2007; Grippo, Gerena et al., 2007) and human (Dumont & Provost, 1999; Ozbay et al., 2007; Pietrzak et al., 2014; Wang, Cai, Qian, & Peng, 2014) animals. The stress-reducing effects of social support, as well as the fact that social impairment is a core feature of major depressive disorder, suggests that social factors should be included in studies evaluating neurocognitive and mental health benefits of exercise. Unfortunately, one of the main confounds in the exercise literature is the level of social support across different exercise paradigms; refer to Chapters II (Keating et al., 2018), III and IV for additional information. Another critical variable that is often impaired in mood disorders and not well-researched in the exercise literature is health-related quality of life.

I.G. EXERCISE AND HEALTH-RELATED QUALITY OF LIFE

As noted above, mood disorders are associated with school and/or work performance issues, impaired interpersonal relationships, decreased productivity, social isolation and increased risk of chronic health issues (Kessler et al., 2009; Whiteford et al., 2015). Individuals can exhibit symptoms of a mood disorder at any age. Prodromal symptoms may be observable in childhood, while the diagnosis of MDD or BD typically occurs under the age of 30 (Kessler et al., 2009; Kessler, Berglunds et al., 2005), a time when many people are establishing careers and families. Thus, poorly managed mood disorders can potentially have long-lasting, negative impacts on perceived quality of life.

Research suggests mood disorders are associated with substantial impairment across multiple physical and mental quality of life outcomes (Cass, Volk, & Nease Jr., 1999; Saarni, Suvisaari, Sintonen, & Pirkola, 2007; Spitzer et al., 1995). Further, though scores may indicate remission on a rating scale for depression symptoms, patients may have ongoing impairments in quality of life that affect overall health and well-being (Zimmerman et al., 2012). Thus, there is a need to better assess how treatment strategies impact quality of life outcomes, especially in people with mental illness (IsHak et al., 2011; National Institute of Mental Health, 2015).

There are few studies evaluating the impact of exercise on quality of life outcomes in people with mood disorders. However, in the studies that have investigated this outcome

measure, improvements in quality of life associated with exercise have been reported (Greer et al., 2016), including in patients with treatment-resistant depression (Carta et al., 2008; Mota-Pereira et al., 2011). A recent meta-analysis of exercise for depression reported an effect size on the HRQOL change score of 0.51, though this paper included only six studies with a variety of diagnoses (e.g. minor depression, heart failure, seniors) (Schuch et al., 2016). In addition, a systematic review has identified improved HRQOL associated with exercise across a variety of physical conditions, including cancer and obesity (Penedo & Dahn, 2005; U.S. Department of Health and Human Services, 1996). Thus, the evidence suggests that regular exercise does have a positive impact on HRQOL, with a need for more research evaluating this outcome measure in adults with a primary diagnosis of a mood disorder.

I.H. CURRENT DISSERTATION: HYPOTHESES AND OVERVIEW OF RESEARCH

The literature on the benefits of exercise in mood disorders reviewed above indicates that there are several knowledge gaps. Firstly, although regular exercise is associated with improved feelings of depression, there are limited data on functional outcomes including social function, cognitive function and quality of life. This gap is particularly important for the treatment of mood disorders, where lingering social and cognitive impairments that impact functioning and quality of life often persist even after mood symptoms have improved. Secondly, another gap for clinical populations, the exercise data almost entirely excludes patients with chronic, recurrent and/or difficult-to-treat mental illness. In addition, the vast majority of studies investigating the benefits of exercise do not evaluate the impact of social support, which could be contributing to positive results. Finally, participation in a high-impact exercise program could be difficult for people with mood disorders, who may experience excessive worry about novel situations, and for older patients, who may not be able to meet the physical demands and/or for those who are prone to pain or injury. Thus, though the literature is promising, more data are needed to confirm the mental health and neurocognitive benefits of regular exercise.

The objective of the current dissertation is to address these knowledge gaps, by looking at the impact of exercise across multiple neurocognitive and functioning outcomes, including social support, in clinical and non-clinical samples. Specifically, this dissertation addresses the following knowledge gaps:

1) Study 1 (Chapter II): In a retrospective chart review, we evaluated the impact of a structured running program in youth and adults with complex psychiatric histories, to determine the potential therapeutic role of exercise in treatment-resistant populations, which are often characterized by lingering non-mood symptoms, and to explore the impact of clinical factors and perceived friendship on outcomes;

2) Study 2 (Chapter III): In a prospective observational study, we evaluated the impact of exercise on cognitive outcomes, health-related quality of life and social functioning in a subset of the sample from study 1, to better understand how exercise impacts multiple areas of dysfunction in youth and adults with difficult-to-treat mood disorders, and;

3) Study 3 (Chapter IV): In a prospective, randomized control trial, we evaluated the potential impact of yoga as an alternative form of exercise that may have fewer barriers for patients with mood disorders and added benefits such as mindfulness, on outcomes of stress, mood, health-related quality of life, social functioning and perceived social support in healthy adults. Using a yoga exercise program also provided an opportunity to explore the role of mindfulness, an inherent element of guided yoga, on study outcomes.

The results from the current dissertation will help address the knowledge gaps surrounding exercise and neurocognitive outcomes, to better understand the complex relationship between exercise, stress, social function, cognitive function and health-related quality of life. Results will help health-care providers better inform people what benefits can realistically be expected from participating in a regular exercise program.

Introduction to Chapter II

The prospective study presented in Chapter III (Study 2) had been going for about a year when I started my PhD. Therefore, in order to better understand the patients and the program, I joined the Team Unbreakable program as a volunteer, joining adult and youth groups on weekly runs. It was during these sessions that I noticed a few things: 1) Participants seemed to enjoy socializing with each other; 2) There were frequent complaints of pain and/or injury; 3) Every week, participants completed the Beck Depression Inventory, the Beck Anxiety Inventory, Cohen's Perceived Stress Scale and a Running Log tool created by the clinical team, reflecting their mood, stress, anxiety and feeling of friendship with group members; and, 4) Occasionally, people came to the sessions even when they were injured and couldn't run. This last observation really struck me: something other than the running was motivating attendance, and it was very likely related to the social support of the program, for at least some of the participants. I then realized that, even though only a subset of patients joined the prospective study, we had a collection of mood outcomes, representing multiple measures over time, that were not being included in the prospective study. So, I approached my thesis committee with the idea to evaluate these data points, to maximize the information we could collect about the program. Everyone was very enthusiastic, and the chart review study began.

I completed the ethics documents, and obtained approval to do the study. From there, I entered hundreds of data points that had been collected at the weekly sessions. In

addition, on the Running Log form which had the question asking participants to rank the Level of Friendship with the group, there was a space for comments. So I collected the comments in order to do a qualitative assessment of the Team Unbreakable experience.

I performed all of the data analyses, with feedback on methodological issues from my supervisors and committee members. Then, I assumed responsibility for writing the manuscript, again with feedback from my committee. I also took responsibility for the formatting, submission and all other aspects of getting the paper to print.

All of the authors on the final manuscript played an important role in getting this study to print. In addition to the support and guidance of my supervisors and committee members, outlined above, all of the authors read and approved the final manuscript. Additionally, Katie, Jeff and Laura Garrick helped with organization of the data, and with the management of the running group, including collecting and helping with clarifying the methodology section. All authors also provided feedback on several poster presentations over the years, helping to refine the final manuscript. Dr. Margaret McKinnon, co-supervisor, was also instrumental in helping to define the process for collecting information on clinical diagnosis and maximizing the integrity of the study.

The final paper was published in the journal *BMJ Open Sport & Exercise Medicine* in June 2018 (see next section).

BMJ Open Sport & Exercise Medicine

Effects of a 12-week running programme in youth and adults with complex mood disorders

Laura E Keating,[1] Suzanna Becker,[1,2] Katie McCabe,[3,4] Jeff Whattam,[4] Laura Garrick,[4] Roberto B Sassi,[1,3,4] Benicio N Frey,[1,3,4] Margaret C McKinnon[1,3,4,5]

To cite: Keating LE, Becker S, McCabe K, *et al*. Effects of a 12-week running programme in youth and adults with complex mood disorders. *BMJ Open Sport & Exercise Medicine* 2018;**4**:e000314. doi:10.1136/bmjsem-2017-000314

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/10.1136/bmjsem-2017-000314)

Accepted 16 April 2018

Check for updates

[1]McMaster Integrative Neuroscience and Discovery, McMaster University, Hamilton, Canada
[2]Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, Canada
[3]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Canada
[4]Mood Disorders Program, St Joseph's Healthcare Hamilton, Hamilton, Canada
[5]Homewood Research Institute, Guelph, Canada

Correspondence to
Dr Margaret C McKinnon, ;
mmckinno@stjosham.on.ca

ABSTRACT

Objective Although numerous studies suggest a salutary effect of exercise on mood, few studies have explored the effect of exercise in patients with complex mental illness. Accordingly, we evaluated the impact of running on stress, anxiety and depression in youth and adults with complex mood disorders including comorbid diagnoses, cognitive and social impairment and high relapse rates.

Methods Participants were members of a running group at St Joseph Healthcare Hamilton's Mood Disorders Program, designed for clients with complex mood disorders. On a weekly basis, participants completed Cohen's Perceived Stress Scale, Beck Depression Inventory (BDI) and Beck Anxiety Inventory (BAI) questionnaires, providing an opportunity to evaluate the effect of running in this population.

Results Data collected for 46 participants from April 2012 to July 2015 indicated a significant decrease in depression ($p<0.0001$), anxiety ($p<0.0001$) and stress ($p=0.01$) scores. Whereas younger participant age, younger age at onset of illness and higher perceived levels of friendship with other running group members ($ps\leq0.04$) were associated with lower end-of-study depression, anxiety and stress scores, higher attendance was associated with decreasing BDI and BAI ($ps\leq0.01$) scores over time.

Conclusions Aerobic exercise in a supportive group setting may improve mood symptoms in youth and adults with complex mood disorders, and perceived social support may be an important factor in programme's success. Further research is required to identify specifically the mechanisms underlying the therapeutic benefits associated with exercise-based therapy programmes.

What are the new findings?

- ► A group-based running programme provided therapeutic benefit to youth and adults with complex mood disorders, characterised by comorbid diagnoses, ongoing cognitive and social impairment and high relapse rates.
- ► The therapeutic benefits of a structured group exercise programme may be impacted by higher attendance, social support and younger participant age.
- ► Clinical features of mental illness, such as age at onset of illness, may also impact programme outcomes.

BACKGROUND

Mood disorders are a prevalent and costly social and health issue affecting 350 million people worldwide.[1] In keeping with established guidelines, antidepressants, mood stabilisers and psychotherapy are considered first-line agents in the treatment of depression and bipolar disorder (BD).[2 3] The response rate to first-line treatment for major depressive disorder (MDD), however, is only about 50%–65% and is associated with significant relapse.[4] Moreover, although approximately 33% of persons are expected to recover fully following first-line treatment,[5] remission is often characterised by residual symptoms including depressed mood, decreased concentration and hopelessness in MDD[6] and in BD[7] and higher rates of mortality across all-cause mortality.[8 9] Medication adherence in patients with mood disorders remains low, ranging from 30% to 70% for antidepressants and from 18% to 52% for mood stabilisers.[10 11] Antidepressant treatment costs represent an additional mental health burden in Canada, having ballooned from $31.4 million in 1981[12] to an estimated $1.2 billion in 2005.[13] These figures suggest that more effective treatment options are needed urgently for the management of mood disorders.

Aerobic exercise as a possible therapeutic intervention for complex mood disorders is supported by several lines of evidence. In animal models, as depressive symptoms increase, physical function decreases; conversely, decreased physical function is associated with increased depressive-like behaviour.[14] In humans, some studies have reported a positive improvement in depressive symptoms after the adoption of exercise across youth[15] and adults[16–19] with MDD; other studies have reported no significant effects in MDD symptoms compared with non-exercising[20] or placebo (stretching)[21] groups. A

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

recent meta-analysis of 15 randomised trials evaluating the effect of exercise on MDD found a significant effect of exercise across a variety of measures of depression, with a mean effect size of 0.77 for all studies and of 0.43 for studies that met higher methodological criteria.[22] Methodological variability may partly underlie the discrepancy of results, including exercise duration and type (aerobic vs non-aerobic) and level of social interaction (e.g., minimal,[21 23] supervised[16 19 21 23] or group-based).[15 24 25] Critically, there also remains little information about the potential therapeutic benefits of exercise on complex mood disorders, including those that are treatment resistant, as most randomised controlled trials exclude individuals with previous poor treatment response.[16 23 26] Moreover, studies that have included participants with treatment-resistant mood disorders did not evaluate the impact of clinical history (e.g., illness duration and comorbid diagnoses) on treatment response.[18 27]

To address the above gaps in the literature, we investigated the impact of exercise in youth and adults with complex clinical histories and treatment-resistant mood disorders, as these patients are rarely included in clinical trials. Since April 2012, a multidisciplinary clinical team in the Mood Disorders Program, St Joseph's Healthcare Hamilton (Hamilton, Ontario) has offered a 12-week group-based recreational running programme aimed at enhancing clinical outcomes in youth and adults with mood and anxiety disorders. As part of the programme evaluation, the team collected weekly self-report measures of stress, anxiety and depression and perceived social support, which provided an opportunity to evaluate the impact of running in youth and adults in a sample that included complex mood disorders. The primary goal of the current study was to assess the impact of a structured aerobic exercise programme on measures of stress, anxiety and depression over 12 weeks in youth and adults with complex mood disorder histories. The secondary objectives were to explore the impact of demographic and clinical factors including: (1) participant age; (2) attendance; (3) clinical history; and (4) perceived social support on outcome measures of stress, anxiety and depression.

METHODS

The current study is a retrospective chart review analysing data that were collected as part of the ongoing evaluation of the Team Unbreakable running group programme. Data were available for participants from August 2012 to July 2015, which spanned 11 running group sessions (see table 1).

Participants

Participants were 46 running group members at St Joseph Healthcare Hamilton's Mood Disorders Program, organised as part of a novel treatment programme for clients with mood disorders in the Hamilton community. Participants were allocated to a youth (n=29; 16–25 years) or adult (n=17; >25 years) group based on their age. Recruitment methods included flyers in and around the hospital and distributing information to local clinics. Referral criteria included: history of BD, MDD or anxiety disorder, including those not in full remission and/or with comorbid diagnoses, and the ability to participate in a 12-week running programme, confirmed by the Physical Activity Readiness Questionnaire (PAR-Q & You).[28] The primary clinical diagnosis of mood disorder was confirmed from review of the patient medical record. A total of 10 participants were excluded from the analyses due to missing diagnostic information in the medical chart (n=8) and the absence of a primary diagnosis of a mood disorder (n=2; one had general anxiety disorder and one had schizoaffective disorder).

Table 1 Characteristics of the running groups

Group	Starting date	Age	Female, n (%)	Number of runners
1	April 2012	Youth	5 (62.5)	8
2	August 2012	Youth	5 (71.4)	7
3	April 2013	Youth	3 (75.0)	4
4	August 2013	Adult	5 (83.3)	6
5	September 2013	Youth	2 (100)	2
6	April 2014	Adult	3 (100)	3
7	April 2014	Youth	0 (0)	3
8	August 2014	Adult	3 (75.0)	4
9	September 2014	Youth	4 (100)	4
10	March 2015	Adult	4 (100)	4
11	March 2015	Youth	1 (100)	1
Total			35 (76.1)	46

Clinical assessments

Beck Depression Inventory second edition (BDI-II; PsychCorp)[29]: a 21-item self-report questionnaire used to assess depressive symptoms.

Beck Anxiety Inventory (BAI; PsychCorp)[30]: a 21-item self-report questionnaire used to assess symptoms of anxiety.

Cohen's Perceived Stress Scale (PSS)[31]: a 10-item self-report questionnaire measuring the degree to which situations are perceived as stressful.

36-Item Short Form Survey (SF-36)[32 33]: a 36-item self-report assessment that measures health-related quality of life. The survey generates a score that can be subdivided into eight subscales: limitations in physical activities, limitations in social activities due to physical health, limitations in usual activities due to physical health, bodily pain, general mental health, limitations in usual activities due to emotional problems, vitality and general health perceptions.

Running log assessments

Before and after every run, participants rated their mood, energy level, enthusiasm, stress and feelings of friendship with other group members on a scale of 0–10. This survey

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

included a question asking participants to rate their level of connection with the group, which provided an estimate of perceived social support.

Running protocol

Participants met twice per week and progressed from mostly walking to mostly running. In the 13th week, participants completed a local 5 km run as a group. Weekly sessions included motivational talks across a range of topics such as mental illness, running strategies, nutrition and mindfulness. The sessions also provided an opportunity for participants to interact with each other, the clinical leads (recreation therapist (JW) and social worker (KM)), and volunteers comprised of hospital staff, faculty and graduate students. The programme was flexible to meet the needs of the participants but started out as a 1-km session of 30 s running and 2 min walking. Each week, the participants went a little farther and increased the time spent running by 30–60 s. The goal was to work up to mostly running for 5 km by week 12.

Statistical analyses

The primary objective was evaluated using: (1) a mixed-model repeated-measures analysis of variance (ANOVA) to evaluate BDI, BAI and PSS score changes over time and (2) assessment of remission and response of BDI scores. Due to variable attendance of participants, there were large amounts of missing data at random time points, resulting in varying sample sizes across analyses. A mixed-model approach was chosen as it is more effective at handling missing data than the general linear model,[34] provided the time points of the missing data are random,[35] and does not assume that repeated observations over time are independent.[34] Remission and response were defined as follows: total BDI <12 to define *remission* of depressive symptoms and a decrease of 50% from baseline to end of study in BDI score to define *response*.[36] The Cochran-Mantel-Haenszel χ^2 was used to assess movement across the BDI ranges (absent, low, moderate and high) from baseline to end of study.[37]

Secondary objectives were assessed using autoregression analyses to identify predictors of BDI, BAI and PSS score changes over time. Factors assessed included age, gender, attendance, age of illness diagnosis (the age the participant first received counselling or medication), comorbid diagnoses and perceived social support. Clinical history was obtained through medical record review. We explored the impact of perceived social support using the responses to the question 'Level of friendship with other group members', which the participants scored on a scale of 1–10 in the Running Log tool. The Running Log social support question was validated by comparing results with the social subscale of the SF-36, which was available for a subset of participants. Finally, we evaluated single item responses of the BDI and the BAI using the mixed-models method to investigate the effect of the running therapy programme on single items of possible clinical significance. All analyses were performed using SAS V.9.4 for Windows.

RESULTS

There were fewer male (11; 23.9%) than female (35; 76.1%) participants; χ^2=12.5, df=1, p=0.0004. The average (±SD) age of the adult group was 45.2 (±12.9) years, and the average age of the youth group was 22.1 (±5.8) years. All patients had a primary diagnosis of a mood disorder. Clinical and demographic data were available for 46 participants and are summarised in table 1. The primary diagnoses for the current sample were major depressive disorder (n=29), BD (n=13), major depressive disorder and dysthymia (n=3) and dysthymia (n=1). In addition, 10 participants had current suicidal ideation, 6 had a history of psychotic symptoms and 25 of the participants had one or more comorbid psychiatric diagnoses.

Mixed-model repeated measures analysis: depression, anxiety and stress scales over time

A mixed-model repeated measures ANOVA of BDI scores revealed a significant decrease in depressive symptoms from baseline to end of study (F=4.5, df=11, 201, p<0001), observable for the youth (F=2.1, df 11, 118, p=0.02) and adult groups (F=4.3, df 11, 72; p<0.0001). Results were similar for BAI (F=4.8, df=11, 186, p<0.0001) and PSS (F=2.3, df=11, 186, p=0.01) scores; results held when adults and youth were analysed separately (see figure 1).

Remission: BDI scores were categorised by levels of depression as absent (≤12); low (13–19); moderate (20–28) and high (≥29).[29] BAI scores were classified as absent (≤9), low (10–18), moderate (19–29) and high (≥30).[38] From baseline to end of running session, there was a decline in the number of participants with moderate or severe BDI scores, with corresponding increases of participants in the low and absent categories. A similar pattern of results was identified for BAI scores (see table 2).

Response to treatment

In adults, baseline compared with end of study BDI scores were 30.8 (±14.5; range 10–58; sample size n=12) versus 18.8 (±12.6; range 11–41; sample size n=5), an overall decrease of approximately 39%. In youth, baseline compared with end-of-study BDI scores were 26.9 (±13.0; range 2–48; sample size n=23) versus 19.5 (±15.5; range 0–59; sample size n=15), an approximately 27% decrease. Nineteen participants had both baseline and end-of-study data available; of these, five participants (26.3%) showed a decrease of 50% or more in their post-BDI score.

Secondary objectives

Autoregression analyses were used to explore the impact of participant age, age at diagnosis, number of comorbid diagnoses and perceived social support (level of friendship with the group) on stress, anxiety and depression. Perceived social support was estimated by the postrunning 'Level of friendship' item in the Running Log. In

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

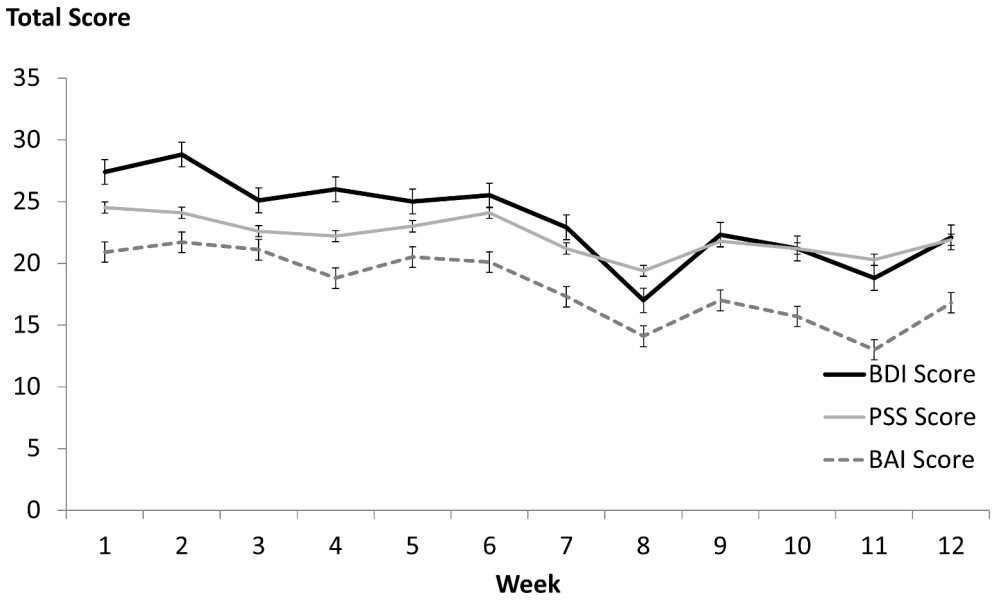


Figure 1 Stress, anxiety and depression scores over time. Figure 1 illustrates the changes in self-report scores of the BDI (solid black line), PSS (solid grey line) and BAI (dashed black line) scores in participants over time. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; PSS, Perceived Stress Scale.

order to validate this variable, we assessed the correlation between the end-of-study postrunning level of friendship score and relevant subscales of the SF-36 questionnaire available for a subset of participants (n=18) and identified correlations between level of friendship and SF-36 mental health subscales of social func tioning (r=0.41, p=0.001), role of emotions in functioning (r=0.37, p=0.003), vitality (r=0.45, p=0.0002) and mental health (r=0.46, p=0.0002). Perceived level of friendship with the group after running was predictive of BDI (t=−4.0 p<0.0001), PSS (t=−2.1, p=0.04) and BAI scores (t=−3.6, p=0.0003), where higher levels of perceived friendship were associated with lower scores on all measures from week 1 to week 12. Attendance was also a significant predictor of mood scores, where higher attendance predicted lower BDI (t=−2.5 p=0.01) and BAI (−3.4, p=0.007) scores, with a trend for lower stress scores (t=−1.7, p=0.084). Age at onset of illness significantly predicted BDI (t=9.4, p<0.0001), BAI (t=6.2, p<0.0001) and PSS (t=6.3, p<0.0001) scores; an earlier age of illness onset was associated with decreased depression, anxiety and stress scores from baseline to end of study. Age was a significant predictor of BDI (t=5.9, p<0.0001), BAI (t=3.3, p=0.001) and PSS (t=6.6, p<0.0001) scores; younger age was associated with lower mood scores over time.

Table 2 Remission rates of baseline compared with end-of-study depression and anxiety scores

	Baseline (n=35) (n (%))	End of study (n=20) (n (%))	Change (%)	Comparison
BDI scores				
High	16 (45.7)	4 (20.0)	−43.8	χ^2= 6.9, df=3, p=0.08
Moderate	10 (28.6)	4 (20.0)	−30.0	
Low	5 (14.3)	6 (30.0)	+52.3	
Absent	4 (11.4)	6 (30.0)	+62.0	
BAI scores				
High	10 (32.2)	1 (4.4)	−86.3	χ^2= 4.6, df=3, p=0.03
Moderate	8 (25.8)	5 (21.7)	−15.9	
Low	5 (16.1)	6 (26.1)	+38.3	
Absent	8 (25.8)	11 (47.8)	+46.0	

BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory.

Programme compliance

The attendance rate was 49.2% (±27.5); not significantly higher for adults (55.0% (±24.6)) compared with youth (44.8% (±28.6); t=1,2, df=44; p=0.2). We split the group into high (attended more than 50% of running sessions, n=23) and low (attended 50% or less running sessions, n=23) attenders and observed a non-significant difference in end-of-programme BDI scores, with those that attended more frequently having lower scores (16.2±14.7) compared with those that attended less frequently (28.8±9.7; t=−1.8, df=23, p=0.092). However, as illustrated in figure 2, this result may be influenced by high variability of the low attendance group.

Additional analyses for this study can be reviewed in the online supplementary data.

DISCUSSION

The results from the present study suggest that adults and youth with complex mood disorders can benefit from a running therapy programme that is supervised by clinical professionals in a group setting that offers social support. Interventions such as exercise are being promoted as having therapeutic benefits to youth and adults with mood disorders.[22] However, most research

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

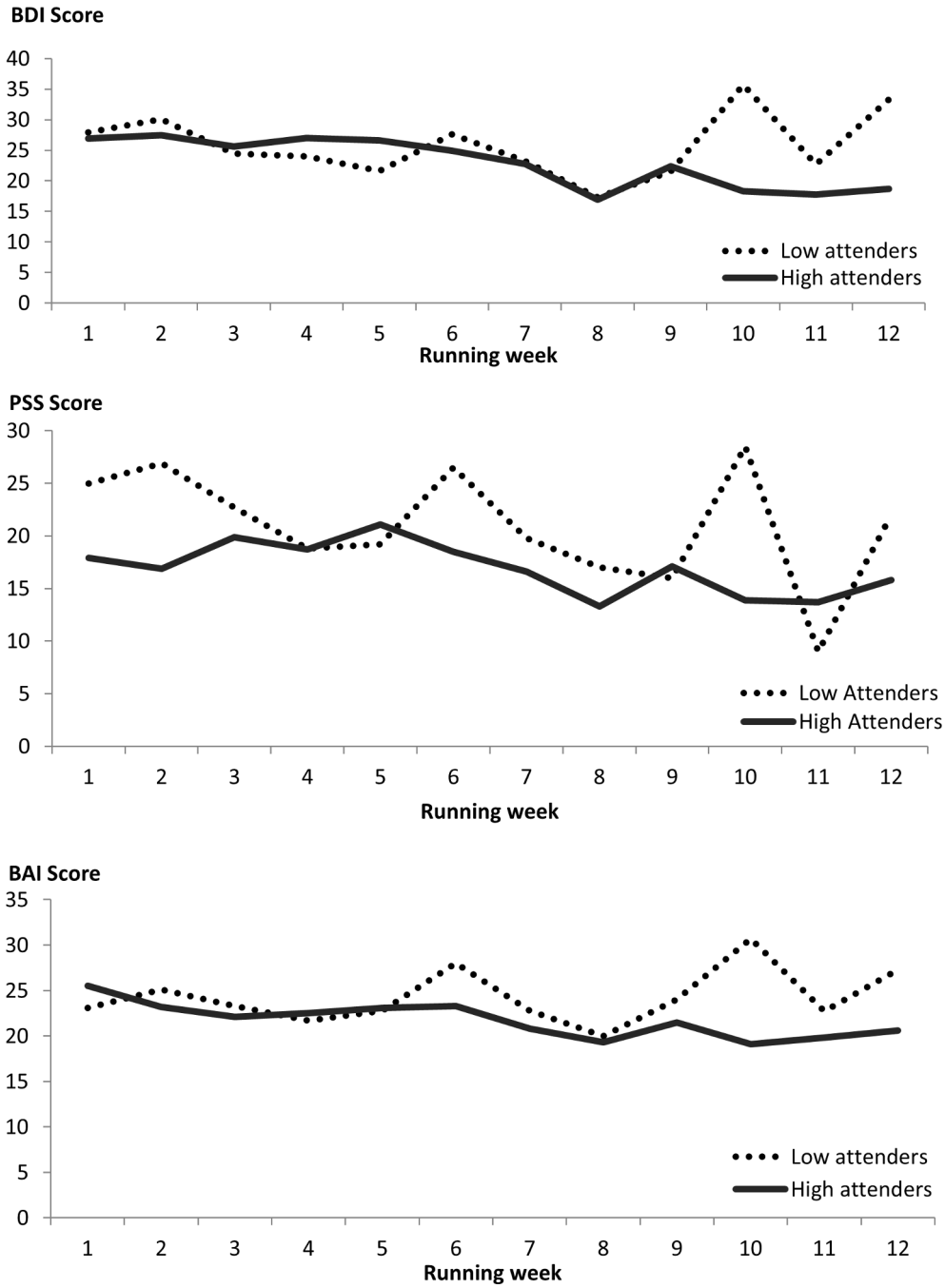


Figure 2 Changes in scores for the BDI (top graph), PSS (middle graph) and BAI (bottom graph) for high and low attenders. Top graph: BDI scores for participants who attended 50% or fewer (dotted black line) compared with more than 50% (solid grey line) sessions over the 12 weeks of the running therapy sessions. Middle graph: PSS scores for participants who attended 50% or fewer (dotted black line) compared with more than 50% (solid grey line) sessions over the 12 weeks of the running therapy sessions. Bottom graph: BAI scores for participants who attended 50% or fewer (dotted black line) compared with more than 50% (solid grey line) sessions over the 12 weeks of the running therapy sessions. BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; PSS, Perceived Stress Scale.

in this area is based on first-episode patients and/or excludes participants with treatment-resistant depression and BD.[39] Critically, this work also rarely evaluates the impact of exercise in terms of clinical outcomes, nor is there research on exercise type, intensity, the role of social support and/or the impact of exercise on functional outcomes.[40] In the current study, we found engagement in a group running programme improved mood symptoms including depression, anxiety and stress in participants with complex mood disorders, over a period of 12 weeks. This finding held for both adult and youth participants with MDD and BD, indicating the running group programme had a positive impact on self-reported symptoms of depression over time. Multiple subitems within the depression inventory also improved over time, including energy, irritability,

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

self-worth and pessimism (refer to online supplementary data). These findings are consistent with previous reports of increased energy and self-esteem levels in adults,[22] even after as little as one running session.[41] Improved mood scores were predicted by younger age, earlier age at onset of mood disorder, as well as higher attendance to the running programme. We also observed a positive impact of the running therapy programme on perceived social support, as reflected by the relationship between increased feelings of friendship and decreased mood scores, suggesting that the opportunity to connect with peers through the running group may positively impact mood outcomes. Given that social dysfunction is a core symptom of mood disorders, the perceived social support in a structured running programme may help improve psychosocial outcomes in this population.[42]

There is abundant research on the positive impact of aerobic[15 16 18 21 25] and non-aerobic (stretching and yoga)[16 27 43] exercise on symptoms of depression, and results have been shown across varying methodologies, samples, exercise programme and assessment strategies. However, most studies exclude complex and/or treatment-resistant populations and do not investigate the impact of other contributing factors such as programme adherence or perceived social support in group or supervised settings. Accordingly, there are knowledge gaps on exercise as a potential therapeutic option for individuals with mood disorders, especially complex forms with comorbid diagnoses and poor response to treatment.

Although the results reported here are encouraging, they should be considered a starting point for further investigation. The large amounts of missing data were a limiting factor for data analyses and interpretation of results. The social support finding, although interesting, was based on an informal tool. Therefore, further research is warranted, using validated questionnaires, to explore the role of perceived social support in structured exercise programme. It is noteworthy that, despite methodological limitations, we identified several positive findings that could result in short-term and long-term clinical and functional benefits to patients with complex mood disorders. As such, the findings reported here should be a starting point for future randomised control trials designed to better understand the potential therapeutic benefits of exercise across the spectrum of mood disorder diagnoses symptoms.

In spite of limited data on clinically relevant variables such as age at onset of illness and comorbid diagnoses, these results also suggest that clinical history may influence outcomes of running for youth and adults with complex mood disorders. Somewhat counterintuitively, we found that both earlier age at onset of illness as well as younger age were associated with lower BDI scores over time. It is possible that the adult group represents a more treatment-resistant form of mood disorder in the current study; future research is recommended to further explore this finding.

CONCLUSIONS

In a sample of youth and adults with complex mood disorders, we demonstrated a positive impact of aerobic exercise on symptoms of depression in a supportive group setting over a 3-month period. The results indicate a need for future research of the long-term effects of aerobic exercise in youth and adults with chronic, recurrent and/or treatment-resistant mood disorders to better understand possible therapeutic effects of a structured exercise programme. Moreover, the impact of clinical factors such as age at onset of mood disorder, duration of illness and comorbid diagnoses as well as perceived social support should be explored to determine how these factors impact outcomes. Future randomised trials are warranted to identify when exercise may be useful as a therapeutic option for patients with chronic and/or treatment-resistant mood disorders, and what clinical and improvements can reasonably be expected in this population.

Acknowledgements We would like thank running coach volunteers Jenna Boyd, Lauren Cudney, Beth Kennedy, Kathryn Litke, Anthony Nazarov, Melissa Parlar and Ryan Pyrke. Esther Pauls from the Running Den is also thanked for her assistance with group leadership. We would also like to acknowledge Danielle Berman from the Ride Away Stigma campaign's fundraising effort.

Contributors LEK was the primary author and performed the majority of the assessments and all of the data analyses. SB was involved in the design of the study, in particular surrounding cognitive assessments, and provided direction to the analyses, interpretation of findings, and writing of the paper. KM, JW and LG assisted with design of the running programme, recruitment of participants and weekly data collection; BNF was involved with the design of the study, providing advice for data analyses and interpretation and for writing of the manuscript; RS was coprincipal Investigator on this study. He was involved in the design of the study and provided guidance surrounding data analyses and interpretation and writing of the manuscript. MM was coprincipal investigator on this study. She was involved in the design of the study provided directions surrounding clinical assessments, interpretation of the findings and writing of the manuscript. All authors read and approved the final manuscript.

Funding St Joseph's Healthcare Hamilton Foundation provided funding to support this study; specifically, we wish to acknowledge the following donors: Ontario Endowment for Children & Youth Recreation Fund at the Hamilton Community Foundation; Canadian Tire Financial Services; FGL Sports Ltd; Telus; and Jackman Foundation.

Competing interests None declared.

Patient consent Not required.

Ethics approval This study was reviewed and approved by the Hamilton Integrated Research Ethics Board (HIREB), reference number 14-671-C. Informed consent was not obtained from the participants of this study as the data were collected as a retrospective chart review.

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement The authors do not have additional, unpublished data from the study to share with other researchers.

Open access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

REFERENCES

1. World Health Organization. *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland: World Health Organization, 2008.
2. Kennedy SH, Lam RW, McIntyre RS, *et al*. CANMAT Depression Work Group. Canadian network for mood and anxiety treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. pharmacological treatments. *Can J Psychiatry* 2016;61:540–60.
3. Yatham LN, Kennedy SH, Parikh SV, *et al*. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord* 2013;15:1–44.
4. Keller MB*et al*. Time to recovery, chronicity, and levels of psychopathology in major depression. *Arch Gen Psychiatry* 1992;49:809–16.
5. Trivedi MH, Rush AJ, Wisniewski SR, *et al*. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28–40.
6. Iacoviello BM, Alloy LB, Abramson LY, *et al*. The early course of depression: a longitudinal investigation of prodromal symptoms and their relation to the symptomatic course of depressive episodes. *J Abnorm Psychol* 2010;119:459–67.
7. Kaya E, Aydemir O, Selcuki D. Residual symptoms in bipolar disorder: the effect of the last episode after remission. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:1387–92.
8. Angst F, Stassen HH, Clayton PJ, *et al*. Mortality of patients with mood disorders: follow-up over 34-38 years. *J Affect Disord* 2002;68(2-3):167–81.
9. Kupfer DJ. The increasing medical burden in bipolar disorder. *JAMA* 2005;293:2528–30.
10. Scott J, Pope M. Nonadherence with mood stabilizers: prevalence and predictors. *J Clin Psychiatry* 2002;63:384–90.
11. Scott J, Pope M. Self-reported adherence to treatment with mood stabilizers, plasma levels, and psychiatric hospitalization. *Am J Psychiatry* 2002;159:1927–9.
12. Hemels ME, Koren G, Einarson TR. Increased use of antidepressants in Canada: 1981-2000. *Ann Pharmacother* 2002;36:1375–9.
13. Mood Disorders Society of Canada. *Quick Facts: Mental Illness & Addiction in Canada*. Guelph, ON, 2009.
14. Greenwood BN, Fleshner M. Exercise, learned helplessness, and the stress-resistant brain. *Neuromolecular Med* 2008;10:81–98.
15. Nabkasorn C, Miyai N, Sootmongkol A, *et al*. Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. *Eur J Public Health* 2006;16:179–84.
16. Blumenthal JA, Babyak MA, Moore KA, *et al*. Effects of exercise training on older patients with major depression. *Arch Intern Med* 1999;159:2349–56.
17. Babyak M, Blumenthal JA, Herman S, *et al*. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosom Med* 2000;62:633–8.
18. Knubben K, Reischies FM, Adli M, *et al*. A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. *Br J Sports Med* 2007;41:29–33.
19. Trivedi MH, Greer TL, Church TS, *et al*. Exercise as an augmentation treatment for nonremitted major depressive disorder: a randomized, parallel dose comparison. *J Clin Psychiatry* 2011;72:677–84.
20. Bonhauser M, Fernandez G, Püschel K, *et al*. Improving physical fitness and emotional well-being in adolescents of low socioeconomic status in Chile: results of a school-based controlled trial. *Health Promot Int* 2005;20:113–22.
21. Blumenthal JA, Babyak MA, Doraiswamy PM, *et al*. Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosom Med* 2007;69:587–96.
22. Josefsson T, Lindwall M, Archer T. Physical exercise intervention in depressive disorders: meta-analysis and systematic review. *Scand J Med Sci Sports* 2014;24:259–72.
23. Krogh J, Videbech P, Thomsen C, *et al*. DEMO-II trial. Aerobic exercise versus stretching exercise in patients with major depression-a randomised clinical trial. *PLoS One* 2012;7:e48316.
24. Veale D, Le Fevre K, Pantelis C, *et al*. Aerobic exercise in the adjunctive treatment of depression: a randomized controlled trial. *J R Soc Med* 1992;85:541–4.
25. Annesi JJ. Changes in depressed mood associated with 10 weeks of moderate cardiovascular exercise in formerly sedentary adults. *Psychol Rep* 2005;96(3 Pt 1):855–62.
26. Daley AJ, Copeland RJ, Wright NP, *et al*. Exercise therapy as a treatment for psychopathologic conditions in obese and morbidly obese adolescents: a randomized, controlled trial. *Pediatrics* 2006;118:2126–34.
27. Mather AS, Rodriguez C, Guthrie MF, *et al*. Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder: randomised controlled trial. *Br J Psychiatry* 2002;180:411–5.
28. Canadian Society for Exercise Physiology. *PAR-Q & You: A Questionnaire for People Aged 15 to 69*, 2002.
29. Beck AT, Steer RA, Brown GK. *Manual for the Beck Depression Inventory*. 2nd edn. San Antonio, TX: Psychological Corporation, 1996.
30. Beck AT, Epstein N, Brown G, *et al*. An inventory for measuring clinical anxiety: psychometric properties. *J Consult Clin Psychol* 1988;56:893–7.
31. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. *J Health Soc Behav* 1983;24:385–96.
32. Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
33. JE WJ, Kosinski M, Keller M. *SF-36 Physical and Mental Health Summary Scales: A Users' Manual. edn*. Boston: The Health Institute, 1994.
34. Wolfinger R, Chang M. *Comparing the SAS® GLM and MIXED Procedures for Repeated Measures*. Cary, NC: SAS® Institute Inc, 1995.
35. Littel RC, Milliken GA, Stroup WW, *et al*. *SAS for Mixed Models. edn*. Cary, NC: SAS Institute Inc, 2006.
36. Riedel M, Möller HJ, Obermeier M, *et al*. Response and remission criteria in major depression--a validation of current practice. *J Psychiatr Res* 2010;44:1063–8.
37. McDonald JH. Cochran–Mantel–Haenszel test for repeated tests of independence. *In: Handbook of Biological Statistics*. 3rd edn. Baltimore, Maryland: Sparky House Publishing, 2014.
38. Beck AT, Steer RA. *Manual for the Beck Anxiety Inventory. edn*. San Antonio, TX: Psychological Corporation, 1990.
39. Malhi GS, Byrow Y. Exercising control over bipolar disorder. *Evid Based Ment Health* 2016;19:103–5.
40. Greer TL, Kurian BT, Trivedi MH. Defining and measuring functional recovery from depression. *CNS Drugs* 2010;24:267–84.
41. Pretty J, Peacock J, Sellens M, *et al*. The mental and physical health outcomes of green exercise. *Int J Environ Health Res* 2005;15:319–37.
42. Greer TL, Trombello JM, Rethorst CD, *et al*. Improvements in psychosocial functioning and health-related quality of life following exercise augmentation in patients with treatment response but nonremitted major depressive disorder: Results from the TREAD study. *Depress Anxiety* 2016;33:870–81.
43. Buffart LM, van Uffelen JG, Riphagen II, *et al*. Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer* 2012;12:559.

BMJ Open Sport Exerc Med: first published as 10.1136/bmjsem-2017-000314 on 15 June 2018. Downloaded from http://bmjopensem.bmj.com/ on 8 July 2018 by guest. Protected by copyright.

Introduction to Chapter III

The prospective study started about one year before I began my PhD, so I was not involved in the study design. In addition, the first few participants were collected by a student who left the program the year I started. I began my training with the assessment of participants TU13 and TU14, and completed all of the baseline and post-running assessments from that point forward. I also fully assumed the responsibility of data collection, data entry, data analyses and the writing of the manuscript. Moving forward, I will be responsible for revising and formatting the paper as we prepare it for submission.

Dr. Margaret McKinnon, co-supervisor, and Dr. Roberto Sassi, thesis committee member, were the co-Principal investigators and were responsible for the design of the study. Dr. Sue Becker was also involved in the study design, in particular around the selection and interpretation of cognitive assessments. Dr. Benicio Frey was involved in the study design as well, providing input on clinical assessments. As noted in the introduction for Chapter II, Katie McCabe, Jeff Whattam and Laura Garrick were responsible for the running of the group, and they additionally helped with recruitment of participants.

All of the members of my thesis committee were involved in reviewing the drafts of the manuscript, and for providing advice on data analyses and interpretation.

All of the authors listed on the prepared manuscript have been involved in preparation of the manuscript, including providing feedback on poster presentations that shaped the final paper. All of the authors have reviewed and will approve the final manuscript when it is submitted for publication.

Running head: The impact of running on cognitive and social function

Impact of a structured, group-based running program on clinical, cognitive and social function in youth and adults with complex mood disorders

Keating, L.E.,[1] Becker, S.,[1,2] McCabe, K.,[3,4] Whattam, J.,[4] Garrick, L.,[4] Sassi, R.B,[1,3,4] Frey, B.N.,[1,3,4] McKinnon, M.[1,3,4,5]

[1]McMaster Integrative Neuroscience and Discovery, McMaster University, Hamilton, ON

[2]Department of Psychology, Neuroscience and Behaviour, McMaster University, Hamilton, ON

[3]Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, ON

[4]Mood Disorders Program, St Joseph's Healthcare Hamilton, Hamilton, ON

[5]Homewood Research Institute, Guelph, ON

III.A. ABSTRACT

The World Health Organization recently identified major depressive disorder as the number one global health threat, calling for more effective treatment strategies. Individuals with mood disorders often report lingering social and cognitive dysfunction, and impaired health-related quality of life (HRQOL), even after mood symptoms have improved. Exercise programs have been associated with improved mood symptoms in patients; however the potential benefits of exercise across functional outcomes in patients with difficult-to-treat mood disorders remain unknown. The goal of the current study was to evaluate the impact of a 12-week structured running program across cognitive, social, and HRQOL outcomes in participants with difficult-to-treat mood disorders. Methods: In a prospective, observational study, patients referred to the St Joseph Healthcare Hamilton Team Unbreakable running program for youth and adults with mood disorders completed a comprehensive assessment battery before and after the 12-week intervention. Results: Pre- and post-intervention data were collected from 18 participants. Improvements were identified on five HRQOL subscales including general health, vitality, role of emotions in functioning, social functioning and mental health (p's$\leq$0.01). We also observed improved performance on cognitive tests assessing working memory and processing speed ($p \leq 0.04$), but not on more complex executive functioning tasks. Regression analyses indicate younger age, shorter illness duration and improved bodily pain predict social and cognitive outcomes. Discussion: Participation in a group-based, structured running program is associated with improved HRQOL and social and cognitive function. Further

studies are needed to better understand the therapeutic benefits of exercise across symptoms of difficult-to-treat mood disorders.

III.B. INTRODUCTION

III.B.i. Mood disorders: Prevalence and cost

Mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), represent a prevalent and costly social and health issue, affecting more than 300 million people worldwide (World Health Organization, 2008). Indeed, the World Health Organization recently identified depression as the leading cause of ill health and disability globally (World Health Organization, 2017). In Canada, the reported prevalence of MDD is 4.7% (Pearson et al., 2013), with an estimated lifetime prevalence of 12% (Kessler et al., 2009; Merikangas et al., 2011; Pearson et al., 2013). Although less common than MDD, the prevalence of BD in Canada has been estimated at 0.4 to 1.5% (McDonald et al., 2015; Pearson et al., 2013), with estimates of 2.2% for lifetime prevalence (Schaffer et al., 2006) and 2.4% for subthreshold BD symptoms (Yatham et al., 2013). The economic burden of mental illness in Canada was estimated at $51 billion in 2008 (Lim, Jacobs, Ohinmaa, Schopflocher, & Dewa, 2008), reflecting direct costs including healthcare (Patel, 2009) and indirect costs including decreased productivity (National Collaborating Centre for Mental Health, 2006; Parker, McCraw, Hadzi-Pavlovic, & Fletcher, 2013). Given the high cost and prevalence of mood disorders, better treatments are urgently needed.

III.B.ii. Mood disorders: Diagnosis and treatment

MDD is characterized by significant mood dysfunction and changes to sleep and eating patterns, impaired cognitive, social and occupational functioning (American Psychiatric Association, 2013a). Bipolar I disorder and bipolar II disorder, which involve a similar constellation of symptoms, are characterized further by the presence of manic and hypomanic episodes, respectively (American Psychiatric Association, 2013b). Both MDD and BD are also associated with increased physical health issues (Public Health Agency of Canada, 2016) and high rates of mortality across a number of causes of death, including suicide (Angst et al., 2002; National Collaborating Centre for Mental Health, 2006). First-line treatment for depression includes pharmacological agents, typically anti-depressants, as well as some psychotherapies (e.g., Cognitive Behavioral Therapy), for management of mood symptoms (Lam, Kennedy et al., 2016) while mood stabilizers, such as lithium, are gold-standard for the treatment of manic and hypomanic symptoms in BD (National Collaborating Centre for Mental Health, 2006; Yatham et al., 2013). Current treatments, however, are characterized by low remission and high relapse rates that have not improved over the past several decades (Keller et al., 1992; Kolovos et al., 2017; National Collaborating Centre for Mental Health, 2006). Success rates may be even lower when patients are included that reflect the heterogeneity seen in clinical practice, that are not restricted based on baseline entry criteria, and where studies employ stricter outcomes that may better predict long-term prognosis such as remission of symptoms, as opposed to response to treatment (Kolovos et al., 2017; Sinyor, Schaffer, & Levitt, 2010).

III.B.iii. Mood disorders: Evaluating treatment outcomes

Critically, research defining treatment efficacy in mood disorders has focused almost exclusively on mood symptoms as these can be assessed by relatively easy-to-administer depression rating scales (Greer, Kurian, & Trivedi, 2010; Lam, Parikh, Michalak, Dewa, & Kennedy, 2016; Trivedi & Greer, 2014) such as the Beck Depression Inventory (Beck, Steer, & Brown, 1996) and the Hamilton Rating Scale for Depression (Hamilton, 1960). However, even patients who meet criteria for remission as assessed by these self-report rating scales following first-line treatment may experience lifelong mood, cognitive and social symptoms that disrupt functional outcomes and quality of life in MDD (Kaya et al., 2007; G. M. MacQueen & Memedovich, 2017; Trivedi et al., 2006) and in BD (Martínez-Arán et al., 2007). Thus, there is an urgent need to identify treatment strategies that improve short- and long-term prognosis for youth and adults with mood disorders, and to quantify the impact of these treatments across mood as well as functional outcomes (Lam, Parikh et al., 2016; G. M. MacQueen & Memedovich, 2017).

III.B.iv. Mood disorders: Exercise as adjunctive treatment

Several lines of evidence indicate that aerobic exercise is associated with an improvement in mood symptoms including depression, stress coping and anxiety. In animals, voluntary aerobic exercise has shown neuroprotective effects on depressive symptoms, including reduced anhedonia (Sigwalt et al., 2011), anxiolytic behaviours (Duman, Schlesinger, Russell, & Duman, 2008) and improved neurocognitive function (van der Borght et al., 2007; van Praag et al., 2005). In humans, results have been less consistent. Some studies

have reported a positive improvement in depressive symptoms after the adoption of exercise across youth (Nabkasorn et al., 2005) and adults (Babyak et al., 2000; Blumenthal et al., 1999; Knubben et al., 2007) with MDD; other studies have reported no significant effects in MDD symptoms compared to non-exercising (Bonhauser et al., 2005; Chalder et al., 2012) or placebo (e.g. stretching)(Blumenthal et al., 2007) controls. However, a recent meta-analysis of 15 randomized trials evaluating the effect of exercise on MDD found a significant effect of exercise across a variety of measures of depression, with a mean effect size of 0.77 over all studies, and 0.43 for studies that met stricter methodological criteria (double-blind and intention-to-treat analyses) (Josefsson et al., 2014). The authors of this meta-analysis note that methodological variability may partly underlie the discrepancy of results in the literature, including exercise types (aerobic vs non-aerobic), durations and frequency of programs and level of social interaction (e.g. none (Blumenthal et al., 2007; Krogh, Videbech, Thomsen, Gluud, & Nordentoft, 2012), one-on-one supervision (Blumenthal et al., 1999; Blumenthal et al., 2007; Knubben et al., 2007; Krogh et al., 2012) and group-based programs (Annesi, 2005b; Nabkasorn et al., 2005; Veale et al., 1992).

III.B.v. Functional outcomes in mood disorders

Compounding the knowledge gaps above, there is little information about the therapeutic effects of exercise on functional outcomes such as social and cognitive functioning and quality of life in patients with mood disorders that do not respond to first-line therapies (Salagre et al., 2017), or who experience recurrent episodes and ongoing functional

impairment (Asher et al., 2016; Lam, Parikh et al., 2016; G. M. MacQueen & Memedovich, 2017), even after mood symptoms have improved (IsHak et al., 2011; Möller, 2008), The majority of research on exercise for depression has also focused on single outcomes, typically improved depression scores, in either non-clinical (Annesi, 2005a; Bonhauser et al., 2005; Rocha et al., 2012) or first-episode/medication naïve patients (Foley et al., 2008; Krogh et al., 2012; McNeil, LeBlanc, & Joyner, 1991; Nabkasorn et al., 2005; Naveen et al., 2013; Naveen et al., 2016). Further, there are only a handful of studies reporting improvements in depressive symptoms following participation in aerobic (Doyne et al., 1987; Mather et al., 2002; Veale et al., 1992) and non-aerobic exercise groups (Doyne et al., 1987; Veale et al., 1992) that included treatment-resistant clinical populations; one study additionally reported improved psychosocial functioning and quality of life (Greer et al., 2016). On balance, therefore, we are missing important information on the impact of exercise and depression in two main clinical areas: 1) across the spectrum of core MDD symptoms that include quality of life, cognitive functioning and social functioning outcomes; and, 2) in recurrent or difficult-to-treat forms of MDD with high burdens of illness and co-morbidity (G. M. MacQueen & Memedovich, 2017). There is also a paucity of literature on the potential therapeutic impact of exercise for patients with BD (Malhi & Byrow, 2016), with some evidence of benefits for depressive symptoms, but potentially detrimental effects of aerobic exercise for patients in an active manic phase (Malhi & Byrow, 2016; Thomson et al., 2015), underscoring the need for further investigation into the safety and efficacy of exercise in BD.

As noted above, although core symptoms of MDD and BD include impaired HRQOL, as well as cognitive and social dysfunction, these symptoms are evaluated as treatment outcomes far less often than mood symptoms. Some studies that have investigated the impact of antidepressant treatment on HRQOL have reported positive findings (Florea et al., 2015; Skevington & Wright, 2001). However, patients switching therapies due to poor initial response to first-line treatment have a lower QOL than those who do respond (Haro et al., 2018); further, a recent meta-analysis found no greater impact of antidepressant compared to placebo on self-report quality of life outcomes (Spielmans & Gerwig, 2014). Thus, further research on the impact of depression treatments on quality of life outcomes is needed. Cognitive functioning deficits observed in individuals with mood disorders include poor performance relative to matched healthy controls on measures of executive functioning (including attention, response inhibition, decision making and information processing), and verbal and nonverbal learning and memory (Foster Green, 2006; Kucyi, Alsuwaidan, Liauw, & McIntyre, 2015; Martínez-Arán et al., 2004; McIntyre et al., 2013; Trivedi & Greer, 2014; Veiel, 1997). Social impairments are also well established core symptoms of MDD (Kupferberg, Bicks, & Hasler, 2016) and BD (Judd et al., 2002), potentially contributing to social isolation in these patients. Importantly, social isolation is a widely used form of stress in animal models of depression (Zanier-Gomes et al., 2015), where enhanced social support may offer protection from stress (Pietrzak et al., 2014; Wang et al., 2014). Impaired HRQOL is also a hallmark feature of difficult-to-treat MDD (Daly et al., 2010; Spitzer et al., 1995) and BD (IsHak et al., 2012), These functional impairments in mood disorders often persist

even after self-reported mood symptoms have improved significantly (Herrera-Guzmán et al., 2009; Lam, Parikh et al., 2016; Möller, 2008; Shilyansky et al., 2016). Thus, potential therapeutic interventions should include comprehensive assessments to understand the impact of therapies on social and cognitive functioning and HRQOL, in addition to mood symptoms (IsHak et al., 2011; Kucyi et al., 2015; Lam, Parikh et al., 2016; G. M. MacQueen & Memedovich, 2017).

III.B.vi. Study 2: Objectives

The objective of the current study was therefore to evaluate the impact of a structured running program for youth and adults with recurrent, difficult-to-treat and/or chronic mood disorders to address the critical knowledge gaps outlined above. Since April 2012, a multidisciplinary clinical team in the Mood Disorders Program at St Joseph's Healthcare Hamilton (Hamilton, Ontario) has offered a 12-week recreational running program, called Team Unbreakable. This group-based program is aimed at providing therapeutic benefit to youth and adults with a diagnosis of a mood disorder, and has as its focus patients with complex clinical histories. All clients enrolled in this program were offered the opportunity to participate in a more intensive study of cognitive and mood-related symptoms, with assessments taken at baseline and end of study. This group provided an opportunity to evaluate the impact of running across many core depressive symptoms, in a difficult-to-treat sample of youth and adults with mood disorders. Previous data on this sample confirmed a positive effect of running on symptoms of stress, anxiety and depression (Keating et al., 2018). Accordingly, the primary objective

of the current study was to evaluate the impact of a structured aerobic exercise program on: i) health-related quality of life; ii) neurocognitive function; and iii) social functioning. Secondary analyses examined changes in self-report measures of depression, anxiety and stress following participation in this program.

III.C. METHODS

This study was reviewed and approved by the Hamilton Integrated Research Ethics Board (HIREB). Data were collected from participants from August 2012 to December 2016.

III.C.i. Study participants

Participants were recruited from a clinical running group administered through St Joseph Healthcare Hamilton's Mood Disorders Program. The running group was part of a novel treatment program for clients with predominately chronic and/or recurrent mood disorders in the local Hamilton community. Recruitment methods included posting flyers in and around the two sites that comprise St Joseph Healthcare Hamilton, as well as sending information about the running group to local clinics for referrals. Participants were allocated to a youth group (16-25 years of age) or an adult group (>25 years of age; see Table 1). Referral criteria included: history of mood disorder and ability to participate in a structured running program on a bi-weekly basis**.** Participants were also required to complete the Physical Activity Readiness Questionnaire (PAR-Q & You, ©Canadian Society for Exercise Physiology) (Canadian Society for Exercise Physiology, 2002) to ensure they were able to meet the physical demands of the running group. A retrospective chart review of the clinical history and treatment response in a larger treatment-seeking sample (n=46) has been published (Keating et al., 2018); the present study includes a subset of this sample that agreed to participate in the present experimental study. Clinical

diagnoses were established by review of the chart record that included diagnoses established through evaluation by a hospital psychologist or psychiatrist.

III.C.ii. Clinical assessments

Beck Depression Inventory® Second edition (BDI-II; licensed by PsychCorp) (Beck et al., 1996): The BDI-II is a 21-item self-report questionnaire that is used to assess depressive symptoms. BDI scores can be divided into four categories of severity: None (no depression), low, moderate and high.

Beck Anxiety Inventory® (BAI; licensed by PsychCorp) (Beck, Epstein, Brown, & Steer, 1988): The BAI is a 21-item self-report questionnaire used to assess the severity of an individual's symptoms of anxiety. BAI scores can also be divided into categories of severity: Low, moderate and high.

Cohen's Perceived Stress Scale (PSS) (Cohen et al., 1983): The PSS is a freely available, widely used self-report instrument for measuring the perception of stress during the past month. The PSS consists of 10 items measuring the degree to which situations are perceived as stressful.

36-Item Short Form Survey (SF-36): The SF-36 is a 36-item self-report assessment used to measure health-related quality of life. Participants respond to questions by selecting a response on a Likert-type scale (Ware Jr., Kosinski, & Keller, 1994; Ware Jr. & Sherbourne, 1992). The survey generates a total score that can be sub-divided into two domains of four subscales each: the physical domain includes physical functioning, limitations due to physical health, bodily pain and general health perceptions. The mental

domain is comprised of social functioning, mental health, limitations in physical activities due to emotional problems and vitality.

III.C.iii. Neurocognitive functioning assessments

Paper Based assessments:

California Verbal Learning Task-II© (Delis, Kramer, Kaplan, & Ober, 2000): Here, the assessor reads a list of 16 words over five trials, and the participant must recall and/or recognize these words over a series of time points. This learning task provides indices of immediate and delayed memory performance, interference, and recognition; an alternate version with different words was used at the post-assessment session.

WAIS-IV Digit Span (Wechsler, 2008): In this subtest, the experimenter reads a list of numbers, and participants are required to repeat numbers in the same sequence presented (forward), in reverse order (backwards), or putting numbers from smallest to largest (sequencing). The Digit Span task assesses working memory and attention, with increasing difficulty of the tests (forward, backward, sequencing) reflecting more complex levels of executive functioning (Reynolds, 1997).

Stroop Color-Word Task (Stroop, 1935): This task taps the ability to suppress a habitual response in favor of a less familiar one, and provides additional indices of simple attention/ processing speed (word reading and colour identification). The Stroop task is a measure of executive function.

Computer Based assessments:

Delayed match to sample (DMS): The DMS was coded in e-prime and was based on the

Cambridge Neuropsychological Test Automated Battery (CANTAB; www.cambridgecognition.com/cantab/) DMS. The participant is shown a complex visual pattern (the sample) and, after a brief delay, four similar images with patterns of a different colour and complex shape. One of the four patterns is identical to the sample, which the participant must identify, while the other three are distracter images.

Mnemonic Similarity Task (MST): This high interference memory task is a variant of the MST developed by Kirwan & Stark (Kirwan & Stark, 2007). A set of images is presented sequentially in randomized order to the participant. During this presentation period, the participant undergoes an incidental encoding task and is not alerted to the fact that they will be prompted subsequently to recognize the images they have seen. In the second part of the task, they are shown another set of images. Some of these images are novel, some are identical to ones presented in the first list, while others are highly similar to images of the same object previously presented ("lures"). The participant is asked to judge whether each object presented in the second list is novel, similar to or the same as a previous image.

Spatial recognition memory (SRM): The SRM, based on the CANTAB SRM, tests visual spatial recognition memory in a 2-choice forced discrimination paradigm. The participant is presented with a white square, which appears in sequence at five different locations on the screen. In the recognition phase, the participant sees a series of five pairs of squares, one of which is in a place previously seen in the presentation phase. The other square is in a new location, and the participant must select the square in the previously seen location.

Paired Associate Learning (PAL), based on the CANTAB PAL, assesses visuo-spatial associative memory and new learning. Boxes are displayed on the screen and are opened in a randomized order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time, and the participant must touch the box where each pattern was originally located. If the participant makes an error, the patterns are re-presented to remind the participant of their locations. The difficulty level increases through the test.

Rapid visual processing (RVP): RVP, based on the CANTAB RVP, is a test of sustained attention and working memory. It is sensitive to dysfunction in the parietal and frontal lobe areas of the brain. A white box appears in the center of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, one at a time, at the rate of 100 digits per minute. Participants must detect target sequences of three successive digits (e.g., 1-2-3) and register responses using the keyboard.

III.C.iv. Running protocol

The running program for this study has been described in detail previously (Keating et al., 2018). Briefly, the group met two times per week and progressed gradually from mostly walking to mostly running. Each week, the participants increased their distance by a small amount (about 0.5 km), and increased the time spent running by 30 to 60 seconds, with a goal of working up to mostly running 5 km by week 12. At the end of the 12-weeks, participants completed a local 5 km run. Weekly sessions included motivational talks by experts across a range of topics. The sessions were facilitated by running coaches

(JW – recreational therapist and KM – social worker), and included volunteers comprised of hospital staff and graduate students.

IIII.C.v. Statistical analyses

Continuous measures were analyzed for normality and skewness, to justify the use of parametric statistics. Pre- and post-intervention differences in continuous variables were analyzed using paired t-tests; all change scores were calculated as post- minus pre-intervention score. Relations among variables of interest were evaluated using the Pearson correlation coefficient and stepwise multiple linear regression analyses. All analyses were performed using SAS© 9.4 for Windows.

III.D. RESULTS

III.D.i. Clinical and demographic results

Data were collected from a total of 18 participants from August 2012 to December 2016 across 10 running cohorts; see Table 1. Another eight participants completed the baseline assessments, but did not complete the post-treatment study assessments; see Table 2. Dropouts were more likely to be male, although there were no significant differences in pre-intervention BDI scores for the dropouts compared to those who completed the end of study assessments. It is important to note that dropping out from the study did not require dropping out of the running group; many study drop outs did complete the running group program, though they did have a lower attendance rate (see Table 2). For the purposes of this paper, therefore, participants were considered dropouts if they did not complete the post-intervention study assessment. There were significantly fewer male than female participants in the study sample (χ^2=11.8, df=1, p=0.0006). Although the youth and adult groups differed in age at onset of diagnosis, with the younger group having an earlier age of onset and higher dropout rate (see Table 1), previous analyses using a larger data set indicated no difference in youth compared to adult runners in terms of outcomes (Keating et al., 2018); therefore, the two groups were analysed together. Participant diagnoses are summarized in Table 2, and illustrate that the participants who completed the study were more likely to have a primary diagnosis of MDD and have an older average age at onset of mood disorder than dropouts, who were more likely to have a primary diagnosis of BD and age at illness onset in their teens. Currently identified co-

morbid diagnoses for the entire sample included: social anxiety disorder (n=11), generalized anxiety disorder (n=9), substance use/abuse (n=5), agoraphobia (n=2), panic disorder (n=1), post-traumatic stress disorder (n=1), dysthymia (with MDD, n=1) and presence of psychotic symptoms (n=3). Though total number of co-morbid diagnoses was not included in these analyses, the clinical histories of the participants indicate this sample included youth and adults with chronic and/or complex mental illness.

Table III.1: Sample demographics

	Entire sample (n=18)	Adult group (n=6)	Youth group (n=12)	Adult compared to youth
Mean ± SD (range)				
Current age (years)	30.2 ± 15.4 (16-62)	48.8 ± 13.8 (30-62)	21.2 ± 2.4 (16-25)	**t=4.9, df= 5.1 p=0.004***
Attendance	60.3 ± 25.4 (8.3-91.2)	67.5 ± 13.4 (50-87.5)	56.4 ± 29.7 (8.3-91.2)	t=0.9, df=15, p=0.3
Baseline BDI	27.6 ± 13.8 (6-60)	32.7 ± 17.4 (10-60)	25.1 ± 11.6 (6-43)	t=1.2, df=16, p=0.3
Age at onset of mood disorder	23.4 ± 14.0 (13-61)	37.0 ± 18.4 (14-61)	16.5 ± 2.3 (13-22)	**t=2.7, df=5.1, p=0.04***
Duration of illness (years)	6.8 ± 6.2 (0-19)	11.8 ± 8.5 (1-19)	4.5 ± 2.7 (0-9)	t=2.1, df=5.5, p=0.08
Proportion: Number (%)				
Female participants	16 (88.9%)	6 (100%)	10 (83.3%)	$\square^2$=1.1, df=1, p=0.3

Table III.2: Demographic characteristics of completers compared to dropouts

	Completed pre- and post-assessments (n=18)	**Completed baseline only[a] (n=8)**	**Comparison**
Mean ± SD (range)			
Current age (years)	30.2 ± 15.6 (16-62)	23.6 ± 4.0 (18-31)	t=-1.7, df= 21.3, p=0.11
Attendance	60.3 ± 25.3 (8.3-91.2)	30.9 ± 25.8 (8.3-83.3)	**t=-2.5, df=22, p=0.02***
Baseline BDI	27.6 (±13.8; 6-60)	22.1 (±12.3; 0-49)	t=-1.0, df=24, p=0.3
Age at onset of mood disorder	23.4 ± 14.2 (13-61)	15.5 ± 2.5 (12-18)	**t=-2.5, df=19.8, p=0.02***
Duration of illness (years)	6.8 ± 6.3 (0-19)	9.8 ± 4.8 (4-15)	t=1.1, df=22, p=0.3
Proportion: Number (%)			
Female participants	16 (89%)	6 (75.0%)	χ^2=0.8, df=1, p=0.4
Baseline diagnosis of MDD	14 (77.8%)	3 (37.5%)	χ^2=4.0, df=1, p=0.05
Baseline diagnosis of BD	3 (16.7%)	5 (62.5%)	χ^2=5.5, df=1, p=0.01

[a]Participants did not necessarily drop out of the running group, but did not complete the end of study assessments

III.D.ii. Pre- and post-intervention assessments

Health-Related Quality of Life SF-36: The SF-36 health-related quality of life questionnaire is divided into eight sub-scales of physical (four sub-scales) and mental health (four sub-scales) functioning; see Table 3. Whereas all of the mental health sub-scale scores (mental health, vitality, social functioning and role of emotions in functioning) showed significant improvement from baseline to end of study, only the general health physical sub-scale showed significant improvement from baseline (see Table 3). The correlation between the SF36 subscales and change in BDI scores are described below, and are displayed in Figure 1.

Neurocognitive function

Complete analyses of the neuropsychological scores are shown in Table 4. Although performance improved on many scales from baseline to end of study, only the forward span subtest of the WAIS Digit Span task and the colour only subtest of the Stroop task, reflecting working memory and processing speed, were significantly improved from baseline compared to end of study.

Table III.3: Health-Related Quality of Life

SF-36 Subscale	Pre-intervention (mean ± SD)	Post-intervention (mean ± SD)	Paired t-test
Physical Fitness	78.0 (±20.4)	84.3 (±16.7)	t=-1.3, df=19, p=0.2
Role of Physical	51.3 (±34.0)	62.5 (±38.5)	t=-1.2, df=19, p=0.2
Bodily Pain	69.6 (±25.8)	70.5 (±22,2)	t=-0.2, df=19, p=0.9
General Health	52.5 (±17.5)	61.3 (±13.5)	**t=-3,0, df=19, p=0.007***
Vitality	26.8 (±14.6)	41.5 (±20.0)	**t=-2.9, df=19, p=0.01***
Social Functioning	46.3 (±25.4)	64.4 (±27.3)	**t=-3.1, df=19, p=0.007***
Role of Emotions	11.7 (±19.6)	41.7 (±41.7)	**t=-2.9, df=19, p=0.009***
Mental Health	44.0 (±17.7)	55.4 (±19.1)	**t=-3.0, df=19, p=0.007***

Table III.4: Neurocognitive assessments

Test	Pre-intervention (mean ±SD)	Post-intervention (mean ±SD)	Paired t-test
CVLT			
Recall Trials 1-5[a]	53.2 ± 7.6	50.3 ± 9.4	t=-1.4, df=16, p=0.2
Short delay free recall[a]	11.6 ± 3.2	12.1 ± 2.8	t=0.9, df=16, p=0.4
Short delay cued recall[a]	12.2 ± 2.2	12.6 ± 2.5	t=1.1, df=16, p=0.3
Long delay free recall[a]	12.2 ± 3.4	11.6 ± 4.0	t=0.6, df=16, p=0.6
Long delay cued recall[a]	12.5 ± 2.8	12.6 ± 2.5	t=-0.3, df=16, p=0.8
Total repetitions[b]	3.0 ± 3.5	1.4 ± 1.6	t=-1.8, df=16, p=0.10
Total intrusions[b]	1.0 ± 1.9	0.7 ± 1.7	t=0.5, df=15, p=0.6
WAIS Digit Span			
Total Score[a]	28.6 ± 5.2	29.8 ± 6.0	t=-1.6, df=17, p=0.13
Forward[a]	10.7 ± 2.6	11.8 ± 2.7	**t=-2.8, df=17, p=0.01***
Backward[a]	8.7 ± 2.4	8.6 ± 2.3	t=-0.3, df= 19, p=0.6
Sequential[a]	8.4 ± 2.0	8.6 ± 2.5	t=0.4, df=17, p=0.8

Stroop Color-Word Task			
Word[a]	90.2 ± 10.3	90.5 ± 12.2	t=-0.2, df=14, p=0.9
Colour[a]	67.2 ± 10.7	71.9 ± 10.8	**t=-2.4 , df=14, p=0.04***
Colour-word interference[a]	44.9 ± 8.2	46.3 ± 10.4	t=-1.0, df=14, p=0.3
Delayed Match to Sample (% matches correct)[a]	86.0 ± 5.4	85.4 ± 11.7	t=-0.2, df=10, p=0.8
Mnemonic Similarity Task (% similar correct)[a]	40.5 ±20.5	44.9 ± 20.1	t=-1.1, df=10, p=0.3
Spatial Recognition Memory (% matches correct)[a]	66.4 ±17.8	68.2 ±14.7	t=-0.5, df=10, p=0.7
Paired Associate Learning (number of trials)[b]	10.6 ± 2.8	10.3 ± 2.7	t=0.3, df=9, p=0.8
Rapid Visual Processing (percent correct)[a]	88.4 ±13.2	89.3 ± 8.6	t=0.2, df= 6, p=0.8

[a]Higher scores indicate improvement; [b]Lower scores indicate improvement

III.D.iii. Multiple linear regression and correlation analyses

Regression: Stepwise multiple regression analysis was performed with change in BDI score as the outcome variable and the following predictor variables: current age, attendance (percentage of sessions), age at illness diagnosis (years), duration of illness (months), and the sub-scales of the SF-36 with the exception of the mental health subscale of the SF-36, as this was highly correlated with BDI. Improvements in BDI scores were predicted by the model that included attendance (parameter estimate -0.13), change in bodily pain score (parameter estimate -0.25), change in vitality score (parameter estimate -0.26) and change in general health (parameter estimate 0.25), accounting for 43% of the variance in BDI change scores (R-squared = 0.43; $F(3,15)=3.7$, $p=0.04$). Correlations between these parameters and BDI change scores were: attendance (-0.34, $p=0.15$), bodily pain ($r = -0.43$, $p=0.05$), vitality ($r = -0.4$, $p=0.06$) and general health ($r = -0.1$, $p=0.8$); see also Figure 1. For all significant predictor variables, an improved (negative) BDI change score was associated with an improved (positive) score.

We predicted *a prio*ri that participation in a running group would be associated with improvements in cognitive (Smith et al., 2010) and social (Greer et al., 2016) function. Therefore, we also performed multiple regression analyses with the Digit Span – Forward task and Stroop colour task change scores as dependent variables for cognitive function and the SF-36 social function change score for social function. The same predictor variables were used as described above. The change in the Digit Span forward task was predicted only by age of participant, where younger participants showed greater

improvement from baseline to end of study (parameter estimate -0.06, F(1, 17) = 8.8, p=0.009, R-squared = 0.34). The improvement in Stroop colour task performance was predicted by shorter duration of illness (parameter estimate -0.6) and improved bodily pain scores (parameter estimate 0.2), explaining 41% of the variance (F=4.8, df=2, 14, p=0.03). Correlations with the Stroop colour task change scores were r=-0.5 (p=0.04) and 0.4 (p=0.1) for duration of illness and bodily pain change score, respectively.

Social functioning was predicted by change in physical functioning (parameter estimate = 0.4) and attendance (parameter estimate = 0.33), explaining 26% of the variance (R-squared=0.26; F (2,17)=2.9, p=0.08). Correlations were r=0.3, p=0.2 for role of physical symptoms in functioning, and r=0.4, p=0.1 for attendance, with higher functioning scores associated with higher physical functioning and attendance scores. Neither age at onset or duration of illness were significant in the models explored.

III.D.iv. Secondary analyses: Mood symptoms

The participants in the current study represent a subsample of those reported on in a previously published paper evaluating mood symptoms in a larger sample of participants in the Team Unbreakable Running Program (Keating et al., 2018); only the subset of the running group members who agreed to be research participants are reported on here. In order to confirm the beneficial effects of exercise observed in this larger sample were present in the smaller subsample of participants reported here, we evaluated pre- and post-intervention scores of stress, anxiety and depression in this group. As expected,

these scores decreased significantly from pre- to post-intervention. The mean BDI score at baseline was 27.7 (±12.6; range 6-60) and at end of the sessions was 20.7 (±14.3; range 4-56), a decrease of 25.3% (t=3.5, df=19, p=0.003). The mean BAI score at baseline was 19.7 (±14.2; range 0-50) and at end of the sessions was 15.3 (±12.9; range 0-47), a decrease of 22.3% (t=2.7, df=20, p=0.02). The mean PSS score at baseline was 25.1 (±6.9; range 12-35) and at end of the sessions was 20.3 (±8.1 range 3-32), a decrease of 19.1% (t=3.8, df=19, p=0.001).

III.E. DISCUSSION

III.E.i Summary of results

In a sample of youth and adults with mood disorders characterized by long duration of illness, recurrent episodes and/or multiple comorbid diagnoses, we report here evidence of improvement across multiple functional symptoms of mood disorders including cognitive function, social function and health-related quality of life after participation in a 12 week running program. Improved neurocognitive functioning was detected on the WAIS forward digit span task and the colour only condition of the Stroop Color-Word task. The WAIS forward digit span task assesses working memory and attention, and has been associated with activation of cortical areas including the dorsolateral prefrontal cortex (DLPFC), bilateral inferior parietal lobule (IPL) and anterior cingulate, a region associated with attentional effort (Gerton et al., 2004). The colour only subtask of the Stroop test is a measure of attention and processing speed, has also been shown to activate cortical regions including the prefrontal, cingulate, and parietal regions (Banich et al., 2000). We also report improvements on the general physical health and all four mental health subscales of the SF36, including vitality, role of emotions in functioning, mental health and social functioning. In terms of clinical history, participants with a diagnosis of BD were more likely to not complete the study than those with MDD, while a shorter duration of illness predicted improvement in Stroop colour task performance. Finally, in keeping with our previous report in a larger sample that included the

participants reported here (Keating et al., 2018), secondary analyses confirmed improved scores on measures of stress, anxiety and depression in the current subsample.

III.E.ii Comparison to the literature

The current neurocognitive improvements in working memory and attention are consistent with a recently published meta-analysis in humans, which reported a small but significant effect of exercise on working memory associated with chronic, but not acute, exercise in healthy populations (Rathore & Lom, 2017). Another meta-analysis exploring cognitive function and aerobic exercise reported improvements in attention and processing speed, effects that were stronger when aerobic exercise was combined with strength training; they did not report improvements in working memory (Smith et al., 2010). Both of these studies reported a moderating effect of age, with older adults more likely to show improvement. However, in the current study, improved scores on the Digit Span forward task were predicted by younger age, suggesting that there was room for improvement in the younger participants, which may not be typical of a healthy, non-depressed sample. Indeed, the varying impact of exercise on executive function tasks in the current study are consistent with literature reviews that illustrate considerable variability across study results (see Guiney and Machado, 2013; Diamond, 2015 (Diamond, 2015; Guiney & Machado, 2013)). In addition, contrary to rodent (van Praag, Christie et al., 1999; van Praag et al., 2005) and healthy young adults (Déry et al., 2013; Heisz et al., 2017; Stroth, Hille, Spitzer, & Reinhardt, 2009) studies reporting improvements for hippocampal-dependent outcomes, we found a non-significant

improvement in the MST task, believed to reflect hippocampal function. Further, a recent meta-analysis examining exercise and cognitive function in adults with depression has reported an absence of benefit across aerobic, anaerobic and mind-body interventions (e.g. yoga) (Brondino et al., 2017). However, the authors used only one outcome measure, defined as "global cognition", which was a single score that combined the changes of all cognitive tests, rather than looking at different types of memory tests (e.g. reflecting working memory, verbal memory, attention, etc) separately. Six of the eight studies reported improvements on one or more cognitive function outcomes, including executive functioning tasks. The two studies that did not report a significant effect of exercise (Krogh, Saltin, Gluud, & Nordentoft, 2009; Krogh et al., 2012) tested only end of study scores between different exercise interventions (aerobic, strength, attention control); no control groups were included. Further, the authors noted that low-impact interventions showed more improvement than high-impact interventions, possibly reflecting improved cognitive function of mind-body interventions, though this result did not quite reach significance ($p=0.09$), Thus, more detailed investigation on the types of memory that might improve with different types of exercise programs is warranted. This variability is characteristic of the cognitive functioning literature in general, which is plagued by methodological differences across exercise intervention programs, control populations, clinical and demographic factors of participants and neurocognitive assessment measures (Brondino et al., 2017; Rathore & Lom, 2017; Smith et al., 2010). It is also noteworthy that the vast majority of research on exercise and cognitive functioning has been done in aging samples, usually to investigate the effects of cognitive

decline (Gómez-Pinilla & Hillman, 2013); there is little information on the impact of exercise on memory in healthy young and middle-aged adults for comparison purposes. The inconsistencies in the literature noted above underscore the need for further research into the influence of clinical and demographic factors such as illness chronicity and age at onset in the effects of exercise on neurocognitive outcomes in mood disorders.

Quality of life is impaired in MDD (Spitzer et al., 1995) and BD (IsHak et al., 2012), and improvements in health, social and cognitive function may represent key outcome measures that are under-reported in the treatment literature and often persist after mood symptoms have improved (IsHak et al., 2011; Möller, 2008; Mota-Pereira et al., 2011). Exercise has been shown to improve health-related quality of life across a number of diagnoses (Penedo & Dahn, 2005), however there is little data for adults with difficult-to-treat mood disorders. In the current study, we report improvements on all four measures of mental health-related quality of life, as well as the general health physical subscale of the SF36, which is consistent with available literature (Carta et al., 2008; Mota-Pereira et al., 2011). In a recent meta-analysis, exercise was associated with significant improvements in both physical and mental quality of life outcomes, though only three of the six studies included adult patients with a primary diagnosis of a mood disorder (MDD) (Schuch et al., 2016). The social functioning subscale, building on the previously published finding in this group of improved feelings of friendship associated with participation in the running group (Keating et al., 2018), provides further evidence that a group-based, structured running program is associated with improvements in social

functioning and/or perceived social support; future research is required to further investigate the impact on social outcomes.

Regression analyses revealed that attendance was positively associated with improved depression and social functioning scores, and several clinical variables were found to predict attendance. Participants with a younger age at onset of illness and/or with a primary diagnosis of BD were more likely to drop out of the study, and had lower attendance scores in the running program. There are no published randomized control studies evaluating exercise in patients with BD (Malhi & Byrow, 2016; Thomson et al., 2015) and patients with BD have reported poor exercise habits (Kilbourne et al., 2007). This suggests that different types of group-based programs and/or engagement strategies should be explored for patients with BD and/or earlier ages at onset of illness, and affirms the importance of exploring clinical features of participants who are involved in a therapeutic running group program.

Our findings add to the literature that suggests structured exercise programs offer beneficial effects on mood symptoms in adults and youth with mood disorders (Hearing et al., 2016; Josefsson et al., 2014), by identifying improvements in social and cognitive functioning and health-related quality of life. To the best of our knowledge, this is the first study to investigate and report positive changes across multiple functional outcomes, including cognitive functioning, in patients with mood disorders in a complex psychiatric sample. Participants in our sample represent a highly challenging, difficult-to-treat

population that is often excluded from research studies. At the time of baseline testing, most of our adult participants were unemployed, extremely ill, had experienced multiple past episodes of depression, and were currently on medications that were simply not effective, while many of the student participants were struggling with and/or had dropped out of school. Thus, the findings reported here provide evidence that a structured running program can provide additional therapeutic benefit to the fifty percent of patients diagnosed with mood disorders that do not fully respond to first-line treatments. That said, some subgroups, for example those with BD and/or with an earlier age at onset, were less likely to attend running sessions and more likely to drop out; these groups require additional research to determine what types of recreational programs may provide therapeutic benefits.

Numerous authors have suggested that in addition to monitoring mood symptoms, measurement of treatment response should include indices of cognitive, social and quality of life outcomes (IsHak et al., 2011; Lam, Parikh et al., 2016; Trivedi & Greer, 2014) as interventions that improve cognitive and social functioning may be associated with improved functional recovery in patients with MDD (Greer et al., 2010; IsHak et al., 2011). Critically, then, these quality of life, social and cognitive improvements, in addition to previously reported mood symptoms (Keating et al., 2018), suggest that a group-based exercise program may be a useful therapeutic option for youth and adults with complex mood disorders, which is often characterized by lingering symptoms and impaired function.

III.E.iii Limitations

Though the results from the current study are encouraging, there are a number of limitations. First, in a very large battery of cognitive tests, we only observed significant changes in two tasks, and in both cases, the changes were found only on the easier subtest, the forward span subtest of the Digit span task, and the colour only subtest of the Stroop task. Given the large number of tests we administered, there is an elevated risk of a type I error rate. If we had used a more conservative p-value of $p \leq 0.01$ to correct for this, only the Digit span forward subtask would have been significantly improved. Moreover, the only variable that predicted this improvement was age of participant. These results should be replicated in a larger sample before we conclude that a structured running program confers benefits on cognitive outcomes in this type of difficult-to-treat clinical population. Second, this study sample includes a heterogeneous group of participants with current and past diagnoses of MDD and BD. Total numbers for each diagnostic category are too small to investigate the impact of specific clinical diagnosis on outcomes. In addition, the data we present did not allow us to tease out possible beneficial effects of running compared to perceived social support. A third limitation of the current study is the relatively short duration of the running intervention (12 weeks), and the lack of long-term follow up. Although the anti-stress and anti-depressant effects of aerobic exercise can be detected acutely even after one exercise session (Pretty, Peacock, Sellens, & Griffin, 2005), the impact on functional outcomes in mood disorders may lag behind improvements in mood symptoms (Lam, Parikh et al., 2016). For example, visual and verbal memory improvements have been reported as detectable

between 14 and 28 weeks (Herrera-Guzmán et al., 2009), longer than the observation period in the present study.

III.E.iv Future research

Future research exploring the role of clinical history, and the impact of group-based exercise programs on mood and functional outcomes, including social and neurocognitive function and quality of life, should be undertaken. Social isolation is well known to contribute to cognitive dysfunction, in particular executive functioning tasks (Cacioppo & Hawkley, 2009), suggesting a large, randomized controlled trial with non-exercising and non-aerobic exercise comparison groups could help to tease out the effects of perceived social support, aerobic exercise and non-aerobic exercise. Given the limited cognitive benefits observed, intervention and assessments should be structured over a longer period of time, at least six months (Lam, Parikh et al., 2016). Additional measures should also be included, for example comprehensive clinical history, as well as biological markers of stress and neuroplasticity. Functional neuroimaging studies to provide greater information about the brain regions that are affected from participation in a structured exercise program would also provide important information about the effects of exercise on brain structure and function over time. Qualitative data (Keating et al., 2018) and anecdotal observation of the youth and adults in the current study also suggest there may be anxiety and stress for patients taking on a new exercise program; in spite of this, we still saw relatively good completion rates in this group of patients with complex mood disorders. Future research investigating factors influencing the motivation of participants

to join and to attend sessions, as well as different ways of measuring stress, might provide new insights on the benefits of exercise on mood disorders, especially given the finding that higher attendance was a predictor of improved depression scores. Future research should also focus on how current age and clinical history including illness chronicity, specific and concurrent diagnoses, and age at onset of illness interact with the effects of group-based exercise programs.

III.E.v. Overall conclusion

The results of the current study suggest that a structured, group-based and supervised aerobic exercise program may have therapeutic benefits across the spectrum of symptoms including social and cognitive functioning and health-related quality of life, in addition to mood symptoms, for youth and adults with mood disorders with unsatisfactory response to first-line treatments. Higher attendance to the program was associated with improved benefits, however, the impact of a group-based running program on participants with early age at onset and/or a diagnosis of BD should be explored in larger samples. Future investigation regarding the role of clinical history and social functioning on exercise programs in youth and adults with mood disorders is implicated.

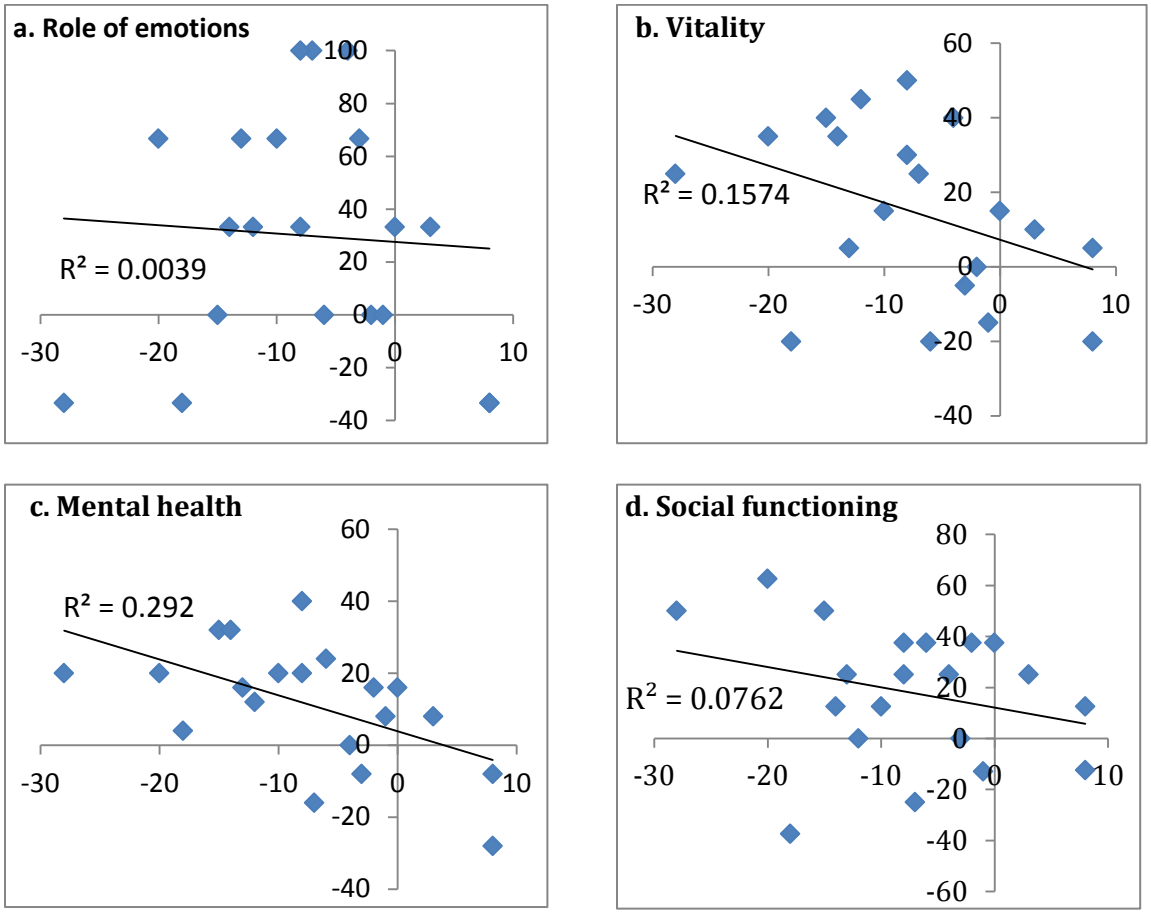
III.E.vi. Acknowledgements

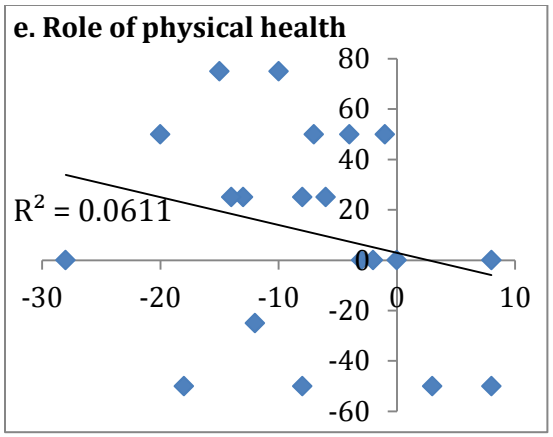
We would like thank running coach volunteers Jenna Boyd, Lauren Cudney, Beth Kennedy, Kathryn Litke, Anthony Nazarov, Melissa Parlar and Ryan Pyrke. Esther Pauls from the Running Den is also thanked for her assistance with group leadership.

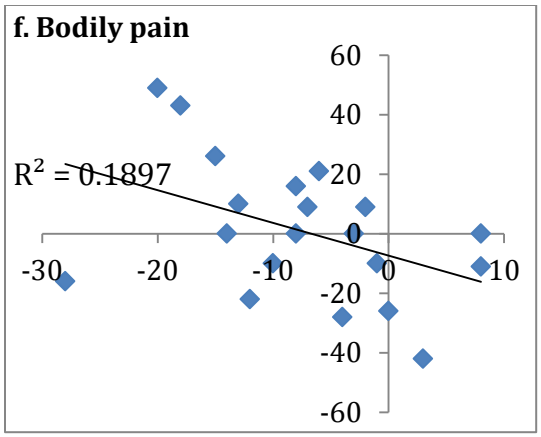
III.E.vii. Funding

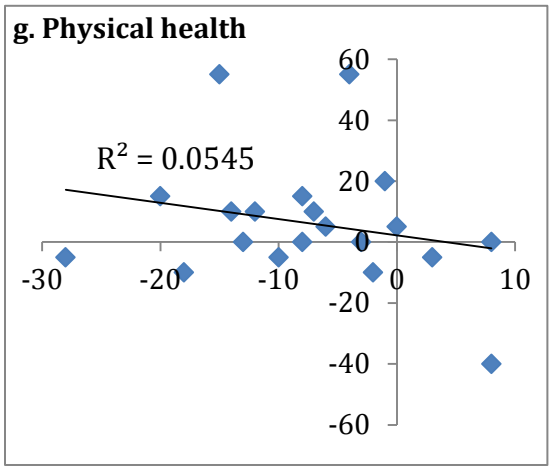
St Joseph's Healthcare Hamilton Foundation provided funding to support this study; specifically, we wish to acknowledge the following donors: Ontario Endowment for Children & Youth Recreation Fund at the Hamilton Community Foundation; Canadian Tire Financial Services; FGL Sports Ltd; Telus; and Jackman Foundation.

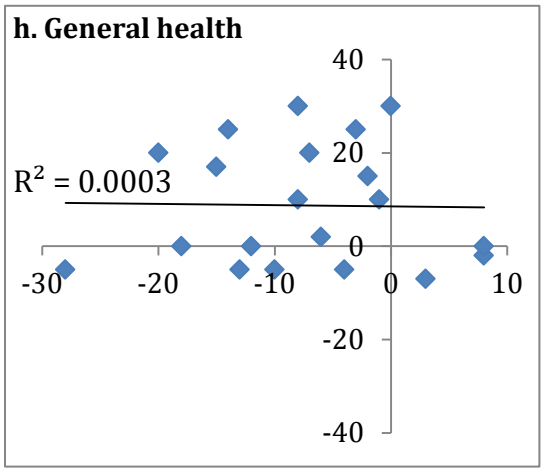
Figure III.1.: Change in BDI scores plotted against change in health-related quality of life subscale scores from pre to post assessments. BDI change score is plotted on the horizontal axis, and the SF36 change score is plotted on the vertical axis; the upper left quadrant of each graph represents improvement on both outcomes. Change scores for the following subscales are pictured below: a) Role of emotions in functioning; b) Vitality; c) Mental health; d) Social functioning; e) Role of physical health in functioning; f) Bodily pain; g) Physical health and h) General health.




e. Role of physical health
R² = 0.0611
80
60
40
20
0
-20
-40
-60
-30
-20
-10
0
10


f. Bodily pain
R² = 0.1897
60
40
20
0
-20
-40
-60
-30
-20
-10
0
10


g. Physical health
R² = 0.0545
60
40
20
0
-20
-40
-60
-30
-20
-10
0
10


h. General health
R² = 0.0003
40
20
0
-20
-40
-30
-20
-10
0
10

Introduction to Chapter IV

As noted in the Introduction to Chapter II, I noted in the Running Group that participants would on occasion come to the pre-running sessions, and then not run, usually due to injury. When reviewing the comments for Study 1, and as a result of volunteering with the group, I further noted that there was a lot of anxiety around meeting the demands of the running program. As a former runner, and current yoga enthusiast, I knew that yoga provided a supportive environment that promoted self-acceptance which, for myself and many people I knew, offered an additional level of stress relief. So, I wanted to explore the impact of yoga on the same outcomes we were evaluating in the running group. Further, I really wanted to explore a little more deeply the perceived social support aspect of structured, group-based exercise programs, and whether social support impacted the benefits we were observing in the running group, and that had been reported in the literature.

So the yoga study was designed to look a little deeper into the exercise and mental health matter, from a personal passion but also to begin to address some of the gaps that exist in the literature. The purpose of the study was to evaluate the effect of a low-impact, group-based exercise program on symptoms of stress, anxiety and depression, but also to investigate the possible relationship of perceived social support on stress, which had not been evaluated in previous studies, to our knowledge. I approached the owners of Chrysalis Yoga in Burlington, where I was a member, to see if they were interested in

partnering on the study. They were very interested, so I applied for a Natural Sciences and Engineering Research Council (NSERC) Engage grant, which supports small projects with industry partner, and we received $25,000 to fund the project. I was fully responsible for all aspects of this project, including the grant application, the Research Ethics Board procedure, hiring and training of the students, recruiting the participants, overseeing data collection, entry and analyses. I also attended most of the yoga sessions to provide support for the participants and to answer any questions.

My thesis supervisors and committee members were actively engaged in all aspects of this study, from the grant preparation, to study design, to writing of the manuscript. Allison Mizzi was an undergraduate student who managed much of the recruitment and data collection for the McMaster study, and provided feedback on the paper as well. My supervisors Dr. Sue Becker and Dr. Margaret McKinnon provided invaluable guidance on shaping the final manuscript into a compelling story on the benefits of yoga and bringing the cognitive control (mindfulness) element into the outcomes assessed.

All of the authors will provide final review and approval for the manuscript before it is submitted for publication, and will approve the final document once it has been accepted for publication.

Running head: Impact of yoga on mood, social and cognitive outcomes

Impact of yoga on stress reduction: Investigating multiple pathways via exercise, cognitive control and social interaction

Keating, L. E.[1], McKinnon, M. C. [1,2,3,4] Mizzi A.,[5] Sassi, R. B.,[1,2,3] Frey, B. N.,[1,2,3] Becker, S. [1,6]

[1]McMaster Integrative Neuroscience and Discovery

McMaster University, Hamilton, ON

[2]Department of Psychiatry and Behavioural Neurosciences

McMaster University, Hamilton, ON

[3]Mood Disorders Program, St Joseph's Healthcare Hamilton, Hamilton, ON

[4]Homewood Research Institute, Guelph, ON

[5]Department of Kinesiology, McMaster University, Hamilton, ON

[6]Department of Psychology, Neuroscience and Behaviour

McMaster University, Hamilton, ON

IV. ABSTRACT

The mental and physical health benefits of exercise are well established, and include improved neurocognitive function and stress reduction. Yoga poses fewer physical barriers than higher-impact exercise programs and confers potential advantages of increased cognitive control over one's mental state, and increased social support, each of which would be expected to impact stress levels via different neural pathways. Here, we examined the impact of yoga on stress and several key neurocognitive outcomes predicted to mediate stress reduction: cognitive control, hippocampal and social functioning. Methods: Healthy, sedentary adults aged 18-65 were randomized to a 12-week structured yoga program or to a wait-listed control group. Participants were assessed at baseline and post-intervention on measures of mood, social function and cognitive performance. Results: The yoga group (n=20) showed improvement on stress (p=0.02), loneliness (p=0.002), and several health-related quality of life subscales (p values $\leq$ 0.03), compared to controls (n=8). Within-group improvements in yoga participants were observed on the Mnemonic Similarity Task (p=0.006) and Paired Associate Learning (p=0.005), potentially reflecting hippocampal memory functions, and on the Stroop colour-word task (p=0.03), a measure of attention and inhibitory control. Regression and mediation analyses revealed that improved social support explained a significant portion of the variance in stress change scores, consistent with the hypothesis that social support mediates the stress-reducing impact of yoga (p-values $\leq$ 0.0005). Discussion: These results suggest yoga confers mental health benefits, as well as

improvements in social support, memory and cognitive control functions, possibly tapping into distinct neural pathways.

IV.B. INTRODUCTION

It is well established that exercise promotes physical health, with benefits including improved cardiovascular fitness and reduced risk of chronic disease (Thompson et al., 2003; Warburton, Nicol, & Bredin, 2006). Emerging research has sparked a recent surge of interest amongst clinicians and researchers regarding the potential neurocognitive and mental health benefits of physical exercise.

IV.B.i. The benefits of voluntary exercise in rodents

In rodents, voluntary exercise (usually wheel-running) has anti-depressant and anxiolytic effects (Duman et al., 2008), reverses stress-induced hippocampal-dependent memory deficits (Kim & Leem, 2016), and imparts resilience against subsequent stress (Kingston et al., 2018; Miller et al., 2018; Schoenfeld, Rada, Pieruzzini, Hsueh, & Gould, 2013). Along with its established impact on stress resilience, exercise further enhances hippocampal memory functions including fine spatial discrimination, maze learning, reversal learning and temporal order recognition memory (Creer et al., 2010; Grace et al., 2009; van Praag, Christie et al., 1999; van Praag, Kempermann, & Gage, 2000; van Praag et al., 2005), as well as markers of brain plasticity (Cotman & Berchtold, 2002; Gómez-Pinilla, Ying, Roy, Molteni, & Edgerton, 2002) and hippocampal neurogenesis (Kempermann et al., 2010; van Praag, Christie et al., 1999; van Praag, Kempermann et al., 1999; van Praag et al., 2005). Exercise also modulates dopaminergic transmission,

and associated learning and memory functions in rodents (Eddy, Stansfield, & Green, 2014; Landau, Lal, O'Neil, Baker, & Jagust, 2009).

IV.B.ii. The benefits of exercise in humans

Consistent with the pre-clinical rodent literature, in humans, exercise has anti-depressant effects (Blumenthal et al., 2007; Dimeo, Bauer, Varahram, Proest, & Halter, 2001; Keating et al., 2018; Krogh, Nordentoft, Sterne, & Lawlor, 2011; Krogh et al., 2012; Martinsen, Medhus, & Sandvik, 1985; Mota-Pereira et al., 2011; Paolucci, Loukov, Bowdish, & Heisz, 2018; Saeed, Antonacci, & Bloch, 2010; Trivedi et al., 2011), and imparts benefits on high interference memory tasks (Déry et al., 2013; Heisz et al., 2017) that have been linked to hippocampal neurogenesis (for a review, see (Becker, 2017)). Exercise has also been linked to improved executive functions, including set-shifting, moderated by a dopaminergic mechanism (Berse et al., 2015). Some (but not all) studies report that exercise improves working memory; a recent meta-analysis determined that its effect is significant but small (effect size was 0.27), and is modulated by age (Rathore & Lom, 2017). Chronic exercise training and higher physical fitness levels are also associated with a range of physiological benefits, including lower levels of chronic inflammation, improved inflammatory and anti-oxidant responses to acute exercise, and changes in serum neurotrophic factors, angiogenesis and cerebral circulation (Asano et al., 1998; Babaei, Alazi Alamdari, Soltani Tehrani, & Damirchi, 2013; Bouzid, Hammouda, Matran, Robin, & Fabre, 2015; Monteiro-Junior et al., 2018; Paolucci et al.,

2018; Petersen & Pedersen, 2005; Seifi-skishahr, Damirchi, Farjaminezhad, & Babaei, 2016). Finally, the monoamine neurotransmitters dopamine, noradrenaline, and serotonin are modulated by exercise (Clark et al., 2015; Lin & Kuo, 2013), and may contribute further to its anti-depressant effects; adequate levels of serotonin are required for neurogenesis (Klempin et al., 2013) and most anti-depressant medications raise levels of dopamine, noradrenaline, and serotonin in the brain (Belmaker & Agam, 2008; Nestler & Carlezon Jr., 2006). Taken together, these data suggest that exercise may impart resilience to stress and depression, among other benefits, via a range of potential mechanisms including regulation of inflammatory response, hippocampal plasticity and neurogenesis, and levels of monoamines. However, adoption of a high-impact fitness regime such as running, as has been used in many previous studies, may pose significant barriers for those with mental health issues, and may be contraindicated for people who have certain physical health issues. Therefore, it is important to explore alternative lifestyle interventions that may protect against stress and depression, while posing less of a barrier to those who are in greatest need of such interventions.

IV.B.iii. Non-exercise interventions: Yoga and mindfulness

Mindfulness is a type of cognitive control, and is commonly defined as the awareness that emerges through paying attention on purpose, in the present moment, and in a nonjudgmental way (Kabat-Zinn et al., 1992). Mindfulness-based meditation represents another lifestyle choice that can have potent anti-stress and anti-depressive effects (Becerra, D'Andrade, & Harms, 2016; Carmody & Baer, 2008; Chambers, Lo, & Allen,

2008; Gothe, Keswani, & McAuley, 2016; Rocha et al., 2012). Mindfulness is also associated with improved psychological well-being, vitality and social functioning (de Vibe et al., 2017; Moliver, Mika, & Khalsa, 2013; Yoshihara, Hiramoto, Sudo, & Kubo, 2011). Long-term practitioners of meditation show changes in multiple brain networks, including the dorsolateral prefrontal cortex (DLPFC) (Tang, Hölzel, & Posner, 2015), primary somatosensory cortex/superior parietal lobule (Fox et al., 2014; Villemure, Ceko, Cotton, & Bushnell, 2015), temporo-parietal junction (Hölzel et al., 2012), visual cortex and precuneus/posterior cingulate cortex (Hölzel et al., 2012; Villemure et al., 2015), superior temporal gyrus (Froeliger, Garland, & Mcclernon, 2012), orbitofrontal cortex (Fox et al., 2014; Froeliger et al., 2012; Villemure et al., 2015), anterior cingulate cortex (ACC) (Fox et al., 2014; Tang et al., 2015; Tang & Tang, 2015), posterior cingulate cortex (PCC) (Hölzel et al., 2012), hippocampus (Fox et al., 2014; Froeliger et al., 2012; Hölzel et al., 2012; Villemure et al., 2015), amygdala (Taren et al., 2015), insula (Fox et al., 2014; Froeliger et al., 2012), and the cerebellum (Fox et al., 2014; Froeliger et al., 2012; Hölzel et al., 2012). Mindfulness meditation practices may act on different neural pathways and impact distinct cognitive domains compared to physical exercise. Whereas exercise exerts effects more reliably on hippocampally-mediated memory functions (in both younger and older participants), and less reliably on working memory (particularly in the elderly), as reviewed above, mindfulness predominantly affects executive functions, including conflict monitoring (A. P. Jha, Krompinger, & Baime, 2007), working memory (Brunner, Abramovitch, & Etherton, 2017; Chambers et al., 2008; Gothe et al., 2016), attention (Bhayee et al., 2016; Chambers et al., 2008) and inhibitory

control (Becerra et al., 2016; Froeliger et al., 2012; Heeren, Van Broeck, & Philippot, 2009), possibly mediated by the DLPFC and ACC (Posner, Sheese, Rothbart, & Tang, 2007; Van Veen & Carter, 2002), although not all studies have found these benefits (Bojic & Becerra, 2017). Mindfulness can be assessed by a variety of means, including direct subjective scales of trait mindfulness and indirect but more objective measures of cognitive control over one's mental state, such as tests of attentional focus and inhibitory control.

IV.B.iv. The positive impact of social support

Social interaction is another lifestyle factor that is strongly implicated in coping with stress and resilience against depression. In a rodent stroke model, social support was linked to improved mortality (30-day survival rates) and increased levels of a protein involved in neurogenesis, brain-derived neurotropic factor (BDNF) (Venna et al., 2014). In humans, social isolation is associated with increased stress (Dumont & Provost, 1999; Wang et al., 2014) and mortality rates (the likelihood of death over a given time) (Holt-Lundstad et al., 2010), and impaired cognitive function (Cacioppo & Hawkley, 2009). Social support is a potential confound in the exercise and cognition literature, as levels of social support vary widely across exercise models used in studies (e.g., individual versus group exercise), and social functioning may improve as a result of participation in a group-based exercise program (Keating et al., 2018). Furthermore, some of the brain structures involved in mindfulness, namely the orbitofrontal cortex (Nestor et al., 2013), DLPFC and dorsomedial PFC, precuneus/PCC, and tempo-parietal regions (Meyer,

Spunt, Berkman, Taylor, & Lieberman, 2012) and the amygdala (Adolphs, 2010; Amara, 2002), have been implicated in social cognition. However, despite variability in social support across paradigms, this factor is rarely evaluated in analyses.

Given that exercise, mindfulness and social support may impart stress resilience via somewhat different mechanisms, a lifestyle intervention that incorporates all three of these factors could have the potential for more significant anti-depressant effects than exercise alone. Yoga is an appealing lifestyle choice that incorporates all of the above mentioned anti-stress factors. Like other forms of exercise, yoga has been associated with reduced levels of stress, depression, anxiety and cortisol (Granath, Ingvarsson, von Thiele, & Lundberg, 2006; Pascoe & Bauer, 2015; Rocha et al., 2012; Subramanya & Telles, 2009), as well as protection against age-related decline in grey matter (Villemure et al., 2015). Moreover, yoga carries a lower risk of physical injury compared to running (Cramer et al., 2015; van Gent et al., 2007). Studies that have examined the neurocognitive impact of yoga suggest that it improves a wide range of medial temporal lobe-related memory functions (verbal memory, visual memory, associative memory) and executive functions (attention, working memory, inhibitory control, mental set shifting) (Bhatia et al., 2017; Brunner et al., 2017; Gothe et al., 2016; Gothe, Kramer, & McAuley, 2014; Gothe & McAuley, 2015; Gothe, Pontifex, Hillman, & McAuley, 2013; Hariprasad et al., 2013; K. Luu & Hall, 2016; Quach, Jastrowski Mano, & Alexander, 2016; Rocha et al., 2012; Sharma et al., 2014; Subramanya & Telles, 2009). The impact of yoga on such a wide range of cognitive domains could be due to a simple improvement in attention that

in turn affects all areas of cognition. On the other hand, yoga may exert separable effects on memory via the exercise component, and on cognitive control functions via the mindfulness component. Yoga classes encourage mindfulness and relaxation by using slow, deep breathing, a practice which is thought to modulate the autonomic nervous system (Jerath, Edry, Barnes, & Jerath, 2006) and ending the class with several minutes of meditation in a deeply relaxing pose (savasana or corpse pose) accompanied by slow deep breathing. Yoga also typically incorporates more directly elements of mindfulness, therefore demanding a high level of focused attention to the instructor and to correctly carrying out each pose, in synchrony with deep breathing. All of these factors suggest that yoga should improve mindfulness and cognitive control, as reflected by measures of attentional focus and inhibitory control. Finally, there is also a social support component to regular yoga, in particular when one commits to a specific class, teacher and/or studio. Therefore, yoga classes represent an ideal model to explore the mental, cognitive and social benefits associated with group exercise as a lifestyle intervention.

IV.B.v. Study 3: Objectives

Given that yoga incorporates elements of exercise, mindfulness and social support, we hypothesized that yoga would exert separable effects on stress via its impact on the hippocampus/medial temporal lobe, the prefrontal cortex, and networks subserving social interaction. The present study was designed to test this hypothesis. We predicted that the impact of yoga training on stress levels would be mediated separately by these three systems, 1) exercise-modulated improvements in hippocampal plasticity and integrity, as

reflected in hippocampal-related memory functions, 2) improvements in prefrontal cognitive control over one's mental state (e.g. mindfulness), as indexed by measures of focused attention and inhibitory control, and 3) networks subserving social interaction, reflected by increased perceived levels of friendship and social support.

In the current study, participants were randomly assigned to a yoga or to a control group, and we assessed pre- and post-intervention performance on a wide battery of mood scales, measures of social functioning and of health-related quality of life, and cognitive tasks, with a focus on tests of hippocampal-related memory functions (high interference visual recognition memory and paired associate learning), executive functions (digit span, Stroop interference, rapid serial visual processing) and social functioning. Analyses were aimed at testing the prediction that yoga would exert effects on mood via three dissociable mechanisms: exercise, mindfulness/cognitive control and social support.

IV.C. METHODS

This study was reviewed and approved by the Hamilton Integrated Research Ethics Board, the McMaster Research Ethics Board and the Humber College Research Ethics Board. A randomized, parallel group study design was employed to determine if a regimented 12-week yoga program improved mental, social and neurocognitive outcomes compared to non-exercising control participants.

IV.C.i. Study participants

Potential participants were between the ages of 18-65 years, and were excluded if they were engaging in physical exercise for more than one hour per week for the majority of weeks in the previous three months (routinely walking e.g., to school or work was considered acceptable), or had a current, untreated mood disorder. Participants completed the PAR-Q & You® test of physical readiness (Canadian Society for Exercise Physiology, 2002) to ensure that they were physically able to participate in the study, and provided written informed consent. Study participants were recruited for two related but different randomized control studies examining the impact of yoga on mood, cognitive and social outcomes. In Yoga study 1, participants were randomized to either a structured yoga program held at the Chrysalis Yoga studio in Burlington, Ontario, Canada, or to a non-exercising wait-listed control group. These participants were recruited from an email sent out to 3,500 members of their community, as well as on local Facebook community groups. By contrast, participants in Yoga study 2 were randomized to either a structured

yoga program or to a visualization control group. These participants were recruited using posters at the McMaster University campus, McMaster's online research site for undergraduates, and posts on Facebook. In Yoga study 2, all participants were required to attend yoga classes taught either on the McMaster University campus in Hamilton, Ontario, Canada.

IV.C.ii. Pre- and post-intervention assessments

Paper-based assessments

Beck Depression Inventory® Second edition (BDI-II; licensed by PsychCorp) (Beck et al., 1996): The BDI-II is a 21-item self-report questionnaire used to assess depressive symptoms.

Beck Anxiety Inventory® (BAI; licensed by PsychCorp) (Beck et al., 1988): The BAI is a 21-item self-report questionnaire used to assess the severity of an individual's symptoms of anxiety.

Cohen's Perceived Stress Scale (PSS) (Cohen et al., 1983): The PSS is a widely used, freely available self-report instrument for measuring the perception of stress. The PSS consists of 10 items measuring the degree to which situations are perceived as stressful.

36-Item Short Form Survey (SF-36): The SF-36 is a 36-item self-report assessment used to measure health-related quality of life. Participants respond to questions by selecting a

response on a Likert-type scale. The survey generates a total score that can be sub-divided into two domains of four subscales each: the Physical Component Score (limitations in physical activities, limitations in social activities due to physical health issues, limitations in usual activities due to physical health issues, bodily pain) and the Mental Component Scale (general mental health, limitations in usual activities due to emotional problems, vitality and general health perceptions) (Ware Jr. et al., 1994; Ware Jr. & Sherbourne, 1992).

NIH Toolbox ® Emotion (Gershon et al., 2013) is a battery that includes measures of social support as assessed by the loneliness, friendship and perceived emotional support scales (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox/intro-to-nih-toolbox/emotion). All items are completed as self-report.

Stroop Color-Word Task (Stroop, 1935): this task assesses inhibitory control, specifically, the ability to suppress a habitual response in favor of a less familiar one, and provides additional indices of selective attention and processing speed (word reading and color identification).

Computer Based assessments:

Mnemonic Similarity Task (MST): We used a variant of Kirwan et al's MST (Kirwan & Stark, 2007) as described by Déry et al (Déry et al., 2013): A set of images was presented sequentially in randomized order to the participant. During the presentation period, the

participant underwent an incidental encoding task and was not alerted to the fact that they would be subsequently prompted to recognize the images they had seen. In the recognition part of the task participants were shown another set of images. Some of these images were the same as ones presented in the presentation trial, some were lure images (highly similar images of the same object presented in list one), and others were new (not previously seen). The participants were asked to judge whether each object presented in the second list was new, similar (highly similar to a previous image) or old (a repetition of a previous image).

Paired Associate Learning (PAL): The CANTAB-like PAL assesses visuo-spatial associative learning and memory, tapping into hippocampal and cortical pathways. It is a useful tool for assessing patients with dementia, Alzheimer's disease, and age-related memory loss. In this assessment, boxes were displayed on the screen and opened in a randomized order and displayed either blank screen or a random pattern. The patterns were then displayed in the middle of the screen, one at a time, and the participant was required to touch the box where the pattern was originally located. If the participant made an error, the trial was restarted, starting at one image and working up to eight, reflecting increased difficulty throughout the test.

Rapid visual information processing (RVP): The CANTAB-like RVP is a highly demanding test of sustained attention. It is sensitive to dysfunction in the parietal and prefrontal cortices. In this assessment, a white box appeared in the center of the computer

screen, inside which digits from 2 to 9 appeared in a pseudo-random order, one at a time, at the rate of 100 digits per minute. Participants were asked to detect target sequences of three digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses using the keyboard.

IV.C.iii. Yoga intervention protocol

In both studies, the yoga groups followed the instructions of the certified yoga teacher. However, the experiences of the control groups in each of the study differed. Specifically, in Yoga Study 1, controls were waitlisted and asked to refrain from engaging in exercise for the study period; in Yoga Study 2, the visualization control participants were required to attend the yoga classes, listen to the instructor and visualize the poses but not engage in any exercise. All participants randomized to the structured yoga program condition attended classes held at the Chrysalis Yoga studio in Burlington, Ontario (Yoga Study 1), or in a private room on campus at McMaster (Yoga Study 2). Given the differing protocol for controls in these two studies, Yoga Study 2 control participants were not included in the analyses presented here. Therefore, a total of 28 participants were recruited and randomized to the Yoga Study 1 ($n=17$) and Yoga Study 2 ($n=6$) groups, or to the Yoga Study 1 wait-listed control group ($n=11$). All participants were female.

Three controls and three yoga participants dropped out, resulting in an end-of-study sample size of 28, with 20 in the yoga group and 8 in the control group. The randomization list was generated for 40 participants a priori, and due to chance sampling,

there were more yoga participants enrolled in the early stages, and more controls assigned to the later stages. Since we were not able to recruit all 40 participants, and because we did not include the controls from the Yoga Study 2, there were fewer controls than yoga participants in the current study.

Each study session took place over 12 weeks in four different sessions. Baseline cognitive, clinical, and functional assessments were carried out within the two weeks prior to the start of yoga sessions (Session 1: June 2015; Session 2: September 2015; Session 3: January 2016; Session 4: January 2017). End-of-study assessments were completed within two weeks following the last yoga class. Baseline and end-of-study assessments included the battery of self-report surveys of mental and physical health and cognitive tests listed above. Pre- and post-program cognitive and clinical tests were performed on a windows computer and on paper.

Yoga classes: Participants assigned to the yoga group participated in 1-hour beginner's hatha yoga asana-style classes led by a certified yoga instructor, twice per week, for 12 weeks. Classes were held in a private, regular temperature room at Chrysalis Yoga Studio in Burlington, Ontario or in a private room on McMaster campus. The instructors led the class in a traditional way, using only a mat with blocks or straps as needed. Classes started with standing poses, moving to sitting, often included an inversion, and always ended with the final savasana resting pose. All poses were taught with modifications to ensure everyone in the class could participate, and the goal was to go deeper into the basic poses over the course of the 12 weeks, and to safely improve balance, flexibility

and strength. Class attendance for all groups was recorded. At the end of the study period, the baseline assessments were repeated, including the battery of cognitive and clinical assessments. The controls were asked to continue with their normal routines during the 12 weeks, and to delay any exercise programs until completion of the end of study assessments. All of the wait-listed controls were offered the opportunity to participate in the study after the 12 weeks, however, their subsequent participation in the yoga component and pre- and post-yoga assessments were not included in the present analyses. All participants received compensation upon completion of baseline and end of study assessments, as well as a complimentary, two-month membership to the yoga studio.

IV.C.iv. Statistical analyses

Between-group differences in mean outcomes were assessed using Student's t-tests. Within-group changes from baseline to end of study were assessed using paired t-tests. We investigated the impact of neurocognitive and social function on stress using regression and mediation analyses, to explore possible indirect effects (Baron & Kenny, 1986). All analyses were performed using SAS® for Windows, version 9.4 (Cary, NC).

IV.D. RESULTS

There was no significant difference in age between the yoga (mean 38.0 ± 14.4, range 19.0 to 65.1) and control (mean = 39.9 ± 16.2, range 19.0 to 64.7; t=0.3, df= 29, p=0.7) participants. All participants were female.

IV.D.i. Stress and mood outcomes

The results of within-group and between-group comparisons of mood scores are summarized in Table IV.1 and pictured in Figure IV.1A. The only measure of mood that was significantly different between the groups was the stress change score (t=2.5, df= 26, p=0.02); yoga participants showed larger pre-to-post improvement in stress levels than controls. Within-group comparisons revealed that whereas yoga participants had significantly lower stress (t=-3.9, df=19, p=0.001) and depression scores (t=-3.1, df=18, p=0.006) at post-test relative to their baseline scores, controls showed no significant change.

IV.D.ii. Social functioning outcomes

The results of within-group and between-group comparisons of scores on measures of perceived social support are summarized in Table IV.1. Between-group comparisons revealed a significant difference between Loneliness scores for yoga compared to control participants (t=3.5, df=26, p=0.002). Within-group comparisons also revealed significant improvement in the Loneliness scale (-2.8 ± 2.7; t=-3.8, df=13, p=0.002) from baseline to

end of study in the yoga group (see also Figure IV.1B); no improvements were observed in the control group.

IV.D.iii. Health-related quality of life

The results of within-group and between-group comparisons of the SF36 health-related quality of life scores are summarized in Table IV.2; the SF36 mental health subscales and the NIH Loneliness Scale are pictured in Figure IV.1B. Between-group comparisons revealed significant impacts of yoga on the role of physical symptoms in functioning (t=-2.7, df=24, p=0.01), bodily pain (t=-2.8, df=24, p=0.01), vitality (t=-2.3, df=24, p=0.03), and mental health (t=-2.3, df=24, p=0.03). Consistent with these between-group results, within-group comparisons revealed that yoga participants had significantly improved scores on all of these same measures of health-related quality of life, in addition to improved general health (t=2.4, df=18, p=0.03), social functioning (t=2.5, df=18, p=0.04) and role of emotions (t= 3.3, df=18, p=0.004) at post-test relative to their baseline scores; no differences were identified for control participants on any of the quality of life measures.

IV.D.iv. Neurocognitive function

The results of within-group and between-group comparisons of scores on measures of cognitive functioning are summarized in Table IV.3. As can be seen in Figure IV.1C, controls showed improved performance on the backwards Digit Span task compared to the yoga participants (t=1.9, df=23, p=0.06); there were no other improvements for the

controls. Within-group analyses revealed improved performance at post-test relative to baseline for the yoga group on two hippocampal-dependent tasks: correct identification of highly similar and challenging lure images in the MST (8.1 ± 11.7; t=3.1, df=19, p=0.006) and percent correct performance on the Paired Associate Learning task (-1.1 ± 1.4; **t=**-3.2, df=18, p=0.005). In addition, we identified improvements on the color only (t=2.0, df=19, p=0.06) and the color-word interference (t=2.4, df=19, p=0.03) conditions of the Stroop test, the latter being a measure of inhibitory control and attention. Of note, though the PAL score is larger for controls than yoga participants (see Figure IV.1), there was a large standard deviation so the result was not significant.

IV.D.v. Linear regression and mediation analyses

Linear regression

In order to investigate the relationships between stress, social functioning and neurocognitive outcomes, we performed multiple regression analyses using only the yoga participants' data to determine what factors might impact the outcome of stress change from baseline, with predictor variables attendance, age, and change scores for social functioning, loneliness, and measures of hippocampal (MST, PAL) and executive (Stroop color-word incongruent task, RVP) functioning. The only factors that were significantly associated with stress change scores were those related to social functioning – changes in SF36 social functioning subscale and the NIH Loneliness scale were significant separately; when both were included in the model, only improved Loneliness scores were

significantly associated with improved stress from baseline to end of study, accounting for 54% of the variability in the model, respectively ($F=19.1$, $df=1, 17$, $p=0.0005$).

Mediation analyses

In order to investigate further whether neurocognitive and social functioning mediated the impact of yoga participation on stress outcomes, we performed mediation analyses with attendance level in yoga classes as the main predictor variable, change in stress scores from baseline to end of study as the outcome variable of interest, and the following change scores as potential mediating factors: SF36 social functioning subscale, NIH Loneliness, MST on similar (lure) trials, PAL total correct, Stroop color-word mismatch and RVP total correct. The change scores for stress were mediated by changes in the SF36 social function subscale ($b=-0.6$, $SE=0.11$, $t=-5.8$, $p<0.0001$) and the NIH Loneliness Scale ($b=0.8$, $SE=0.09$, $t=8.4$, $p<0.0001$) scores. However, none of the neurocognitive measures were found have significant mediating effects ($p>0.2$). These results were consistent when the McMaster yoga participants were excluded from the analyses. The regression and mediation results, taken together, suggest that improved social functioning associated with participation in a structured group yoga program may explain, in part, improved stress scores, and may involve overlapping pathways of stress response and social functioning. The relationship between perceived social support and perceived stress is illustrated in Figure IV.2. Perceived stress scores, plotted on the Y axis, indicate improvement from baseline if they are negative. The social subscales scores are plotted on the X axis. The yoga group participants are indicated by the black

diamonds, while the control group participants are indicated by the grey circles. The shaded areas of each graph indicate the quadrant where both scores improved from baseline. Scores that cluster around the axis indicate little or no improvement. As the figures show, the yoga participants tend to cluster in the quadrant where both scores improved, indicated by the shaded areas of the three graphs. However, the control participants tend to cluster along the X and Y axes, indicating little change from baseline. To control for outliers potentially affecting results in the control group, we computed the 95% percentile confidence interval around the correlation between Loneliness and Stress change scores using bootstrapping to generate 500 datasets of the R-squared statistic). The estimated R-square was 0.44, with a 95% confidence interval of 0.01 and 0.87, confirming the statistically significant positive correlation was not driven by the outlier data point in the top right quadrant for the control group (see Figure IV.2a).

Table IV.1: Self-report measures of mental health and functioning

	Between-sample analyses: Change from baseline			**Within-sample analyses: Change from baseline**	
Assessment tool	**Yoga**	**Control**	**Yoga compared to Control**	**Yoga**	**Control**
Mood Scales					
BDI[b]	-6.8 ± 9.6	-0.6 ± 7.5	t=1.6, df=25, p=0.12	**t=-3.1, df=18, p=0.006**	t=-0.2, df=7, p=0.8
BAI[b]	-3.5 ± 9.9	2.3 ± 8.7	t=1.4, df=25, p=0.2	t=-1.6, df=19, p=0.13	t=0.7, df=7, p=0.5
PSS[b]	-4.2 ± 4.9	1.9 ± 8.1	**t=2.5 df= 25, p=0.02**	**t=-3.9, df=19 p=0.001**	t=0.7, df=7, p=0. 5
NIH Toolbox ® Emotion					
Emotional Support[a]	1.9 ± 6.2	0.13 ± 6.6	t=-0.7, df= 26, p=0.5	t=1.4, df=19, p=0.2	t=0.05, df=7, p=1.0
Friendship[a]	1.4 ± 5.3	0.8 ± 6.5	t=-0.2, df=26, p=0.8	t= 1.2, df=19, p=0.3	t=0.4, df=7, p=0.7
Loneliness[b]	-2.6 ± 2.9	1.5 ± 2.4	**t=3.5, df=26, p=0.002**	**t=-4.0, df=19, p=0.0008**	t=1.7, df=7, p=0.13

Table IV.2: Health-related quality of life

	Between-sample analyses: Change scores			**Within-sample analyses: Change scores**	
Assessment tool	**Yoga**	**Control**	**Yoga compared to Control**	**Yoga**	**Control**
SF-36 Health-Related Quality of Life scale[a]					
Physical functioning	2.9 ± 15.2	-7.9 ± 13.5	t=-1.6, df=24 p=0.11	t=0.8, df=18, p=0.4	t=-1.5, df=6, p=0.2
Role of physical	31.6 ± 37.1	-14.3 ± 43.0	**t=-2.7, df=24, p=0.01**	**t=3.7, df=18, p=0.002**	t=-0.9, df=6, p=0.4
Bodily pain	14.5 ± 19.2	-8.6 ± 17.4	**t=-2.8, df=24, p=0.01**	**t=3.3, df=18, p=0.004**	t=-1.3, df=6, p=0.2
General health	8.4 ± 15.4	0.1 ± 14.2	t=-1.2, df=24, p=0.2	**t=2.4, df=18, p=0.03**	t=0.03, df=6, p=1.0
Vitality	16.1 ± 15.0	-0.7 ± 19.9	**t=-2.3, df=24, p=0.03**	**t=4.7, df=18, p=0.0002**	t=-0.1, df=6, p=0.9
Social functioning	12.6 ± 24.3	-1.8 ± 22.2	t=-1.4, df=24, p=0.2	**t=2.5, df=18, p=0.04**	t=-0.2, df=6, p=0.8
Role of emotions	28.1 ± 37.3	0 ± 43.0	t=-1.6, df=24, p=0.11	**t=3.3, df=18, p=0.004**	t=0, df=6, p=1.0
Mental health	13.3 ± 16.7	-3.3 ± 14.0	**t=-2.3, df=24, p=0.03**	**t=3.5, df=18, p=0.003**	t=-0.6, df=6, p=0.6

[a] Higher/positive scores indicate improvement; [b] Lower/negative scores indicate improvement

Table IV.3: Neurocognitive assessments

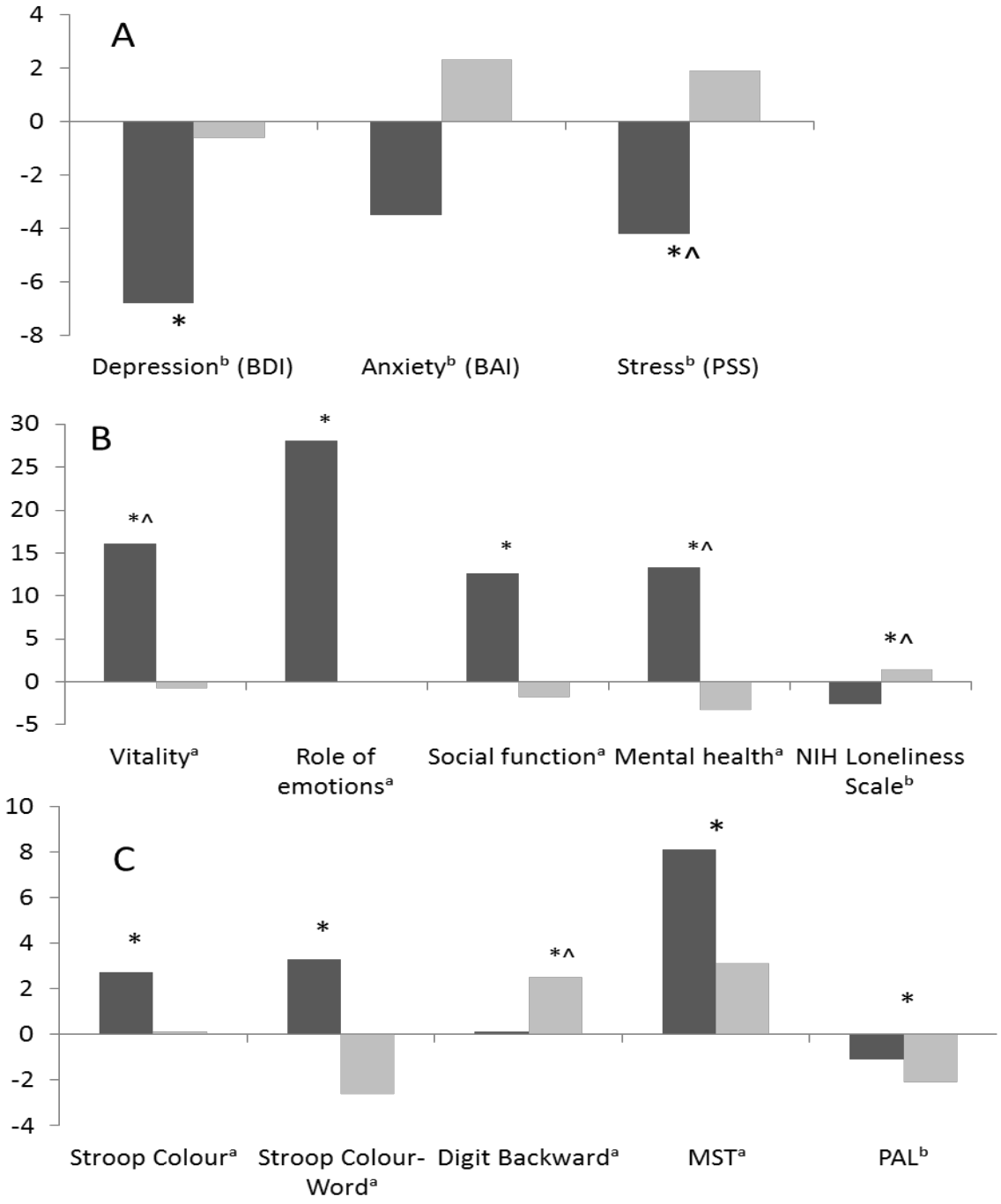
	Between-sample analyses: Change from baseline			**Within-sample analyses: Change from baseline**	
Assessment tool	**Yoga**	**Control**	**Yoga compared to Control**	**Yoga**	**Control**
Measures of Executive Function					
Stroop Color-Word Task					
Word only[a]	2.3 ± 14.5	0.1 ± 9.7	t=-0.4, df=26, p=0.7	t=0.7, df=19, p=0.5	t=0.04, df=7, p=0.97
Colour only[a]	2.7 ± 6.0	0.1 ± 7.7	t=-0.9, df=26, p=0.4	**t=2.0, df=19, p=0.06**	t=0.05, df=7, p=0.96
Colour-word interference[a]	3.3 ± 6.2	-2.6 ± 12.1	t=-1.3, df=8.5, p=0.2	**t=2.4, df=19, p=0.03**	t=-0.6, df=7, p=0.6
WAIS Digit Span					
Forward task[a]	-0.3 ± 2.6	0 ± 2.2	t=0.3, df=23, p=0.8	t=-0.5, df=18, p=0.6	t=0, df=6, p=1.0
Backward task[a]	0.1 ± 2.7	2.5 ± 2.3	**t=1.9, df=23, p=0.06**	t=0.2, df=18, p=0.9	**t=2.6, df=6, p=0.05**
Sequential task[a]	0.1 ± 2.3	-0.3 ± 1.0	t=-0.4, df=23, p=0.7	t=0.2, df=18, p=0.8	t=-0.8, df=6, p=0.5
RVP[a]	-5.0 ± 14.2	-2.3 ± 6.6	t=0.7, df=25.2, p=0.5	t=-1.6, df=19, p=0.13	t=1.0, df=7, p=0.4

Table IV.3: Neurocognitive Assessments continued

Measures of Hippocampal-Dependent Memory					
MST[a]	8.1 ± 11.7	3.1 ± 19.1	t=-0.9, df=26, p=0.4	**t=3.1, df=19, p=0.006**	t=-0.5, df=7, p=0.7
PAL[b]	-1.1 + 1.4	-2.1 ± 4.3	t=-0.7, df=7.8, p=0.5	**t=-3.2, df=18, p=0.005**	t=-1.4, df=7, p=0.2

[a] Higher/positive scores indicate improvement; [b] Lower/negative scores indicate improvement

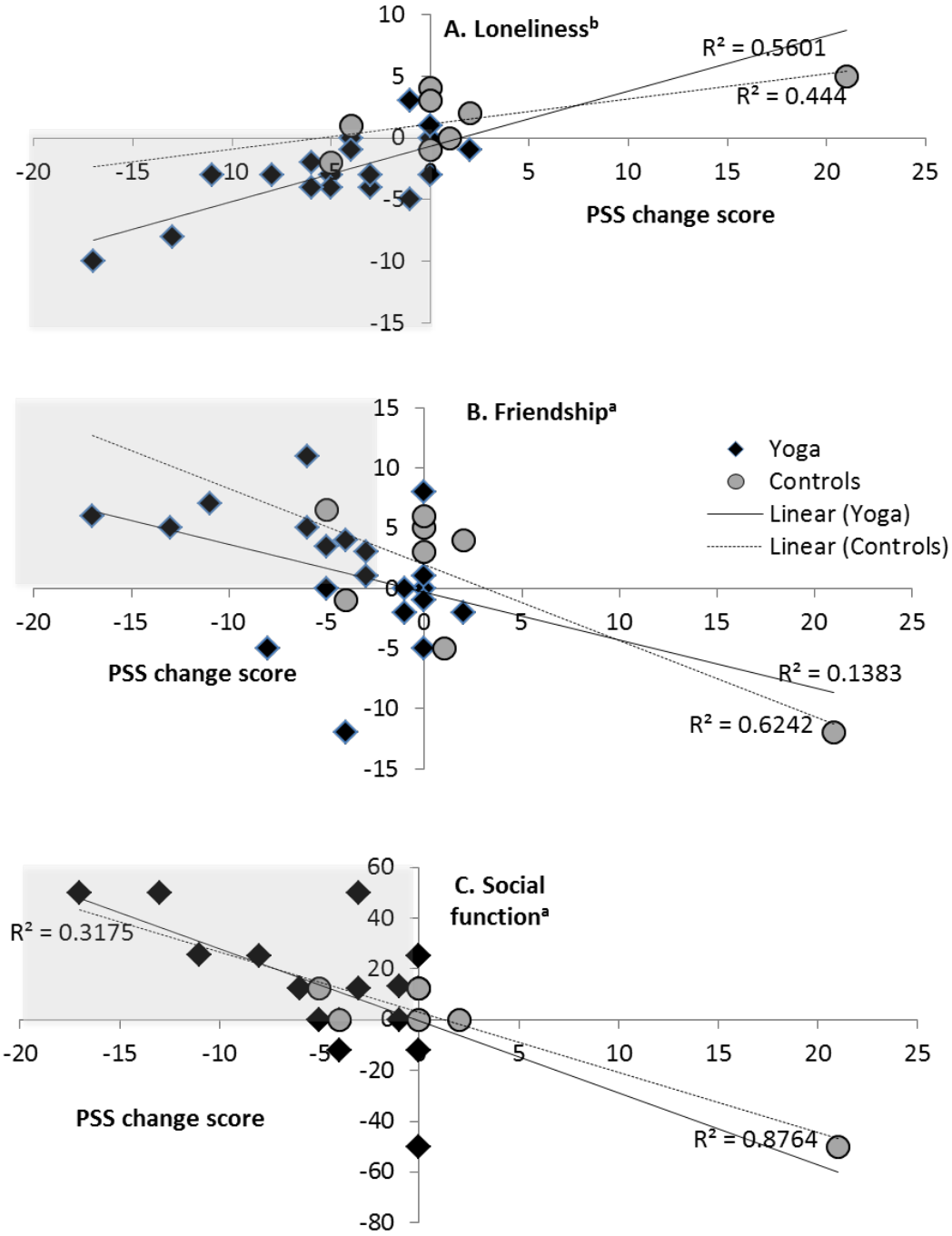
Figure IV.1: Changes in mood, social and neurocognitive functioning scores from pre to post assessment



[a]Higher/positive score indicates improvement
[b]Lower/negative score indicates improvement
*Within-group $p<0.04$ ^Between-group $p<0.05$

Figure IV.2: Stress and social support change scores

A. Loneliness subscale (negative scores are improved); B. Friendship subscale (positive scores are improved); C. Social functioning subscale (positive scores are improved)



IV.E. DISCUSSION

IV.E.i. Summary of results

The current study evaluated the social, mood-related and cognitive benefits of participating in a structured yoga program, with a specific goal to investigate the roles of perceived social support, exercise (as indexed by hippocampally-mediated memory functions) and mindfulness or cognitive control over one's mental state (as indexed by measures of attention and inhibitory control) in contributing to stress reduction and improved mood. As expected, whereas the yoga group had significant improvements in depression and stress scores, there were no significant improvements in the non-exercising control participants. We also observed improvements in the yoga participants on several health-related quality of life subscales, including bodily pain, the role of physical symptoms in functioning, general health, vitality, the role of emotions in functioning, social functioning and mental health, as well as improvements in perceived social isolation, as measured by the NIH Toolbox® Loneliness scales (Gershon et al., 2013). The yoga group also showed improved performance not only on the two putatively hippocampal-dependent memory tests – the MST, a test of high interference memory and potential correlate of improved hippocampal neurogenesis (Becker & Wojtowicz, 2006; Déry et al., 2013; Kirwan, Jones, Miller, & Stark, 2007), and on the PAL, a visuo-spatial associative memory tasks which reflects hippocampal integrity (de Rover et al., 2011) -- but also on cognitive control, with improved performance on the color and color-word interference Stroop subtasks, measures of processing speed, inhibitory control and

selective attention(Banich et al., 2000; Pardo, Pardo, Janer, & Raichle, 1990). Although improvements in measures of memory, cognitive control and social function were observed in the yoga group, regression and mediation analyses identified only social functioning, and no cognitive factors, as explaining and potentially mediating the relationship between yoga and stress from baseline to end of study.

IV.E.ii. Comparison to the literature

The neurocognitive benefits observed in the yoga group are consistent with studies reporting improved executive function and working memory associated with participation in yoga (Brunner et al., 2017; Gothe & McAuley, 2015) and mindfulness programs (Becerra et al., 2016; Bhayee et al., 2016; Chambers et al., 2008; Froeliger et al., 2012; Heeren et al., 2009). Further, the ability to differentiate highly similar lures in the MST has been shown to improve after high-impact exercise training in healthy young adults (Déry et al., 2013; Heisz et al., 2017) and to be impaired in aged adults (Yassa et al., 2011) and those with hippocampal damage (Kirwan et al., 2012). Thus, our findings of improved performance on the MST and on the CANTAB-like PAL task in the yoga participants are consistent with our prediction that yoga would impart an exercise-based benefit on hippocampally-mediated memory functions.

The impact of yoga on mood reported herein is also consistent with well-established exercise-related improvements in symptoms of depression (Josefsson et al., 2014) and stress (Pascoe & Bauer, 2015). We also report the positive impact of participation in a

structured group program on several measures of health-related quality of life, which is consistent with cross-sectional (Anokye, Trueman, Green, Pavey, & Taylor, 2012; Laforge et al., 1999), but not intervention (Imayama et al., 2011), studies. Data from rodent studies suggest further that the benefits of exercise are counteracted by excess stress in a forced exercise paradigm (Lerman et al., 2002; Svensson et al., 2016); this might explain why people who voluntarily participate in exercise, as captured in a cross-sectional design, might have better outcomes than those in a RCT, where the exercise is mandated by the study group assignment, and motivation for participation is not usually reported.

Although few exercise studies have examined the social support aspect, the finding of improved social support in a group-based yoga program reported here is consistent with recently published findings of improved feelings of friendship in youth and adults with mood disorders in a group-based running program (Keating et al., 2018) and for improved HRQOL including social functioning associated with mindfulness (de Vibe et al., 2017). Here, we describe the novel finding that improved social support may partially mediate the impact of yoga on stress reduction. On the other hand, we did not find either hippocampal memory or cognitive control functions to be significant in mediation analyses. The pattern of social, neurocognitive and mood benefits presented here is broadly consistent with the current literature which implicates different but overlapping neural pathways associated with exercise and mindfulness benefits. Better understanding of the relations between these functional outcomes could be beneficial for stress

management in general, and may be especially helpful for the therapeutic use of exercise programs to improve outcomes for people with mood disorders.

IV.E.iii. Implications for underlying systems

The current results are consistent with at least three different underlying pathways, contributing to the mental and neurocognitive benefits associated with a mindfulness- and group-based yoga program. The exercise component of the program may have had a positive effect on the PAL and on the high interference trials of the MST task via the hippocampus, as discussed above. By contrast, the mindfulness component may have had a positive impact cognitive control functions via cortical structures including the DLPFC, orbitofrontal cortex and ACC (Fox et al., 2014; Posner et al., 2007; Tang et al., 2015; Tang & Tang, 2015; Van Veen & Carter, 2002), regions that have also been implicated in social functioning (Adolphs, 2010; Amara, 2002; Meyer et al., 2012; Nestor et al., 2013). However, in contrast to our predictions, social support, but not cognitive function, was a significant predictor in the mediation analysis, indicating social support was associated with stress reduction in our sample. Unfortunately, the design of our study did not allow us to assess the direction of causality of social support on stress reduction (or vice versa), nor the potentially direct relation between increased mindfulness and enhanced performance on measures of cognitive control; see next section for details.

IV.E.iv. Limitations

The current study has several limitations. One possible effect is time of year as the end of study assessments were sometimes conducted at times when life events such as holidays or final exams could be associated with elevated stress levels. Unfortunately, the current sample size was not big enough to evaluate possible seasonal effects. A second limitation concerns the time of day that testing was completed. As most of the sample included working women and students, assessments were often done in the evening, perhaps after a long day that could have impacted cognitive functioning. However, both controls and yoga participants were exposed to these conditions, which were consistent at baseline and end of study, thus any possible effect of timing should have been the same across evaluation sessions. A third limitation could be the length of the intervention itself, as there is some evidence that cognitive benefits may take up to six months to respond to the effects of yoga (Rocha et al., 2012), and may improve at a slower pace than mood symptoms (Herrera-Guzmán et al., 2009). Anecdotal observation and conversation with the study participants further suggests that beginning a yoga program was in itself stressful, possibly causing further delay of observable benefits. Therefore, a longer intervention period with repeated evaluations would provide better insight as to how yoga might impact stress, mood, social and cognitive outcomes over time. Fourth, though the regression and mediation analyses indicate that improved social functioning is significantly related to improved end-of-study stress scores, we are not able to determine whether there is an indirect *causal* relationship between yoga and stress reduction via social support. In order to evaluate this, we would need to assess both social support and

stress at multiple time points in a longitudinal study design (Baron & Kenny, 1986; MacKinnon, Fairchild, & Fritz, 2007). Our findings are consistent with the hypothesis that social functioning mediated the improvement in stress scores; however, because social support and stress were assessed at the same end of study time point, we cannot rule out other alternative explanatory models, e.g. yoga impacted another variable that we did not assess, in turn causing improved social support and stress scores, or improved stress scores caused improvements in social support. In addition, the single post-intervention time point does not allow us to investigate the stability of this relationship over time (MacKinnon et al., 2007). Therefore, the most we can conclude from this analysis is that social function is related to the improved stress outcome scores; whether or not this is a causal relationship, or includes other factors (for example, improved depression scores), should be explored in future research. Finally, the sample size was small, particularly among the control group; further research with a larger group of participants would help to address some of the knowledge gaps in this area.

IV.E.v. Future Research

The Yoga study 2 participants represent a pilot for a larger study of yoga compared to a visualization control group. Participants assigned to the visualization control group are required to attend the same classes as the yoga group, and listen to the instructor, therefore they will have the same relaxing, mindfulness and social connection to the group as the yoga participants, which will enable us to tease out the benefits of exercise compared to social functioning on mood and stress outcomes. In addition, given that

cognitive benefits may take up to six months to be detectable (Rocha et al., 2012), the current study should be replicated over a longer period of time, also allowing for investigation of possible effects of time of year on stress outcomes. Neuroimaging studies could provide additional insight into the pathways involved in moderating observable outcomes, and how different types of exercise impact neural networks. Finally, more direct assessments of mindfulness would be a useful adjunct to assess the impact of yoga on stress reduction via its role in improving mindfulness.

IV.E.vi. Overall conclusion

The current study provides support that participation in a structured, group-based yoga program is associated with improved mood, cognitive, and social function in otherwise healthy, sedentary adults. These results are broadly consistent with our predictions that group-based exercise programs can impact at least three separate systems: the hippocampus/medial temporal lobe via the exercise component, prefrontal cognitive control systems via the mindfulness component, and the social cognition pathway via social support. Although yoga led to improvements in multiple measures including memory, cognitive control, social support and stress, our more specific prediction that these three pathways would mediate the impact of yoga on stress reduction garnered limited support, with evidence that social support is the only factor significantly related to the stress-reducing impact of yoga. Improved understanding of the psychological benefits associated with exercise programs that include cognitive demand and social support could have implications for people with mental illness, which is characterized by social,

mental and cognitive impairments. The current study provides a foundation for further investigation of this intricate and important relation between exercise, social support, stress and psychological and neurocognitive outcomes.

IV.E.vii. Acknowledgements

Thanks to McMaster PNB administrative staff and to our partners and collaborators at Chrysalis Yoga in Burlington. Special thanks to yoga instructors Richard Filc at McMaster, and Jennifer Denney and Deborah McNairn at Chrysalis Yoga. We also thank undergraduate students in the Becker Lab Nina Dabic and Sandra Cooper for their assistance with recruitment and assessments of the McMaster study participants.

IV.E.viii. Funding

This study was funded by the Natural Sciences and Engineering Research Council Applied Research and Development grant (ARD1 476315-14).

V.A. DISCUSSION OVERVIEW

Given their high prevalence, inadequate response to first-line treatment strategies, and long-term functional impairments, mood disorders are a significant social and economic issue, (Kendler, 2016; Kendler et al., 1999; Kessler et al., 2009); see also Section I.C.i, and introductions in Chapters II and III. Observations that voluntary wheel-running in rodents is associated with improved cognitive functioning (Grace et al., 2009; Miller et al., 2018; van der Borght et al., 2007; van Praag et al., 2005) and stress resilience (Gerecke, Kolobova, Allen, & Fawer, 2013; Kingston et al., 2018; Miller et al., 2018) suggest that exercise may be an effective adjunctive treatment for mood disorders, including MDD and BD. To date, numerous studies have reported benefits of regular exercise, including reduced symptoms of depression. However, there is considerable variability across study designs – including types of exercise (e.g., running, yoga,), participant characteristics (e.g., elderly, healthy, first-episode mental illness), and levels of social support – with little information as to how these factors might influence clinical outcomes. Moreover, much of the extant literature focuses heavily on measuring the effects of exercise on depression symptoms in first-episode patients, usually those with MDD, to the exclusion of functional outcomes in patients with more chronic and recurrent MDD. Furthermore, there are almost no data on exercise outcomes in patients with a primary diagnosis of BD. Accordingly, it is difficult to parse apart whether exercise confers global benefits across mental, neurocognitive, social and quality of life symptoms of MDD and/or BD, or if benefits accrue primarily for a limited number of

outcomes (e.g., mood symptoms) in a subset of patients (e.g. first-episode MDD). The studies presented in the current dissertation represent a new approach to investigating the benefits of mental and functional health benefits of exercise, to better understand the potential therapeutic benefits for patients with a primary diagnosis of a mood disorder.

Specifically, we addressed several knowledge gaps in the literature surrounding exercise, mental health and functional outcomes. In study 1 (Chapter II), using a retrospective design, to address the lack of data on patients with difficult-to-treat mood disorders, we examined the impact of a high-impact, group-based exercise program on mood symptoms. In study 2 (Chapter III), using a prospective, observational design, we examined the effect of a high-impact, group-based exercise program on cognitive and social function and quality-of-life outcomes in a subset of patients from study 1, to address the lack of data on outcomes other than mood symptoms in difficult-to-treat patients. In study 3 (Chapter IV), using a randomized control trial design, we evaluated whether participation in a low- impact, group-based yoga program was associated with mood, cognitive, social and quality-of-life benefits in healthy adults, to address potential barriers deterring people with mood disorders from participating in running and other forms of high-impact exercise, and to examine the role of mindfulness on cognitive outcomes. Filling these knowledge gaps is important to fully understand the therapeutic benefits of exercise in patients with mood disorders, including identification of factors (e.g., social support) that may serve as underlying mechanisms for observed improvements.

V.B. SUMMARY OF RESEARCH RESULTS

V.B.I. SUMMARY OF STUDY 1

In this chart review study, we evaluated data that were collected for quality assurance purposes to assess the impact of a running group within the Mood Disorders Program at St Joseph Healthcare Hamilton. Here, we explored the impact of a structured, group-based running program on symptoms of stress, anxiety and depression in youth and adults with chronic and/or recurrent (difficult-to-treat) mood disorders. The objective of this study was to determine if previously documented benefits of exercise in patients with characteristically treatment-responsive mood disorders (e.g., first-episode depression) would extend to patients with more difficult-to-treat, refractory forms of illness. As most of the participants in this study had chronic and/or recurring mood disorders, we explored the effect of clinical factors available from medical charts, specifically, age at onset of illness and duration of illness, on mood outcomes. Furthermore, to determine the therapeutic impact of the program on clinical outcomes, we explored response (a 50% decrease in score from baseline to end of study) and remission (end of study scores below specific thresholds associated with disease severity of none, low, moderate or high) rates for symptoms of depression in response to the exercise treatment. Finally, as social impairment is a common and under-investigated symptom of mood disorders, we explored a simple assessment tool that gathered data on perceived levels of friendship with the running group as a surrogate for social functioning.

Results from study 1 suggested that participation in a 12-week group-based running program improved symptoms of stress, anxiety and depression from baseline to end of study in patients with difficult-to-treat mood disorders, including MDD, BD and dysthymia (Keating et al., 2018). Factors that predicted better end-of-study depression, anxiety and stress scores included younger participant age, younger age at onset of illness (characteristic of the youth group) and higher perceived levels of friendship with other running group members; higher attendance was associated with lower end-of-study depression and anxiety scores. These findings suggest that older participants may have represented a more treatment-resistant group, and indicate further a positive relation between regular attendance and mood benefits. We also found high rates of remission as measured by both depression and anxiety scores in the sample.

In secondary analyses, participants reported improved levels of perceived friendship on a simple assessment tool designed by the running program team. In a subsample analysis (based on the data collected for study 2; see Chapter II., Methods section), we found a high correlation between the friendship item score and the SF36 social functioning subscale, indicating this item has validity as a marker for perceived social support. This finding was also consistent with a qualitative assessment of patient comments gathered at the sessions, as many participants noted a feeling of social connection with the group as the sessions progressed (see Chapter II, supplemental data (Keating et al., 2018)). The other common themes in the qualitative assessment were related to experiences of pain and/or injury, and feelings of anxiety around ability to meet the demands of the program.

Overall, the results of this study suggest that a structured, group-based running program is an effective treatment for mood symptoms in patients with difficult-to-treat mood disorders, and is associated further with improved feelings of friendship. Injury, pain and/or anxiety, however, are potential barriers to participation. To evaluate further the potential therapeutic benefits of this program, in study 2 (Chapter III), we explored cognitive, social and quality-of-life outcomes in a subsample of patients from study 1.

V.B.ii. SUMMARY OF STUDY 2

The objective of study 2 was to investigate the impact of the running program on functional outcomes beyond mood symptoms in patients with difficult-to-treat mood disorders. In a subgroup of the patients from study 1, we focused specifically on neurocognitive and quality-of-life outcomes that included social functioning. In a prospective, observational study, participants in the running group program were invited to complete a comprehensive clinical and neurocognitive battery of tests at the beginning and at the end of the 12-week running intervention. A total of 18 participants with MDD, BD and/or dysthymia completed the pre- and post-running assessments.

Outcomes included a weak improvement in working memory (as indexed by the WAIS Digit Span forward subtest) and in processing speed and simple attention (Stroop colour only task) following participation in the running group, with a small effect size for each (Cohen's d=0.18 and 0.17 for WAIS and Stroop, respectively). We did not observe a significant improvement in the more complex executive functioning tasks such as

inhibition in the Stroop interference subtest, or the more difficult working memory Digit Span backwards or sequential subtests (Reynolds, 1997). This suggests that more complex types of executive functioning did not improve in this study, suggesting exercise may not confer global improvement across all types of cognitive functioning. We also found significant improvements on five of eight HRQOL subscales, including one physical (general health) and all four mental (vitality, role of emotions, social functioning and mental health) subscales.

Regression analyses revealed higher attendance and improved general health, bodily pain and vitality scores were associated with improved depression scores, while cognitive improvement was predicted by younger age (for the WAIS digit forward task), shorter illness duration and improved pain scores (for the Stroop colour only task). Improved social functioning was predicted by higher attendance and better physical functioning.

Taken together, these findings suggest that a structured, group-based running program can have a positive effect on cognitive, social and HRQOL outcomes in patients with mood disorders, although we acknowledge the cognitive improvements might not withstand correction for multiple comparisons. These findings in difficult-to-treat patients have important implications, as functional impairments tend to persist in patients, even when mood symptoms have improved.

Studies 1 and 2 represent a novel approach to evaluating functional treatment outcomes of an exercise program in patients with mood disorders, by investigating symptoms and functional outcomes across the spectrum of the diagnosis, and including difficult-to-treat patients. However, several outcomes from studies 1 and 2 suggest there could be benefits to replicating the findings in a low-impact exercise program. First, relatively low attendance rates (49.2% and 60.3%, respectively) indicate low motivation to attend for many participants, possibly related to barriers related to anxiety and injury/pain associated with participation in the running program. Furthermore, improved physical functioning was predictive of improved mood and cognitive function, although most of the physical subscales of the SF-36 did not improve significantly in this sample. To address these limitations, we replicated the pre- and post-intervention assessments in study 2 with a low-impact exercise program in study 3.

V.B.iii. SUMMARY OF STUDY 3

The third study in this dissertation (Chapter IV) was motivated by qualitative findings that in spite of improved perceived social support and mood, some running group participants experienced running-related injuries and had high levels of anxiety concerning running, suggesting a need to explore whether a low-impact, group-based exercise program would be associated with benefits similar to those observed in studies 1 and 2. Therefore, the objective of this study was to evaluate mood, cognitive, social and quality-of-life outcomes in a structured, group-based, low-impact exercise program, in adults without a current diagnosis of a mood disorder. We elected to perform this study in

a non-clinical sample to understand the potential benefits of exercise in healthy adults as a starting point for future research, noting a lack of data, especially for cognitive functioning outcomes, in adults without a clinical or medical diagnosis. We chose a yoga intervention for several reasons: 1) a beginner-style yoga class could be designed as a low-impact exercise program with reduced potential for injury; 2) yoga classes typically incorporate teachings of self-acceptance and include a deeply relaxing pose (savasana), which promotes stress reduction and could encourage attendance; and, 3) yoga incorporates the teaching of mindfulness, the practice of being fully aware and non-judgmental in the present moment, and based on the literature, was expected to have a greater impact on executive functions than an exercise-only program. Indeed, a recent meta-analysis provides further justification for these predictions, reporting a higher attendance rate in low-impact exercise programs, and better improvements in cognitive functioning outcomes among participants with MDD when the exercise program included a higher level of cognitive demand (e.g. increased attention, as is characteristic of programs such as Tai-chi and yoga) (Sun, Lanctot, Herrmann, & Gallagher, 2018). Therefore, we replicated the assessment battery of stress, mood, HRQOL, neurocognitive functioning and social functioning outcome measures from studies 1 and 2 in a randomized control trial of healthy adults, using a low-impact yoga class in place of the running intervention. We employed a wait-list control group to control for potential effects of a placebo treatment effect, simple effects of improvement in symptoms across time, and test-retest practice effects. In addition, we added the NIH Toolbox® for Emotion (National Institutes of Health and Northwestern University, 2012) to investigate

in greater detail potential changes of perceived social support outcomes in group-based exercise programs. We also explored the relationship between social and cognitive functioning and stress outcomes.

In study 3, we found significant improvements in stress and loneliness scores, and in physical (role of physical and bodily pain) and mental (vitality and mental health) HRQOL subscales in the yoga compared to wait-list control participants. Within-group changes from baseline to end of study revealed improved depression and all HRQOL scores except physical functioning in the yoga group; no within-group changes were observed in the control group. It is important to note that, although participants with a current diagnosis of a mood disorder were excluded from the study, there was evidence in some participants of sub-syndromal symptoms of depression at baseline, as we were able to detect a significant decrease in BDI and stress scores by the end of the study. On cognitive measures, yoga participants improved on the MST task, believed to reflect hippocampal function, and on the colour only and colour-word interference Stroop tests, measures of processing speed and ability to overcome interference and inhibit prepotent responses, respectively. The observed improvement in inhibitory control (Stroop colour-word interference subtest) is consistent with our prediction that the mindfulness component of yoga would confer benefits on cognitive control. This relationship should be explored in future research.

In a mediation analysis, we found that improved social functioning and decreased loneliness were correlated with the effect of exercise on stress outcomes, although no such effects of cognitive function were observed. This is consistent with our hypothesis that the social support component of the exercise classes was an important element of observed stress-reduction benefits, and underscores further the importance of social support in group-based exercise programs. The limitations of the design preclude an ability to evaluate the possible causation of social functioning and stress reduction (see also Chapter IV, Section IV.E.iii. Limitations). Therefore, future research should assess social functioning and stress at multiple time points, to establish whether it plays a causal role in mediating the stress-reduction benefits of exercise in mood disorders.

In study 3, we found improvements across stress, mood, HRQOL, and social and cognitive function outcomes, all of which are impaired in patients with mood disorders. Although we did not collect safety data, no one dropped out of the program due to injury. Furthermore, a focus on mindfulness and stress-reduction could encourage attendance, which at 64.5% was higher for the yoga participants than the prospective running group participants (study 2) and much higher than the entire running group (study 1). Higher attendance rates in the yoga compared to running groups suggest that yoga may encourage attendance and retention more than running. However, this difference should be interpreted with caution until the yoga intervention has been replicated in a difficult-to-treat clinical sample comparable to that of studies 1 and 2, as patients may have lower motivation as part of their clinical presentation. Nonetheless, the results of study 3

provide evidence that a low-impact yoga program could provide adjunctive therapeutic benefits for patients with mood disorders.

V.B.iv. Study limitations

Detailed methodological limitations for each of the three studies are noted in Chapters II (Discussion), III (III.E.iii. Limitations) and IV (IV.E.iv. Limitations). One additional limitation that is applicable to both study 2 (Chapter III) and 3 (Chapter IV) is that our findings are based on multiple t-test comparisons. Based on the findings presented here and in the literature, future research protocols should be designed with fewer, more targeted predictions and involving more complex statistical analyses to better evaluate outcomes.

V.C. IMPLICATIONS OF FINDINGS FOR MOOD DISORDERS AND STRESS MANAGEMENT

There are several important implications from the current findings, both for people with mood disorders and for healthy adults. The mood findings in studies 1 and 3 suggest that high- and low-impact, group-based exercise programs are associated with improved stress, anxiety and depression scores in adults with and without mood disorders, consistent with findings reported in the literature on first-episode and healthy populations (Josefsson et al., 2014). These findings provide support for exercise as adjunctive treatment for patients with chronic, recurring and/or non-remitted mood disorders. The identification of interventions that improve the ability to manage stress has implications for all individuals, regardless of diagnosis. Besides being a common trigger of mood disorders (Kendler et al., 1999), stress is associated with decreased quality-of-life (Colovic, Lecic-Tosevski, Mandic, & Toskovic, 2009), impaired cognitive function (Marin et al., 2011) and significant social and economic burdens (K. MacQueen, 2007). Thus, the positive effects of group-based exercise programs on mood and stress symptoms represent a first step towards better management strategies for stress-related illness and/or other types of mental illness.

Other factors that are impaired in mood disorders include cognitive functioning and quality-of-life. The results of studies 2 and 3 suggest that different types of exercise are associated with different improvements in cognitive benefits and HRQOL. The cognitive

function results reported here are consistent with our hypothesis tested in study 3 that although exercise alone is associated with simple executive functioning improvements (study 2), exercise that includes a greater degree of cognitive demand and attentional focus may be associated with more complex executive functioning improvements. Although voluntary aerobic exercise has been associated with improvements in hippocampal-dependent memory function in rodents (Castilla-Ortega et al., 2014; Patki et al., 2014; van Praag, Christie et al., 1999) and high-intensity interval training has been associated with improved performance on a high-interference memory task, the MST, in humans (Déry et al., 2015; Heisz et al., 2017), we did not see those improvements in the more moderate running therapy program reported here. Given the cognitive impairment associated with mood disorders and chronic stress, future research is needed to better understand the types of benefits to be expected across exercise programs and clinical diagnoses. The HRQOL results in studies 2 and 3 reflect a new standard for evaluating the impacts of exercise on functional outcomes, to evaluate both physical and mental quality-of-life outcomes. Our results suggest further that an exercise program associated with both physical and mental improvements may be important to maximize exercise-related benefits.

One of the most interesting themes in the current dissertation is the finding of improved social functioning, across different measures and samples, in all three studies. These results underscore the significant impact of social support on outcomes, and suggest that some of the variability in the literature might be explained by different levels of social

support offered across exercise programs. Social support, therefore, offers multiple potential direct and indirect benefits for exercise programs. Direct benefits may include improvements in social functioning, while indirect effects could include higher compliance to a program (e.g., promoting higher attendance) and may be associated with decreased stress. Notably, social isolation is associated with multiple negative consequences: increased stress, with increased risk of multiple health issues, including mortality (see Section I.F.). The results presented point towards the additional need for more information on the role of social support in exercise programs, to better understand the impact of this factor on exercise-related clinical and/or therapeutic benefits.

Overall, our findings suggest that exercise may provide therapeutic benefit as an adjunctive therapy for the treatment of mood disorders, which is characterized by low response to treatment and lifelong social and cognitive impairments. Furthermore, as benefits were observed across both high- and low-impact exercise, the future of treatment may lie in the customization of lifestyle programs that include exercise, in order to meet the varying needs of patients, a practice in keeping with personalized medicine. Indeed, the idea of managing chronic health issues using lifestyle strategies is common for medical diagnoses, a trend that is starting to be explored for diseases of the brain.

V.D. LIFESTYLE FACTORS AND HEALTH MANAGEMENT

The use of lifestyle interventions to supplement medical health care for physical illness is not a new concept: the Heart and Stroke foundation promotes healthy lifestyle choices (involving diet, exercise and stress management) to prevent premature heart disease and stroke in up to 80% of patients (Heart & Stroke Foundation, 2018). Another example is chronic kidney disease, where healthy lifestyles that include regular exercise and specialized diets are also promoted as part of routine care (Levin et al., 2008), and are associated with improved mortality (Ricardo et al., 2015). Exercise-related cognitive benefits have also been reported in medical patient populations (K. Luu & Hall, 2016), and exercise-related improvements in symptoms of stress, anxiety and depression have been reported in cancer patients (Buffart et al., 2012; Galvão & Newton, 2005). Data from the current studies contribute to an emerging trend for healthcare providers to focus on lifestyle factors for managing disorders of the brain.

In what may be a landmark new way to treat brain disorders, a novel treatment paradigm for Alzheimer's disease prescribes personalized lifestyle plans involving exercise, dietary supplements, mindfulness and cognitive training to reverse cognitive decline in patients (Bredesen et al., 2016). Results from the current study, taken together with the literature to date and impact of lifestyle changes on other health conditions, suggest personalized approaches to treatment for mental illness involving exercise, social support, and cognitive demand should be explored.

V.E. FUTURE RESEARCH

Several future research areas have previously been suggested to address study limitations; refer to Discussion sections in Chapters II, III and IV. Briefly, we acknowledge that the studies summarized here have the following general limitations: 1) small sample sizes; 2) increased risk of Type I errors (false positives), due to multiple uncorrected analyses; and, 3) clinical heterogeneity of participants in studies 1 and 2. To address these limitations, future investigation with larger groups over longer periods, controlling for multiple comparisons and with more homogeneous clinical samples should be explored. Further, social functioning should be explored as a primary predictor variable for outcomes of stress, depression and cognitive function, given the findings reported here.

Taken together, the results from the current studies suggest additional areas of research. Conversations with participants in all of the studies presented within, as well as qualitative data from study 1 (Keating et al., 2018), provide evidence for increased anxiety and stress as a direct consequence of taking on a new exercise program. In spite of this, we saw relatively good study outcomes, even in the clinical population. As noted in Chapter I, mild to moderate levels of stress can also be a positive factor, promoting resilience and enhanced functioning, with the voluntary nature of exercise also impacting stress levels. Research investigating factors influencing the motivation of participants to join these studies, and to attend sessions, as well as different ways of measuring stress, might provide new insights on how exercise programs influence feelings of positive

compared to negative stress, and how these levels impact compliance and motivation, in addition to cognitive and mental health outcomes.

The previous section outlines how lifestyle changes are increasingly being used by clinicians to manage physical and mental disorders. There is relatively little evidence for the therapeutic benefits of diet in mood disorders, however, there is evidence that a complex dietary supplement can have positive impacts on mood symptoms (reduced anhedonia) and hippocampal function when combined with exercise in rodent models of chronic stress (Hutton et al., 2015). Personalized approaches that promote exercise, cognitive demand, relaxation/mindfulness and social support should be explored in more detail, perhaps adding complex dietary supplements to the model.

The role of exercise with enhanced cognitive demand, for example, mindfulness, as investigated in study 3, compared to exercise alone should be further explored. Whereas the findings of study 2 suggest that exercise alone might be associated with limited improvements in working memory and processing, the results of study 3 suggest improvements in more complex executive function tests might be associated with more attentively demanding forms of exercise such as yoga. However, we note that the findings also reflect cognitive functioning in two different samples, one with difficult-to-treat mental illness, the other a healthy sample not being treated for a mood disorder. Therefore, this link should be explored further in clinical samples.

The emerging importance of social functioning outcomes also should be explored further. Specifically, a larger, longitudinal, study of youth and adults with difficult-to-treat mood disorders should be undertaken, across different types of exercise interventions, with social function as a predictor variable on outcomes of interest for mood disorders including stress, mood symptoms, cognitive function and quality-of-life. Collecting data over multiple time points might provide additional insights on the potentially mediating or moderating role of social functioning on mood and stress outcomes in exercise studies.

V.F FINAL CONCLUSIONS

The results presented here contribute to the growing body of literature suggesting that structured exercise programs, both high- and low-impact, can confer mood, social, cognitive and HRQOL benefits in adults and youth with mood disorders and in healthy adults.

Specifically, we report that: a) group-based exercise programs may be beneficial as adjunctive treatment for symptoms of depression, anxiety and stress in chronic and/or recurrent MDD, although future research is required to determine the benefits of high-impact exercise for patients with BD; b) exercise may be associated with improvements in memory and executive functions, though the effects may be stronger for programs like yoga that are more attentively demanding; c) social functioning is improved in youth and adults who participate in exercise programs, regardless of the exercise impact, and may partially moderate improved stress scores; d) both high- and low-impact exercise programs are associated with improved HRQOL, especially for the mental health subscales; and, e) while we investigated the impact of yoga on mood in a healthy sample, our findings of a significant impact of mood suggest that a low- impact yoga intervention is a viable option for youth and adults who suffer from mood disorders and may be intimidated by the expectations of a running program, with benefits similar to a structured, group-based running program. In conclusion, the results presented here provide a solid foundation for further investigation of the complex relations between

exercise, stress, cognitive function, social function and quality of life, and the potential benefits of exercise as an adjunctive treatment for mental illness.

VI. REFERENCES

Adolphs, R. (2010). What does the amygdala contribute to social cognition? *Annals of the New York Acadamy of Sciences, 1191*(1), 42-61.

Akers, K. G., Martinez-Canabal, A., Restivo, L., Yiu, A. P., De Cristofaro, A., Hsiang, H.-L., et al. (2014). Hippocampal neurogenesis regulates forgetting during adulthood and infancy. *Science, 344*(598), DOI: 10.1126/science.1248903.

Altman, J., & Das, G. D. (1965). Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. *Journal of Comparative Neurology, 124*(3), 319-336.

Amara, D. G. (2002). The primate amygdala and the neurobiology of social behavior: implications for understanding social anxiety. *Biological Psychiatry, 51*(1), 11-17.

American Psychiatric Association. (2013a). *Diagnostic and Statistical Manual of Mental Disorders* (Vol. 5th edition). Washington, DC: American Psychiatric Association.

American Psychiatric Association. (2013b). *Diagnostic and Statistical Manual of Mental Disorders* (Fifth edition ed.).

Angst, F., Stassen, H. H., Clayton, P. J., & Angst, J. (2002). Mortality of patients with mood disorders: Follow-up over 34-38 years. *Journal of Affective Disorders, 68,* 167-181.

Annesi, J. J. (2005a). Changes in depressed mood associated with 10 weeks of moderate cardiovascular exercise in formerly sedentary adults. *Psychological Reports, 96*(3), 855-862.

Annesi, J. J. (2005b). Correlations of depression and total mood disturbance with physical activity and self-concept in preadolescents enrolled in an after-school exercise program. *Psychological Reports, 96*(3 Pt 2), 891-898.

Anokye, N. K., Trueman, P., Green, C., Pavey, T. G., & Taylor, R. S. (2012). Physical activity and health related quality of life. *BMC Public Health, 12*(624), doi:10.1186/1471-2458-1112-1624.

Asano, M., Kaneoka, K., Nomura, T., Asano, K., Sone, H., Tsurumaru, K., et al. (1998). Increase in serum vascular endothelial growth factor levels during altitude training. *Acta Physiologica Scandinavica, 162*(4), 455-459.

Asher, G. N., Gartlehner, G., Gaynes, B. N., Amick, H. R., Forneris, C., Morgan, L. C., et al. (2016). Comparative benefits and harms of complementary and alternative medicine therapies for initial treatment of major depressive disorder: Systematic review and meta-analysis. *Journal of Alternative and Complementary Medicine, DOI: 10.1089/acm.2016.0261*.

Babaei, P., Alazi Alamdari, K., Soltani Tehrani, B., & Damirchi, A. (2013). Effect of six weeks of endurance exercise and following detraining on serum brain derived neurotrophic factor and memory performance in middle aged males with metabolic syndrome. *Journal of Sports Medicine and Physical Fitness, 53*(4), 437-443.

Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., et al. (2000). Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine, 62,* 633-638.

Banich, M. T., Milham, M. P., Atchley, R., Cohen, N. J., Webb, A., Wszalek, T., et al. (2000). fMRI studies of Stroop tasks reveal unique roles of anterior and posterior brain systems in attentional selection. *Journal of Cognitive Neuroscience, 12*(6), 988–1000.

Baron, R. M., & Kenny, D. A. (1986). The moderator-mediator variable distinction in social psychological research: Conceptual, strategic and statistical considerations. *Journal of Personality and Social Psychology, 51*, 1173-1182.

Becerra, R., D'Andrade, C., & Harms, C. (2016). Can specific attentional skills be modified with mindfulness training for novice practitioners? *Current Psychology, 36*(3), 657–664.

Beck, A. T., Epstein, N., Brown, G., & Steer, R. A. (1988). An inventory for measuring clinical anxiety: Psychometric properties. *Journal of Consulting and Clinical Psychology, 56*, 893-897.

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *Manual for the Beck Depression Inventory Second Edition (BDI-II)*. San Antonio, TX: Psychological Corporation.

Becker, S. (2017). Neurogenesis and pattern separation: time for a divorce. *Wiley Interdisciplinary Reviews: Cognitive Science, e1427*, doi: 10.1002/wcs.1427.

Becker, S., MacQueen, G., & Wojtowicz, J. M. (2009). Computational modeling and empirical studies of hippocampal neurogenesis-dependent memory: effects of interference, stress and depression. *Brain Research, 1299*, 45-54.

Becker, S., & Wojtowicz, J. M. (2006). A model of hippocampal neurogenesis in memory and mood disorders. *Trends in Cognitive Sciences, 11*(2), 70-76.

Belmaker, R. H., & Agam, G. (2008). Major depressive disorder. *New England Journal of Medicine, 358*(1), 55-68.

Berse, T., Rolfes, K., Barenberg, J., Dutke, S., Kuhlenbäumer, G., Völker, K., et al. (2015). Acute physical exercise improves shifting in adolescents at school: evidence for a dopaminergic contribution. *Frontiers in Behavioral Neuroscience, 9*(196), doi: 10.3389/fnbeh.2015.00196.

Bhatia, T., Mazumdar, S., Wood, J., He, F., Gur, R. E., Gur, R. C., et al. (2017). A randomised controlled trial of adjunctive yoga and adjunctive physical exercise training for cognitive dysfunction in schizophrenia. *Acta Neuropsychiatrica, 29*(2), 102-114.

Bhayee, S., Tomaszewski, P., Lee, D. H., Moffat, G., Pino, L., Moreno, S., et al. (2016). Attentional and affective consequences of technology supported mindfulness training: a randomised, active control, efficacy trial. *BMC Psychology, 4*(60), DOI 10.1186/s40359-40016-40168-40356.

Bjørnebekk, A., Mathé, A. A., & Brené, S. (2005). The antidepressant effect of running is associated with increased hippocampal cell proliferation. *International Journal of Neuropsychopharmacology, 8*, 357-368.

Blumenthal, J. A., Babyak, M., Moore, K. A., Craighead, E., Herman, S., Khatri, P., et al. (1999). Effects of exercise training on older patients with major depression. *Archives of Internal Medicine, 159*(19), 2349-2356.

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., et al. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine, 69*(7), 587-596.

Bojic, S., & Becerra, R. (2017). Mindfulness-based treatment for bipolar disorder: A systematic review of the literature. *Europe's Journal of Psychology, 13*(3), 573–598.

Bonhauser, M., Fernandez, G., Püschel, K., Yañez, F., Montero, J., Thomspon, B., et al. (2005). Improving physical fitness and emotional well-being in adolescents of low socioeconomic status in Chile: results of a school-based controlled trial. *Health Promotion International, 20*(2), 113-122.

Bouzid, M. A., Hammouda, O., Matran, R., Robin, S., & Fabre, C. (2015). Influence of physical fitness on antioxidant activity and malondialdehyde level in healthy older adults. *Applied Physiology, Nutrition, and Metabolism, 40*(6), 582-589. https://doi.org/510.1139/apnm-2014-0417.

Bredesen, D. E., Amos, E. C., Canick, J., Ackerley, M., Raji, C., Fiala, M., et al. (2016). Reversal of cognitive decline in Alzheimer's disease. *Aging, 8*(6), 1250-1258.

Brondino, N., Rocchetti, M., Fusar-Poli, L., Codrons, E., Correale, L., Vandoni, M., et al. (2017). A systematic review of cognitive effects of exercise in depression. *Acta Psychiatrica Scandinavica, 135*(4), 285-295.

Brunner, D., Abramovitch, A., & Etherton, J. (2017). A yoga program for cognitive enhancement. *PLoS ONE, 12*(8), e0182366. https://doi.org/0182310.0181371/journal.pone.0182366.

Buffart, L. M., van Uffelen, J. G. Z., Riphagen, I. I., Brug, J., van Mechelen, W., Brown, W. J., et al. (2012). Physical and psychosocial benefits of yoga in cancer patients and survivors, a systematic review and meta-analysis of randomized controlled trials. *BMC Cancer, 12*(559), doi:10.1186/1471-2407-1112-1559.

Cacioppo, J. T., & Hawkley, L. C. (2009). Perceived social isolation and cognition. *Trends in Cognitive Sciences, 13*(10), 447-454.

Cacioppo, J. T., Hawkley, L. C., Norman, G. J., & Berntson, G. G. (2011). Social isolation. *Annals of the New York Acadamy of Sciences, 1231*(1), 17-22.

Campbell, S., Marriott, M., Nahmias, C., & MacQueen, G. M. (2004). Lower hippocampal volume in patients suffering from depression: A meta-analysis. *American Journal of Psychiatry, 161*(4), 598-607.

Canadian Society for Exercise Physiology. (2002). *PAR-Q & You: A Questionnaire for People Aged 15 to 69*.

Carmody, J., & Baer, R. A. (2008). Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. *Journal of Behavioral Medicine, 3*(1), 23-33.

Carta, M. G., Hardoy, M. C., Pilu, A., Sorba, M., Floris, A. L., Mannu, F. A., et al. (2008). Improving physical quality of life with group physical activity in the adjunctive treatment of major depressive disorder. *Clinical Practice and Epidemiology in Mental Health, 4*(1), doi:10.1186/1745-0179-1184-.

Cass, A. R., Volk, R. J., & Nease Jr., D. E. (1999). Health-related quality of life in primary care patients with recognized and unrecognized mood and anxiety disorders. *The International Journal of Psychiatry in Medicine, 29*(3), 293-309.

Castilla-Ortega, E., Rosell-Valle, C., Pedraza, C., Rodríguez de Fonseca, F., Estivill-Torrús, G., & Santín, L. J. (2014). Voluntary exercise followed by chronic stress strikingly increases mature adult-born hippocampal neurons and prevents stress-induced deficits in ?what?when?where? memory. *Neurobiology of Learning and Memory, 109*, 62-73.

Chalder, M., Wiles, N. J., Campbell, J., Hollinghurst, S. P., Haase, A. M., Taylor, A. H., et al. (2012). Facilitated physical activity as a treatment for depressed adults: randomised controlled trial. *British Medical Journal, 344*, e2758.

Chambers, R., Lo, B. C. Y., & Allen, N. B. (2008). The impact of intensive mindfulness training on attentional control, cognitive style and affect. *Cognitive Therapy and Research, 32*, 303-322.

Clark, P. J., Amat, J., McConnell, S. O., Ghasem, P. R., Greenwood, B. N., Maier, S. F., et al. (2015). Running reduces uncontrollable stress-evoked serotonin and potentiates stress-evoked dopamine concentrations in the rat dorsal striatum. *PLoS ONE, 10*(11), e0141898. doi:0141810.0141371/journal.pone.0141898.

Clelland, C. D., Choi, M., Romberg, C., Clemenson Jr., G. D., Fragniere, A., Tyers, P., et al. (2009). A functional role for adult hippocampal neurogenesis in spatial pattern separation. *Science, 325*(5937), 210-213.

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of Health and Social Behaviour, 24*(December), 385-396.

Colovic, O., Lecic-Tosevski, D., Mandic, V., & Toskovic, O. (2009). The impact of stress related disorders on quality of life. *Psychiatria Danubina, 21*(2), 199-205.

Conrad, C. D. (2008). Chronic stress-induced hippocampal vulnerability: The glucocorticoid vulnerability hypothesis. *Reviews Neuroscience, 19*(6), 395-411.

Cotman, C. W., & Berchtold, N. C. (2002). Exercise: a behavioral intervention to enhance brain health and plasticity. *Trends in Neurosciences, 25*(6), 295-301.

Cramer, H., Ward, L., Saper, R., Fishbein, D., Dobos, G., & Lauche, R. (2015). The safety of yoga: A systematic review and meta-analysis of randomized controlled trials. *American Journal of Epidemiology, 4*(15), 281–293.

Creer, D. J., Romberg, C., Saksida, L. M., van Praag, H., & Bussey, T. J. (2010). Running enhances spatial pattern separation in mice. *Proceedings of the National Academy of Sciences USA, 107*, 2367-2372.

Daly, E. J., Trivedi, M. H., Wisniewski, S. R., Nierenberg, A. A., Gaynes, B. N., Warden, D., et al. (2010). Health-related quality of life in depression: a STAR*D report. *Annals of Clinical Psychiatry, 22*(1), 43-55.

de Rover, M., Pironti, V. A., McCabe, J. A., Acosta-Cabroner.o, J., Arana, F. S., Morein-Zamir, S., et al. (2011). Hippocampal dysfunction in patients with mild cognitive impairment: a functional neuroimaging study of a visuospatial paired associates learning task. *Neuropsychologia, 49*(7), 2060-2070.

de Vibe, M., Bjørndal, A., Fattah, S., Dyrdal, G. M., Halland, E., & Tanner-Smith, E. E. (2017). Mindfulness-based stress reduction (MBSR) for improving health, quality of life and social functioning in adults: a systematic review and meta-analysis. *Campbell Systematic Reviews, 11*, DOI: 10.4073/csr.2017.4011.

Delgado y Palacios, R., Campo, A., Henningsen, K., Verhoye, M., Poot, D., Dijkstra, J., et al. (2011). Magnetic resonance imaging and spectroscopy reveal differential hippocampal changes in anhedonic and

resilient subtypes of the chronic mild stress rat model. *Biological Psychiatry, 70*, 449–457.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test® – Second Edition (CVLT® -II)*. San Antonio, TX: The Psychological Corporation.

Denver, R. J. (2009). Structural and functional evolution of vertebrate neuroendocrine stress systems. *Annals of the New York Acadamy of Sciences, 1163*(April), 1-16. doi: 10.1111/j.1749-6632.2009.04433.x.

Déry, N., Goldstein, A., & Becker, S. (2015). A role for adult hippocampal neurogenesis at multiple time scales: A study of recent and remote memory in humans. *Behavioral Neuroscience, 129*(4), 435-449.

Déry, N., Pilgrim, M., Gibala, M., Gillen, J., Wojtowicz, J. M., MacQueen, G. M., et al. (2013). Adult hippocampal neurogenesis reduces memory interference in humans: opposing effects of aerobic exercise and depression. *Frontiers in Neuroscience, 7*(66), doi: 10.3389/fnins.2013.00066.

Diamond, A. (2015). Effects of physical exercise on executive functions: Going beyond simply moving to moving with thought. *Annals of Sports Medicine and Research, 2*(1), 1011.

Dimeo, F., Bauer, M., Varahram, I., Proest, G., & Halter, U. (2001). Benefits from aerobic exercise in patients with major depression: a pilot study. *British Journal of Sports Medicine, 35*(2), 114-117.

Doyne, E. J., Ossip-Klein, D. J., Bowman, E. D., Osborn, K. M., McDougall-Wilson, I. B., & Neimeyer, R. A. (1987). Running versus weight lifting in the treatment of depression. *Journal of Consulting and Clinical Psychology, 55*(5), 748-754.

Droste, S. K., Gesing, A., Ulbricht, S., Muller, M. B., Linthorst, A. C., & Reul, J. M. (2003). Effects of long-term voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis. *Endocrinology, 144*, 3012-3023.

Droste, S. K., Schweizer, M. C., Ulbricht, S., & Reul, J. M. H. M. (2006). Long-term voluntary exercise and the mouse hypothalamic-pituitary-adrenocortical axis: Impact of concurrent treatment with the antidepressant drug tianeptine. *Journal of Neuroendocrinology, 18*, 915-925.

Duman, C. H., Schlesinger, L., Russell, D. S., & Duman, R. (2008). Voluntary exercise produces antidepressant and anxiolytic behavioral effects in mice. *Brain Research, 1199*, 148-158.

Dumont, M., & Provost, M. A. (1999). Resilience in adolescents: Protective role of social support, coping strategies, self-esteem, and social activities on experience of stress and depression. *Journal of Youth and Adolescence, 28*(3), 343-363.

Eddy, M. C., Stansfield, K. J., & Green, J. T. (2014). Voluntary exercise improves performance of a discrimination task through effects on the striatal dopamine system. *Learning and Memory, 21*(7), 334-337.

El Yacoubi, M., Bouali, S., Popa, D., Naudon, L., Leroux-Nicollet, I., Hamon, M., et al. (2003). Behavioral, neurochemical, and electrophysiological characterization of a genetic mouse model of depression. *Proceedings of the National Academy of Sciences USA, 100*(10), 6227–6232.

Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., et al. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences USA, 108*(7), 3017-3022.

Eriksson, P. S., Perfilieva, E., Björk-Eriksson, T., A-M., A., Nordborg, C., D.A., P., et al. (1998). Neurogenesis in the adult human hippocampus. *Nature Medicine, 4*(11), 1313-1317.

Evans, G. W., & Schamberg, M. A. (2009). Childhood poverty, chronic stress, and adult working memory. *Proceedings of the National Academy of Sciences USA, 106*(16), 6545-6549.

Finnegan, R., & Becker, S. (2015). Neurogenesis paradoxically decreases both pattern separation and memory interference. *Frontiers in Systems Neuroscience, 9*(136), doi: 10.3389/fnsys.2015.00136.

Florea, I., Danchenko, N., Brignone, M., Loft, H., Rive, B., & Abetz-Webb, L. (2015). The effect of vortioxetine on health-related quality of life in patients with major depressive disorder. *Clinical Therapeutics, 37*(10), 2309-2323.e2306.

Foley, L. S., Prapavessis, H., Osuch, E. A., De Pace, J., Murphy, B. A., & Podolinsky, N. J. (2008). An examination of potential mechanisms for exercise as a treatment for depression: A pilot study. *Mental Health and Phsyical Activity, 1*(2), 69-73.

Foster Green, M. (2006). Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. *Journal of Clinical Psychiatry, 67*(10), e12.

Fox, K. C. R., Nijeboer, S., Dixon, M. L., Floman, J. L., Ellamil, M., Rumak, S. P., et al. (2014). Is meditation associated with altered brain structure? A systematic review and meta-analysis of morphometric neuroimaging in meditation practitioners. *Neuroscience and Biobehavioral Reviews, 43*, 48–73.

Froeliger, B., Garland, E. L., & Mcclernon, F. J. (2012). Yoga meditation practitioners exhibit greater gray matter volume and fewer reported cognitive failures: Results of a preliminary voxel-based morphometric analysis. *Evidence-Based Complementary and Alternative Medicine, 821307*, doi:10.1155/2012/821307.

Galvão, D. A., & Newton, R. U. (2005). Review of exercise intervention studies in cancer patients. *Journal of Clinical Oncology, 23*(4), 899-909.

Gerecke, K. M., Kolobova, A., Allen, S., & Fawer, J. L. (2013). Exercise protects against chronic restraint stress-induced oxidative stress in the cortex and hippocampus. *Brain Research, 1509*, 66-78.

Gershon, R. C., Wagster, M. V., Hendrie, H. C., Fox, N. A., Cook, K. F., & Nowinski, C. J. (2013). NIH Toolbox for assessment of neurological and behavioral function. *Neurology, 80*(11 Suppl 3), S2-S6.

Gerton, B. K., Brown, T. T., Meyer-Lindenberg, A., Kohn, P., Holt, J. L., Olsen, R. K., et al. (2004). Shared and distinct neurophysiological components of the digits forward and backward tasks as revealed by functional neuroimaging. *Neuropsychologia, 42*(2004), 1781-1787.

Goldstein, A., Déry, N., Pilgrim, M., Ioan, M., & Becker, S. (2016). Stress and binge drinking: a toxic combination for the teenage brain. *Neuropsychologia, 90*(251-260 doi:10.1016/j.neuropsychologia.2016.07.035).

Gómez-Pinilla, F., & Hillman, C. (2013). The influence of exercise on cognitive abilities. *Comprehensive Physiology, 3*(1), 403-428.

Gómez-Pinilla, F., Ying, Z., Roy, R. R., Molteni, V. R., & Edgerton, V. R. (2002). Voluntary exercise induces a BDNF-mediated mechanism that promotes neuroplasticity. *Journal of Neurophysiology, 88*, 2187-2195.

Gothe, N. P., Keswani, R. K., & McAuley, E. (2016). Yoga practice improves executive function by attenuating stress levels. *Biological Psychology, 121*(Pt A), 109-116.

Gothe, N. P., Kramer, A. F., & McAuley, E. (2014). The effects of an 8-week Hatha yoga intervention on executive function in older adults. *Journals of Gerontology Series A: Biological and Medical Sciences, 69*(9), 1109-1116.

Gothe, N. P., & McAuley, E. (2015). Yoga and cognition: A meta-analysis of chronic and acute effects. *Psychosomatic Medicine, 77*(7), 784-797.

Gothe, N. P., Pontifex, M. B., Hillman, C., & McAuley, E. (2013). The acute effects of yoga on executive function. *Journal of Physical Activity and Health, 10*(4), 488-495.

Gould, E., & Tanapat, P. (1999). Stress and hippocampal neurogenesis. *Biological Psychiatry, 46*(11), 1472-1479.

Grace, L., Hescham, S., Kellaway, L. A., Bugarith, K., & Russell, V. A. (2009). Effect of exercise on learning and memory in a rat model of developmental stress. *Metabolic Brain Disease, 24*(4), 643-657.

Granath, J., Ingvarsson, S., von Thiele, U., & Lundberg, U. (2006). Stress management: A randomized study of cognitive behavioural therapy and yoga. *Cognitive Behaviour Therapy, 35*(1), 3-10.

Greenwood, B. N., & Fleshner, M. (2008). Exercise, learned helplessness, and the stress-resistant brain. *Neuromolecular Medicine, 10*, 81-98.

Greenwood, B. N., Spence, K. G., Crevling, D. M., Clark, P. J., Craig, W. C., & Fleshner, M. (2013). Exercise-induced stress resistance is independent of exercise controllability and the medial prefrontal cortex. *European Journal of Neuroscience, 37*(3), 469–478. doi:410.1111/ejn.12044.

Greer, T. L., Kurian, B. T., & Trivedi, M. H. (2010). Defining and measuring functional recovery from depression. *CNS Drugs, 24*(4), 267-284.

Greer, T. L., Trombello, J. M., Rethorst, C. D., Carmody, T. J., Jha, M. K., Liao, A., et al. (2016). Improvements in psychosocial functioning and health-related quality of life following exercise augmentation in patients with treatment response but nonremitted major depressive disorder: Results from the TREAD study. *Depression and Anxiety, 33*(9), 870-881.

Grippo, A. J., Beltz, T. G., & Johnson, A. K. (2003). Behavioral and cardiovascular changes in the chronic mild stress model of depression. *Physiology and Behavior, 78*(4-5), 703-710.

Grippo, A. J., Cushing, B. S., & Carter, C. S. (2007). Depression-like behavior and stressor-induced neuroendocrine activation in female prairie voles exposed to chronic social isolation. *Psychosomatic Medicine, 69*(2), 149-157.

Grippo, A. J., Gerena, D., Huang, J., Kumar, N., Shah, M., Ughreja, R., et al. (2007). Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles. *Psychoneuroendocrinology, 32*(8-10), 966-980.

Guiney, H., & Machado, L. (2013). Benefits of regular aerobic exercise for executive functioning in healthy populations. *Psychonomic Bulletin and Review, 20*(1), 73-86.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery & Psychiatry, 23*, 56-62.

Hariprasad, V. R., Koparde, V., Sivakumar, P. T., Varambally, S., Thirthalli, J., Varghese, M., et al. (2013). Randomized clinical trial of yoga-based intervention in residents from elderly homes: Effects on cognitive function. *Indian Journal of Psychiatry, 55*(7), 357-363.

Haro, J. M., Lamy, F.-X., Jönsson, B., Knapp, M., Brignone, M., Caillou, H., et al. (2018). Characteristics of patients with depression initiating or switching

antidepressant treatment: baseline analyses of the PERFORM cohort study. *BMC Psychiatry*, *18*(80), doi: 10.1186/s12888-12018-11657-12883.

Hearing, C. M., Chang, W. C., Szuhany, K. L., Deckersbach, T., Nierenberg, A. A., & Sylvia, L. G. (2016). Physical exercise for treatment of mood disorders: A critical review. *Current Behavioral Neuroscience Reports*, *3*(4), 350-359 doi: 310.1007/s40473-40016-40089-y.

Heart & Stroke Foundation. (2018). *100 Things You Can Do in Minutes*. Retrieved June 20, 2018, 2018, from http://www.heartandstroke.ca/-/media/pdf-files/ebooks/100-healthy-things-en.ashx?la=en&hash=E58F8BA1458D80A26A444D3AD500BFDFC2293DFD

Heeren, A., Van Broeck, N., & Philippot, P. (2009). The effects of mindfulness on executive processes and autobiographical memory specificity. *Behaviour Research & Therapy*, *47*, 403-409.

Heisz, J. J., Clark, I. B., Bonin, K., Paolucci, E. M., Michalski, B., Becker, S., et al. (2017). The effects of physical exercise and cognitive training on memory and neurotrophic factors. *Journal of Cognitive Neuroscience*, *29*(11), 1895-1907.

Henningsen, K., Andreason, J. T., Bouzinova, E. V., Jayatissa, M. N., Jensen, M. S., Redrobe, J. P., et al. (2009). Cognitive deficits in the rat chronic mild stress model for depression: Relation to anhedonic-like responses. *Behavioral Brain Research*, *198*, 136-141.

Herrera-Guzmán, I., Gudayol-Ferré, E., Herrera-Abarca, J. E., Herrera-Guzmán, D., Montelongo-Pedraza, P., Padrós Blázquez, F., et al. (2009). Major depressive

disorder in recovery and neuropsychological functioning: Effects of selective serotonin reuptake inhibitor and dual inhibitor depression treatments on residual cognitive deficits in patients with major depressive disorder in recovery. *Journal of Affective Disorders, 123*, 341-350.

Hoffman, B. M., Blumenthal, J. A., Babyak, M. A., Smith, P. J., Rogers, S. D., Doraiswamy, P. M., et al. (2008). Exercise fails to improve neurocognition in depressed middle-aged and older adults. *Medicine and Science in Sports and Exercise, 40*(7), 1344-1352.

Holt-Lundstad, J., Smith, T. B., & Layton, J. B. (2010). Social relationships and mortality risk: A meta-analytic review. *PLoS Medicine, 7*(7), e1000316. doi:1000310.1001371/journal.pmed.1000316.

Hölzel, B. K., Carmody, J., Vangel, M., Congleton, C., Yerramsetti, S. M., Gard, T., et al. (2012). Mindfulness practice leads to increases in regional brain gray matter density. *Psychiatry Research, 191*(1), 36-43.

House, J. S., Landis, K. R., & Umberson, D. (1988). Social relationships and health. *Science, 241*(4865), 54-545.

Hutton, C. P., Déry, N., Lemon, J. A., Rollo, C. D., Boreham, D. R., Fahnestock, M., et al. (2015). Synergistic effects of diet and exercise on hippocampal function in chronically stressed mice. *Neuroscience, 308*, 180-193.

Iacoviello, B. M., Alloy, L. B., Abramson, L. Y., & Choi, J. Y. (2010). The early course of depression: A longitudinal investigation of prodromal symptoms and their

relation to the symptomatic course of depressive episodes. *Journal of Abnormal Psychology, 119*(3), 459-467.

Imayama, I., Alfano, C. M., Cadmus Bertram, L. A., Wang, C., Xiao, L., Duggan, C., et al. (2011). Effects of 12-month exercise on health-related quality of life: a randomized controlled trial. *Preventive Medicine, 52*(5), 344-351.

IsHak, W. W., Brown, K., Aye, S. S., Kahloon, M., Mobaraki, S., & Hanna, R. (2012). Health-related quality of life in bipolar disorder. *Bipolar Disorders, 14*(1), 6-18. doi: 10.1111/j.1399-5618.2011.00969.x.

IsHak, W. W., Greenberg, J. M., Balayan, K., Kapitanski, N., Jeffrey, J., Fathy, H., et al. (2011). Quality of life: The ultimate outcome measure of interventions in major depressive disorder. *Harvard Review of Psychiatry, 195*(5), 229–239.

Jacobs, B. L., van Praag, H., & Gage, F. H. (2000). Adult brain neurogenesis and psychiatry: A novel theory of depression. *Molecular Psychiatry, 5*(3), 262-269.

Jerath, R., Edry, J. W., Barnes, V. A., & Jerath, V. (2006). Physiology of long pranayamic breathing: Neural respiratory elements may provide a mechanism that explains how slow deep breathing shifts the autonomic nervous system. *Medical Hypotheses, 67*(3), 566-571.

Jha, A. P., Krompinger, J., & Baime, M. J. (2007). Mindfulness training modifies subsystems of attention. *Cognitive, Affective and Behavioral Neuroscience, 7*(2), 109-119.

Jha, S., Dong, B., & Sakata, K. (2011). Enriched environment treatment reverses depression-like behavior and restores reduced hippocampal neurogenesis and

protein levels of brain-derived neurotrophic factor in mice lacking its expression through promoter IV. *Translational Psychiatry, 1*(e40), doi:10.1038/tp.2011.1033.

Josefsson, T., Lindwall, M., & Archer, T. (2014). Physical exercise intervention in depressive disorders: Meta-analysis and systematic review. *Scandinavian Journal of Medicine and Science in Sports, 24*, 259-272.

Judd, L. L., Akiskal, H. S., Schettler, P. J., Endicott, J., Maser, J., Soloman, D. J., et al. (2002). The long-term natural history of the weekly symptomatic status of bipolar I disorder. *Archives of General Psychiatry, 59*, 530-537.

Kabat-Zinn, J., Massion, A. O., Kristellar, J., Peterson, L. G., Fletcher, K. E., Pbert, L., et al. (1992). Effectiveness of a meditation-based stress reduction program in the treatment of anxiety disorders. *American Journal of Psychiatry, 149*, 936-943.

Kaya, E., Aydemir, Ö., & Selcuki, D. (2007). Residual symptoms in bipolar disorder: The effect of the last episode after remission. *Progress in Neuro-Psychopharmacology and Biological Psychiatry, 31*, 1387-1392.

Keating, L. E., Becker, S., McCabe, K., Whattam, J., Garrick, L., Frey, B. N., et al. (2018). Effects of a 12-week running program in youth and adults with complex mood disorders. *BMJ Open Sport & Exercise Medicine, 4*(e000314), doi: 10.1136/bmjsem-2017-000314.

Keller, M. B., Lavori, P. W., Mueller, T. I., Endicott, J., Coryell, W., Hirschfield, R. M. A., et al. (1992). Time to recovery, chronicity, and levels of psychopathology in major depression. *Archives of General Psychiatry, 49*(10), 809-816.

Kempermann, G. (2002). Regulation of adult hippocampal neurogenesis – implications for novel theories of major depression. *Bipolar Disorders, 4*(1), 17-33.

Kempermann, G., Fabel, K., Ehninger, D., Babu, H., Leal-Galicia, P., Garthe, A., et al. (2010). Why and how physical activity promotes experience-induced brain plasticity. *Frontiers in Neuroscience, 4*(189), doi:10.3389/fnins.2010.00189.

Kendler, K. S. (1983). Overview: a current perspective on twin studies of schizophrenia. *American Journal of Psychiatry, 140*, 1413–1425.

Kendler, K. S. (2016). The phenomenology of major depression and the representativeness and nature of DSM criteria. *American Journal of Psychiatry, 173*(8), 771–780; doi: 710.1176/appi.ajp.2016.15121509.

Kendler, K. S., Karkowski, L. M., & Prescott, C. A. (1999). Causal relationship between stressful life events and the onset of major depression. *American Journal of Psychiatry, 156*, 837-841.

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, V., Bhat, V., Blier, P., et al. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments. *The Canadian Journal of Psychiatry*(1-21).

Kessler, R. C. (1997). The effects of stressful life events on depression. In J. T. Spence, J. M. Darley & D. J. Foss (Eds.), *Annual Review of Psychology* (Vol. 48, pp. 191-214). Palo Alto, California: Annual Reviews Inc.

Kessler, R. C. (2003). Epidemiology of women and depression. *Journal of Affective Disorders, 74*(1), 5-13.

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J., Chatterji, S., Lee, S., Ormel, J., et al. (2009). The global burden of mental disorders: An update from the WHO World Mental Health (WMH) surveys. *Epidemiologia e Psichiatria Sociale, 18*(1), 28-33.

Kessler, R. C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K. R., et al. (2003). The epidemiology of major depressive disorder results from the National Comorbidity Survey Replication (NCS-R). *Journal of the American Medical Association, 289*, 3095-3105.

Kessler, R. C., Berglunds, P., Demler, O., Jin, R., Merikangas, K. R., & Walters, E. E. (2005). Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 62*(6), 593-602.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of twelve-month DSM-IV Disorders in the National Comorbidity Survey Replication (NCSR). *Archives of General Psychiatry, 62*(6), 617-627.

Kilbourne, A. M., Rofey, D. L., McCarthy, J. F., Post, E. P., Welsh, D., & Blow, F. C. (2007). Nutrition and exercise behavior among patients with bipolar disorder1. *Bipolar Disorders, 9*(5), 443-452.

Kim, D.-M., & Leem, Y.-H. (2016). Chronic stress-induced memory deficits are reversed by regular exercise via Ampk-mediated BDNF induction. *Neuroscience, 324*, 271-285.

Kingston, R. C., Smith, M., Lacey, T., Edwards, M., Best, J. N., & Markham, C. M. (2018). Voluntary exercise increases resilience to social defeat stress in Syrian hamsters. *Physiology and Behavior, 188*, 194-198.

Kirby, E. D., Muroy, S. E., Sun, W. G., Covarrubias, D., Leong, M. J., Barchas, L. A., et al. (2013). Acute stress enhances adult rat hippocampal neurogenesis and activation of newborn neurons via secreted astrocytic FGF2. *eLife, 2*(e00362), DOI: 10.7554/eLife.00362.

Kirwan, C. B., Hartshorn, A., Stark, S. M., Goodrich-Hunsaker, N. J., Hopkins, R. O., & Stark, C. E. L. (2012). Pattern separation deficits following damage to the hippocampus. *Neuropsychologia, 50*(10), 2408-2414.

Kirwan, C. B., Jones, C. K., Miller, M. I., & Stark, C. E. L. (2007). High-resolution fMRI investigation of the medial temporal lobe. *Human Brain Mapping, 28*(10), 959-966.

Kirwan, C. B., & Stark, C. E. L. (2007). Overcoming interference: An fMRI investigation of pattern separation in the medial temporal lobe. *Learning and Memory, 14*(9), 625-633.

Kivimäki, M., & Steptoe, A. (2018). Effects of stress on the development and progression of cardiovascular disease. *Nature Reviews Cardiology, 15*, 215-229.

Kivimäki, M., Virtanen, M., Elovainio, M., Kouvonen, A., Väänänen, A., & Vahtera, J. (2006). Work stress in the etiology of coronary heart disease: a meta-analysis. *Scandinavian Journal of Work, Environment & Health, 32*(6), 431-442.

Klempin, F., Beis, D., Mosienko, V., Kempermann, G., Bader, M., & Alenina, N. (2013). Serotonin is required for exercise-induced adult hippocampal neurogenesis. *The Journal of Neuroscience, 33*(19), 8270 – 8275.

Knubben, K., Reischier, F. M., Adli, M., Schlattmann, P., Bauer, M., & Dimeo, F. (2007). A randomised, controlled study on the effects of a short-term endurance training programme in patients with major depression. *British Journal of Sports Medicine, 41*, 29-33 doi: 10.1136/bjsm.2006.030130.

Kolovos, S., van Tulder, M. W., Cuijpers, P., Prigent, A., Chevreul, K., Riper, H., et al. (2017). The effect of treatment as usual on major depressive disorder: A meta-analysis. *Journal of Affective Disorders, 210*, 72-81 doi: 10.1016/j.jad.2016.1012.1013.

Krogh, J., Nordentoft, M., Sterne, J. A. C., & Lawlor, D. A. (2011). The effect of exercise on clinically depressed adults: a systematic review and meta-analysis of randomized controlled trials. *Journal of Clinical Psychiatry, 72*, 529-538.

Krogh, J., Saltin, B., Gluud, C., & Nordentoft, M. (2009). The DEMO Trial: A randomized, parallel-group, observer-blinded clinical trial of strength versus aerobic versus relaxation training for patients with mild to moderate depression. *Journal of Clinical Psychiatry, 70*(6), 790-800.

Krogh, J., Videbech, P., Thomsen, C., Gluud, C., & Nordentoft, M. (2012). DEMO-II Trial. Aerobic exercise versus stretching exercise in patients with major depression—A randomised clinical trial. *PLoS ONE, 7*(10), e48316. doi:48310.41371/journal.pone.0048316.

Kubesch, S., Bretschneider, V., Freudenmann, R., Weidenhammer, N., Lehmann, M., Spitzer, M., et al. (2003). Aerobic endurance exercise improves executive functions in depressed patients. *Journal of Clinical Psychiatry, 64*(9), 1005-1012.

Kubesch, S., Walk, L., Spitzer, M., Kammer, T., Lainburg, A., Heim, R., et al. (2009). A 30-Minute physical education program improves students' executive attention. *Mind, Brain and Education, 3*(4), 235-242.

Kucyi, A., Alsuwaidan, M. T., Liauw, S. S., & McIntyre, R. S. (2015). Aerobic physical exercise as a possible treatment for neurocognitive dysfunction in bipolar disorder. *Postgraduate Medicine, 122*(6), 107-116.

Kupfer, D. J. (2005). The increasing medical burden in bipolar disorder. *Journal of the American Medical Association, 293*(20), 2528-2530.

Kupferberg, A., Bicks, L., & Hasler, G. (2016). Social functioning in major depressive disorder. *Neuroscience and Biobehavioral Reviews, 69*, 313-332.

Laforge, R. G., Rossi, J. S., Prochaska, J. O., Velicer, W. F., Levesque, D. A., & McHorney, C. A. (1999). Stage of regular exercise and health-related quality of life. *Preventive Medicine, 28*(4), 349-360.

Lalanza, J. F., Sanchez-Roige, S., Cigarroa, I., Gagliano, H., Fuentes, S., Armario, A., et al. (2015). Long-term moderate treadmill exercise promotes stress-coping strategies in male and female rats. *Scientific Reports, 5*(doi:10.1038/srep16166).

Lam, R. W., Kennedy, S. H., Parikh, S. V., MacQueen, G. M., Milev, R. V., & Ravindran, A. V. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with Major Depressive Disorders. *The Canadian Journal of Psychiatry, 61*(9), 540-560.

Lam, R. W., Parikh, S. V., Michalak, E. E., Dewa, C. S., & Kennedy, S. H. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) consensus recommendations for functional outcomes in major depressive disorder. *Annals of Clinical Psychiatry, 27*(2), 142-149.

Landau, S. M., Lal, R., O'Neil, J. P., Baker, S., & Jagust, W. J. (2009). Striatal dopamine and working memory. *Cerebral Cortex, 19*(2), 445-454.

Lee, J., Duan, W., & Mattson, M. P. (2002). Evidence that brain-derived neurotrophic factor is required for basal neurogenesis and mediates, in part, the enhancement of neurogenesis by dietary restriction in the hippocampus of adult mice. *Journal of Neurochemistry, 82*(6), 1367-1375.

Lerman, I., Harrison, B. C., Freeman, K., Hewett, T. E., Allen, D. L., Robbins, J., et al. (2002). Genetic variability in forced and voluntary endurance exercise performance in seven inbred mouse strains. *Journal of Applied Physiology, 92*, 2245-2255.

Levin, A., Hemmelgarn, B., Culleton, B., Tobe, S., McFarlane, P., Ruzicka, M., et al. (2008). Guidelines for the management of chronic kidney disease. *Canadian Medical Association Journal, 179*(11), 1154-1162; DOI: https://doi.org/1110.1503/cmaj.080351.

Li, S., Wang, C., Wang, W., Dong, H., Hou, P., & Tang, Y. (2008). Chronic mild stress impairs cognition in mice: From brain homeostasis to behavior. *Life Sciences, 82*(934-942).

Lim, K.-L., Jacobs, P., Ohinmaa, A., Schopflocher, D., & Dewa, C. S. (2008). *A new population-based measure of the economic burden of mental illness in Canada*. Ottawa, Ontario: Public Health Agency of Canada.

Lin, T.-W., & Kuo, Y.-M. (2013). Exercise benefits brain function: The monoamine connection. *Brain Sciences, 3*(1), 39-53.

Luu, K., & Hall, P. A. (2016). Hatha yoga and executive function: A systematic review. *Journal of Alternative and Complementary Medicine, 22*(2), 125-133.

Luu, P., Sill, O., Gao, L., Becker, S., Wojtowicz, J. M., & Smith, D. (2012). The role of adult hippocampal neurogenesis in reducing interference. *Behavioral Neuroscience, 126*(3), 381-391.

MacKinnon, D. P., Fairchild, A. J., & Fritz, M. S. (2007). Mediation analysis. *Annual Review of Psychology, 58*(593), doi: 10.1146/annurev.psych.1158.110405.085542.

MacQueen, G. M., & Memedovich, K. A. (2017). Cognitive dysfunction in major depression and bipolar disorder: Assessment and treatment options. *Psychiatry and Clinical Neurosciences, 71*, 18-27.

MacQueen, K. (2007). Dealing with the stressed. *Maclean's*.

Makinodan, M., Rosen, K. M., Ito, S., & Corfas, G. (2012). A critical period for social experience–dependent oligodendrocyte maturation and myelination. *Science, 14*(337), 1357–1360.

Malhi, G. S., & Byrow, Y. (2016). Exercising control over bipolar disorder. *Evidence-Based Mental Health, 19*(4), 103-105.

Marin, M.-F., Lord, C., Andrews, J., Juster, R.-P., Sindi, S., Arsenault-Lapierre, G., et al. (2011). Chronic stress, cognitive functioning and mental health. *Neurobiology of Learning and Memory, 96*(4), 583-595.

Martínez-Arán, A., Vieta, E., Reinares, M., Colom, F., Torrent, C., Sánchez-Moreno, J., et al. (2004). Cognitive function across manic or hypomanic, depressed, and euthymic states in bipolar disorder. *American Journal of Psychiatry, 161*, 262-270.

Martínez-Arán, A., Vieta, E., Torrent, C., Sanchez-Moreno, J., Goikolea, J. M., Salamero, M., et al. (2007). Functional outcome in bipolar disorder: the role of clinical and cognitive factors. *Bipolar Disorders, 9*(1-2), 103-113.

Martinsen, E. W., Medhus, A., & Sandvik, L. (1985). Effects of aerobic exercise on depression: a controlled study. *British Medical Journal, 291*, 109.

Mather, A. S., Rodriguez, C., Guthrie, M. F., McHarg, A. M., Reid, I. C., & McMurdo, M. E. T. (2002). Effects of exercise on depressive symptoms in older adults with poorly responsive depressive disorder. *British Journal of Psychiatry, 180*, 411-415.

McDonald, K. C., Bulloch, A. G. M., Duffy, A., Bresee, L., Williams, J. V. A., Lavorato, D. H., et al. (2015). Prevalence of bipolar I and II disorder in Canada. *Canadian Journal of Psychiatry, 60*(3), 151-156.

McEwen, B. S. (1999). Stress and hippocampal neuroplasticity. *Annual Review of Neuroscience, 22*, 105-122.

McEwen, B. S. (2006). Plasticity of the hippocampus: Adaptation to chronic stress and allostatic load. *Annals of the New York Acadamy of Sciences, 933*(1), 265-277.

McIntyre, R. S., Cha, D. S., Soczynska, J. K., Woldeyohannes, H. O., Gallaugher, L. A., Kudlow, P., et al. (2013). Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. *Depression and Anxiety, 30*(6), 515-527.

McKinnon, M. C., Yucel, K., Nazarov, A., & MacQueen, G. M. (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *Journal of Psychiatry and Neuroscience, 34*(1), 41-54.

McNeil, J. K., LeBlanc, E. M., & Joyner, M. (1991). The effect of exercise on depressive symptoms in the moderately depressed elderly. *Psychology and Aging, 6*(3), 487-488.

Merikangas, K. R., Jin, R., He, J.-P., Kessler, R. C., Lee, S., Sampson, N. A., et al. (2011). Prevalence and correlates of bipolar spectrum disorder in the World Mental Health Survey Initiative. *Archives of General Psychiatry, 68*(3), 241-251.

Meyer, M. L., Spunt, R. P., Berkman, E. T., Taylor, S. E., & Lieberman, M. D. (2012). Evidence for social working memory from a parametric functional MRI study. *Proceedings of the National Academy of Sciences USA, 109*(6), 1883-1888.

Miller, R. M., Marriott, D., Trotter, J., Hammond, T., Lyman, D., Call, T., et al. (2018). Running exercise mitigates the negative consequences of chronic stress on dorsal hippocampal long-term potentiation in male mice. *Neurobiology of Learning and Memory, 149*, 28-38.

Moffitt, T. E., Caspi, A., Taylor, A., Kokua, J., Milne, B. J., Polanczyk, G., et al. (2010). How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychological Medicine, 40*(6), 895-897.

Moliver, N., Mika, E. M., & Khalsa, S. B. S. (2013). Yoga experience as a predictor of psychological wellness in women over 45 years. *International Journal of Yoga, 6*(1), 11-19.

Möller, H. J. (2008). Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. *World Journal of Biological Psychiatry, 9*(2), 102-114. doi: 110.1080/15622970801981606.

Monteiro-Junior, R. S., de Tarso Maciel-Pinheiro, P., da Matta Mello Portugal, E., da Silva Figueiredo, L. F., Terra, R., Carneiro, L. S. F., et al. (2018). Effect of

exercise on inflammatory profile of older persons: Systematic review and meta-analyses. *Journal of Physical Activity and Health, 15*(1), 64-71.

Mota-Pereira, J., Carvalho, S., Silverio, J., Fonte, D., Pizarro, A., Teixeira, J., et al. (2011). Moderate physical exercise and quality of life in patients with treatment-resistant major depressive disorder. *Journal of Psychiatry Research, 45*(1657-1659).

Murinova, J., Hlavacova, N., Chmelova, M., & Riecansky, I. (2017). The evidence for altered BDNF expression in the brain of rats reared or housed in social isolation: A systematic review. *Frontiers in Behavioral Neuroscience, 11*(101), doi: 10.3389/fnbeh.2017.00101.

Muroy, S. E., Long, K. L. P., Kaufer, D., & Kirby, E. D. (2016). Moderate stress-Induced social bonding and oxytocin signaling are disrupted by predator odor in male rats. *Neuropsychopharmacology, 41*, 2160–2170.

Nabkasorn, C., Miyai, N., Sootmongkol, A., Junprasert, S., Yamamoto, H., Arita, M., et al. (2005). Effects of physical exercise on depression, neuroendocrine stress hormones and physiological fitness in adolescent females with depressive symptoms. *European Journal of Public Health, 16*(2), 179-184.

Nakashiba, T., Cushman, J. D., Pelkey, K. A., Renaudineau, S., Buhl, D. L., McHugh, T. J., et al. (2012). Young dentate granule cells mediate pattern separation, whereas old granule cells facilitate pattern completion. *Cell, 149*(1), 188-201.

National Collaborating Centre for Mental Health. (2006). *Bipolar disorder: The management of bipolar disorder in adults, children and adolescents, in primary*

and secondary care. London, UK: The British Psychological Society and the Royal College of Psychiatrists.

National Institute of Mental Health. (2015). *Strategic Plan for Research*. Retrieved June 13, 2018, from https://www.nimh.nih.gov/about/strategic-planning-reports/nimh_strategicplanforresearch_508compliant_corrected_final_149979.pdf

National Institutes of Health and Northwestern University. (2012). *NIH Toolbox ® Emotion*, from http://www.nihtoolbox.org/WhatAndWhy/Emotion/SocialRelationships/Pages/default.aspx

Naveen, G. H., Thirthalli, J., Rao, M. G., Varambally, S., Christopher, R., & Gangadhar, B. N. (2013). Positive therapeutic and neurotropic effects of yoga in depression: A comparative study. *Indian Journal of Psychiatry*, *55*(supple 3), S400-S404.

Naveen, G. H., Varambally, S., Thirthalli, J., Rao, M., Christopher, R., & Gangadhar, B. N. (2016). Serum cortisol and BDNF in patients with major depression—effect of yoga. *International Review of Psychiatry*, *28*(3), 273-278.

Nestler, E. J., & Carlezon Jr., W. A. (2006). The mesolimbic dopamine reward circuit in depression. *Biological Psychiatry*, *59*, 1151-1159.

Nestor, P. G., Nakamura, M., Niznikiewicz, M., Thompson, E., Levitt, J. J., Choate, V., et al. (2013). In search of the functional neuroanatomy of sociality: MRI subdivisions of orbital frontal cortex and social cognition. *Social Cognitive and Affective Neuroscience*, *8*(4), 460-467.

Nierenberg, A. A., Husain, M. M., Trivedi, M. H., Fava, M., Warden, D., Wisniewski, S. R., et al. (2010). Residual symptoms after remission of major depressive disorder with citalopram and risk of relapse: a STAR*D report. *Psychological Medicine, 41*(1), 41-50.

Novak, C. M., Burghardt, P. R., & Levine, J. A. (2012). The use of a running wheel to measure activity in rodents: Relationship to energy balance, general activity, and reward. *Neuroscience and Biobehavioral Reviews, 36*(3), 1001-1014.

Öhman, L., Nordin, S., Bergdahl, J., Slunga Birgander, L., & Stigsdotter Neely, A. (2007). Cognitive function in outpatients with perceived chronic stress. *Scandinavian Journal of Work, Environment & Health, 33*(3), 223-232.

Ozbay, F., Johnson, D. C., Dimoulas, E., Morgan III, C. A., Charney, D., & Southwick, S. (2007). Social support and resilience to stress: From neurobiology to clinical practice. *Psychiatry, 4*(5), 35-40.

Paolucci, E. M., Loukov, D., Bowdish, D. M. E., & Heisz, J. J. (2018). Exercise reduces depression and inflammation but intensity matters. *Biological Psychology, 133*, 79-84.

Pardo, J. V., Pardo, P. J., Janer, K. W., & Raichle, M. E. (1990). The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proceedings of the National Academy of Sciences USA, 87*, 256-259.

Parker, G., McCraw, S., Hadzi-Pavlovic, D., & Fletcher, K. (2013). Costs of the principal mood disorders: A study of comparative direct and indirect costs incurred by

those with bipolar I, bipolar II and unipolar disorders. *Journal of Affective Disorders, 149*(1-3), 46-55.

Pascoe, M. C., & Bauer, I. E. (2015). A systematic review of randomised control trials on the effects of yoga on stress measures and mood. *Journal of Psychiatric Research, 68*, 270-282.

Patel, A. (2009). The cost of mood disorders. *Psychiatry, 8*(2), 76-80.

Patki, G., Solanki, N., Atrooz, F., Ansari, A., Allam, F., Jannise, B., et al. (2014). Novel mechanistic insights into treadmill exercise based rescue of social defeat-induced anxiety-like behavior and memory impairment in rats. *Physiology and Behavior, 130*, 135-144.

Paykel, E., Ramana, R., Cooper, Z., Hayhurst, H., Kerr, J., & Barocka, A. (1994). Residual symptoms after partial remission: An important outcome in depression. *Psychological Medicine, 25*(6), 1171-1180.

Pearson, C., Janz, T., & Ali, J. (2013). *Mental and substance use disorders in Canada*. Retrieved June 6, 2018, 2018

Penedo, F. J., & Dahn, J. R. (2005). Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Current Opinion in Psychiatry, 18*(2), 189-193.

Peng, Y.-L., Liu, Y.-N., Liu, L., Wang, X., Jiang, C.-L., & Wang, Y.-X. (2012). Inducible nitric oxide synthase is involved in the modulation of depressive behaviors induced by unpredictable chronic mild stress. *Journal of Neuroinflammation, 9*(75), doi.org/10.1186/1742-2094-1189-1175.

Petersen, A. M. W., & Pedersen, B. K. (2005). The anti-inflammatory effect of exercise. *Journal of Applied Physiology, 98*(4), 1154-1162.

Pietrzak, R. H., Feder, A., Singh, R., Schechter, C. B., Bromet, E. J., Katz, C. L., et al. (2014). Trajectories of PTSD risk and resilience in World Trade Center responders: an 8-year prospective cohort study. *Psychological Medicine, 44*(1), 205-219.

Posner, M. I., Sheese, B., Rothbart, M., & Tang, Y. Y. (2007). The anterior cingulate gyrus and the mechanism of self-regulation. *Cognitive, Affective and Behavioral Neuroscience, 7*, 391-391.

Pretty, J., Peacock, J., Sellens, M., & Griffin, M. (2005). The mental and physical health outcomes of green exercise. *International Journal of Environmental Health Research, 15*(5), 319-337.

Public Health Agency of Canada. (2016). *Report from the Canadian Chronic Disease Surveillance System: Mood and Anxiety Disorders in Canada, 2016*. Ottawa, Ontario: Government of Canada.

Quach, D., Jastrowski Mano, K. E., & Alexander, K. (2016). A randomized controlled trial examining the effect of mindfulness meditation on working memory capacity in adolescents. *Journal of Adolescent Health, 58*(5), 489-496.

Rathore, A., & Lom, B. (2017). The effects of chronic and acute physical activity on working memory performance in healthy participants: a systematic review with meta-analysis of randomized controlled trials. *Systematic Reviews, 6*(124), DOI 10.1186/s13643-13017-10514-13647.

Reul, J. M. H. M., Collins, A., Saliba, R. S., Mifsud, K. R., Carter, S. D., Gutierrez-Mecinas, M., et al. (2015). Glucocorticoids, epigenetic control and stress resilience. *Neurobiology of Stress, 1*, 44-59.

Reynolds, C. F. (1997). Forward and backward memory span should not be combined for clinical analysis. *Archives of Clinical Neuropsychology, 12*(1), 29-40.

Ricardo, A. C., Anderson, C. A., Yang, W., Zhang, X., Fischer, M. J., Dember, L. M., et al. (2015). Healthy lifestyle and risk of kidney disease progression, atherosclerotic events, and death in CKD: findings from the Chronic Renal Insufficiency Cohort (CRIC) Study. *American Journal of Kidney Disease, 65*(3), 412-424 doi: 410.1053/j.ajkd.2014.1009.1016.

Riedel, M., Möller, H.-J., Obermeier, M., Schennach-Wolff, R., Bauer, M., Adli, M., et al. (2010). Response and remission criteria in major depression: A validation of current practice. *Journal of Psychiatric Research, 44*, 1063-1068.

Rocha, K. K. F., Ribeiro, A. M., Rocha, K. C. F., Sousa, M. B. C., Albuquerque, F. S., Ribeiro, S., et al. (2012). Improvement in physiological and psychological parameters after 6 months of yoga practice. *Consciousness and Cognition, 21*, 843-850.

Rossi, C., Angelucci, A., Costantin, L., Braschi, C., Mazzantini, M., Babbini, F., et al. (2006). Brain-derived neurotrophic factor (BDNF) is required for the enhancement of hippocampal neurogenesis following environmental enrichment. *European Journal of Neuroscience, 24*(7), 1850-1856.

Saarni, S. I., Suvisaari, J., Sintonen, H., & Pirkola, S. (2007). Impact of psychiatric disorders on health-related quality of life: general population survey. *British Journal of Psychiatry, 190*(4), 326-332 doi.org/310.1192/bjp.bp.1106.025106.

Saeed, S. A., Antonacci, D. J., & Bloch, R. M. (2010). Exercise, yoga, and meditation for depressive and anxiety disorders. *American Family Physician, 81*, 981-986.

Sahay, A., Scobie, K. N., Hill, A. S., O'Carroll, C. M., Kheirbek, M. A., Burghardt, N. S., et al. (2011). Increasing adult hippocampal neurogenesis is sufficient to improve pattern separation. *Nature, 472*(7344), 466-470. doi: 410.1038/nature09817.

Salagre, E., Solé, B., Tomoika, Y., Fernandes, B. S., Hidalgo-Mazzei, D., Garriga, M., et al. (2017). Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives. *Journal of Affective Disorders, 221*(2017), 205-221.

Santarelli, L., Saxe, M., Gross, C., Surget, A., Battaglia, F., Dulawa, S., et al. (2003). Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science, 301*(5634), 805-809.

Saxe, M. D., Battaglia, F., Wang, J.-W., Malleret, G., David, D. J., Monckton, J. E., et al. (2006). Ablation of hippocampal neurogenesis impairs contextual fear conditioning and synaptic plasticity in the dentate gyrus. *Proceedings of the National Academy of Sciences USA, 103*(46), 17501–17506.

Schaffer, A., Cairney, J., Cheung, A., Veldhuizen, S., & Levitt, A. (2006). Community survey of bipolar disorder in Canada: lifetime prevalence and illness characteristics. *Canadian Journal of Psychiatry, 51*(1), 9-16.

Schoenfeld, T. J., Rada, P., Pieruzzini, P. R., Hsueh, B., & Gould, E. (2013). Physical exercise prevents stress-induced activation of granule neurons and enhances local inhibitory mechanisms in the dentate gyrus. *The Journal of Neuroscience, 33*(18), 7770-7777.

Schuch, F. B., Vancampfort, D., Rosenbaum, S., Richards, J., Ward, P. B., & Stubbs, B. (2016). Exercise improves physical and psychological quality of life in people with depression: A meta-analysis including the evaluation of control group response. *Psychiatry Research, 241*, 47–54.

Schweizer, M. C., Henniger, M. S. H., & Sillaber, I. (2009). Chronic mild stress (CMS) in mice: Of anhedonia, 'anomalous anxiolysis' and activity. *PLoS ONE, 4*(1), e4326. doi:4310.1371/journal.pone.0004326.

Segerstrom, S. C., & Miller, G. E. (2004). Psychological stress and the human immune system: A meta-analytic study of 30 years of inquiry. *Psychological Bulletin, 130*(4), 601-630.

Seifi-skishahr, F., Damirchi, A., Farjaminezhad, M., & Babaei, P. (2016). Physical training status determines oxidative stress and redox changes in response to an acute aerobic exercise. *Biochemistry Research International, 3757623*(http://dx.doi.org/10.1155/2016/3757623).

Selye, H. (1975). *The stress of life*. New York, NY: McGraw-Hill.

Sharma, V. K., Rajajeyakumar, M., Velkumary, S., Subramanian, S. K., Bhavanani, A. B., Madanmohan, et al. (2014). Effect of fast and slow pranayama practice on

cognitive functions in healthy volunteers. *Journal of Clinical and Diagnostic Research, 8*(1), 10-13.

Shilyansky, C., Williams, L. M., Gyurak, A., Harris, A., Usherwood, T., & Etkin, A. (2016). Effect of antidepressant treatment on cognitive impairments associated with depression: a randomised longitudinal study. *Lancet Psychiatry, 3*(5), 425-435.

Sigwalt, A. R., Budde, H., Helmich, I., Glaser, V., Ghisoni, K., Lanza, S., et al. (2011). Molecular aspects involved in swimming exercise training reducing anhedonia in a rat model of depression. *Neuroscience, 192*(September), 661-674.

Silva-Gomez, A. B., Rojas, D., Juarez, I., & Flores, G. (2003). Decreased dendritic spine density on prefrontal cortical and hippocampal pyramidal neurons in postweaning social isolation rats. *Brain Research, 983*, 128-136.

Sinyor, M., Schaffer, A., & Levitt, A. (2010). The sequenced treatment alternatives to relieve depression (STAR*D) trial: a review. *Canadian Journal of Psychiatry, 55*(3), 126-135.

Skevington, S. M., & Wright, A. (2001). Changes in the quality of life of patients receiving antidepressant medication in primary care: Validation of the WHOQOL–100. *The British Journal of Psychiatry, 178*(3), 261-267.

Smith, P. J., Blumenthal, J. A., Hoffman, B. M., Cooper, H., Strauman, T. A., Welsh-Bohmer, K., et al. (2010). Aerobic exercise and neurocognitive performance: a meta-analytic review of randomized controlled trials. *Psychosomatic Medicine, 72*(3), 239-252.

Smoller, J. W., & Finn, C. T. (2003). Family, twin, and adoption studies of bipolar disorder. *American Journal of Medical Genetics Part C (Seminars in Medical Genetics), 123C*, 48-58.

Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature, 476*, 458-461.

Spielmans, G. I., & Gerwig, K. (2014). The efficacy of antidepressants on overall well-being and self-reported depression symptom severity in youth: a meta-analysis. *Psychotherapy and Psychosomatics, 83*, 158-164.

Spitzer, R. L., Kroenke, K., LInzer, M., Hahn, S. R., Williams, J. B. W., Verloin deGruy, F., et al. (1995). Health-related quality of life in primary care patients with mental disorders. *Journal of the American Medical Association, 274*(19), 1511-1517.

Stranahan, A. M., Khalil, D., & Gould, E. (2006). Social isolation delays the positive effects of running on adult neurogenesis. *Nature Neuroscience, 9*, 526-533.

Stroop, J. R. (1935). Studies of interference in serial verbal reactions. *Journal of Experimental Psychology, 18*(6), 643-661.

Stroth, S., Hille, K., Spitzer, M., & Reinhardt, R. (2009). Aerobic endurance exercise benefits memory and affect in young adults. *Neuropsychological Rehabilitation, 19*(2), 223-243.

Subramanya, P., & Telles, S. (2009). Effect of two yoga-based relaxation techniques on memory scores and state anxiety. *Biopsychosocial Medicine, 3*(8), doi.org/10.1186/1751-0759-1183-1188.

Sullivan, P. F., Neale, M. C., & Kendler, K. S. (2000). Genetic epidemiology of major depression: Review and meta-analysis. *American Journal of Psychiatry, 157*, 1552-1562.

Sun, M., Lanctot, K., Herrmann, N., & Gallagher, D. (2018). Exercise for cognitive symptoms in depression: A systematic review of interventional studies. *Canadian Journal of Psychiatry, 63*(2), 115-128.

Svensson, M., Rosvall, P., Boza-Serrano, A., Andersson, E., Lexell, J., & Deierborg, T. (2016). Forced treadmill exercise can induce stress and increase neuronal damage in a mouse model of global cerebral ischemia. *Neurobiology of Stress, 5*(2016), 8-18.

Tafet, G. E., & Nemeroff, C. B. (2016). The links between stress and depression: Psychoneuroendocrinological, genetic, and environmental interactions. *Journal of Neuropsychiatry and Clinical Neurosciences, 28*, 77-88.

Tang, Y.-Y., Hölzel, B. K., & Posner, M. I. (2015). The neuroscience of mindfulness meditation. *Nature Reviews Neuroscience, 16*, 213-225.

Tang, Y.-Y., & Tang, R. (2015). Short-term meditation increases blood flow in anterior cingulate cortex and insula. *Frontiers in Psychology, 6*(212), doi:10.3389/fpsyg.2015.00212.

Taren, A. A., Gianaros, P. J., Greco, C. M., Lindsay, E. K., Fairgrieve, A., Brown, K. W., et al. (2015). Mindfulness meditation training alters stress-related amygdala resting state functional connectivity: A randomized controlled trial. *Social Cognitive and Affective Neuroscience, 10*(12), 1758–1768.

Thompson, P. D., Buchner, D., Piña, I. L., Balady, G. J., Williams, M. A., Marcus, B. H., et al. (2003). Exercise and physical activity in the prevention and treatment of atherosclerotic cardiovascular disease. *Circulation, 107*, 3109-3116.

Thomson, D., Turner, A., Lauder, S., Gigler, M. E., Berk, L., Singh, A. B., et al. (2015). A brief review of exercise, bipolar disorder, and mechanistic pathways. *Frontiers in Psychology, 6*(147), doi: 10.3389/fpsyg.2015.00147.

Trivedi, M. H., & Greer, T. L. (2014). Cognitive dysfunction in unipolar depression: Implications for treatment. *Journal of Affective Disorders, 152-154*, 19-27.

Trivedi, M. H., Greer, T. L., Church, T. S., Carmody, T. J., Grannemann, B. D., Galper, D. I., et al. (2011). Exercise as an augmentation treatment for nonremitted major depressive disorder: A randomized, parallel dose comparison. *Journal of Clinical Psychiatry, 72*(5), 677-684.

Trivedi, M. H., Rush, A. J., Wisniewski, S. R., Nierenberg, A. A., Warden, D., Ritz, L., et al. (2006). Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *American Journal of Psychiatry, 163*(1), 28-40.

U.S. Department of Health and Human Services. (1996). *Physical Activity and Health: A Report of the Surgeon General*. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion.

Valtorta, N. K., Kanaan, M., Gilbody, S., Ronzi, S., & Hanratty, B. (2016). Loneliness and social isolation as risk factors for coronary heart disease and stroke:

systematic review and meta-analysis of longitudinal observational studies. *Heart, 102*, 1009–1016.

van der Borght, K., Havekes, R., Bos, T., Eggen, B., & van der Zee, E. (2007). Exercise improves memory acquisition and retrieval in the Y-maze task: Relationship with hippocampal neurogenesis. *Behavioral Neuroscience, 121*(2), 324-334.

van Gent, R. N., Siem, D., van Middelkoop, M., van Os, A. G., Bierma-Zeinstra, S. M., & Koes, B. W. (2007). Incidence and determinants of lower extremity running injuries in long distance runners: A systematic review. *British Journal of Sports Medicine, 41*(8), 469-480.

van Praag, H., Christie, B. R., Sejnowski, T. J., & Gage, F. H. (1999). Running enhances neurogenesis, learning, and long-term potentiation in mice. *Proceedings of the National Academy of Sciences USA, 96*(23), 13427-13431.

van Praag, H., Kempermann, G., & Gage, F. H. (1999). Running increases cell proliferation and neurogenesis in the adult mouse dentate gyrus. *Nature Neuroscience, 2*, 266-270.

van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews, 1*, 191-198.

van Praag, H., Shubert, T., Zhao, C., & Gage, F. H. (2005). Exercise enhances learning and hippocampal neurogenesis in aged mice. *Journal of Neuroscience, 25*, 8680-8685.

Van Veen, V., & Carter, C. S. (2002). The anterior cingulate as a conflict monitor: fMRI and ERP studies. *Physiology and Behavior, 77*, 477-482.

Vasques, P. E., Moraes, H., Silveira, H., Deslandes, A. C., & Laks, J. (2011). Acute exercise improves cognition in the depressed elderly: the effect of dual-tasks. *Clinics (Sao Paulo), 66*(9), 1553-1557.

Veale, D., Le Fevre, K., Pantelis, C., de Souza, V., Mann, A., & Sargeant, A. (1992). Aerobic exercise in the adjunctive treatment of depression: a randomized controlled trial. *Journal of the Royal Society of Medicine, 85*, 541-544.

Veiel, H. O. F. (1997). A preliminary profile of neuropsychological deficits associated with major depression. *Journal of Clinical and Experimental Neuropsychology, 19*(4), 587-603.

Venna, V. R., Xu, Y., Doran, S. J., Patrizz, A., & McCullogh, L. D. (2014). Social interaction plays a critical role in neurogenesis and recovery after stroke. *Translational Psychiatry, 4*(e351), doi:10.1038/tp.2013.1128.

Villemure, C., Ceko, M., Cotton, V. A., & Bushnell, M. C. (2015). Neuroprotective effects of yoga practice: age-, experience-, and frequency-dependent plasticity. *Frontiers in Human Neuroscience, 9*(281), doi: 10.3389/fnhum.2015.00281.

Walker, E. R., McGee, R. E., & Druss, B. G. (2015). Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. *JAMA Psychiatry, 72*, 334-341.

Wang, X., Cai, L., Qian, J., & Peng, J. (2014). Social support moderates stress effects on depression. *International Journal of Mental Health Systems, 8*(41), 1-5.

Warburton, W. E. R., Nicol, C. E., & Bredin, S. S. D. (2006). Health benefits of physical activity: the evidence. *Canadian Medical Association Journal, 174*(6), 801-809.

Ware Jr., J. E., Kosinski, M., & Keller, M. (1994). *SF-36 Physical and Mental Health Summary Scales: A Users' Manual*. Boston: The Health Institute.

Ware Jr., J. E., & Sherbourne, C. D. (1992). The MOS 36 Item Short Form Health Survey (SF 36). 1. Conception Framework and Item Selection. *Medical Care, 30*(6), 473-483.

Watanabe, Y., Gould, E., & McEwen, B. S. (1992). Stress induces atrophy of apical dendrites of hippocampal CA3 pyramidal neurons. *Brain Research, 588*, 341-345.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV)*. San Antonio, TX: Pearson.

Weinstein, A. M., Voss, M. W., Prakash, R. S., Chaddock, L., Szabo, A., White, S. M., et al. (2012). The association between aerobic fitness and executive function is mediated by prefrontal cortex volume. *Brain, Behavior and Immunity, 26*, 811-819.

Westenbroek, C., Den Boer, J. A., Veenhuis, M., & Ter Horst, G. J. (2004). Chronic stress and social housing differentially affect neurogenesis in male and female rats. *Brain Research Bulletin, 64*(4), 303-308.

Whiteford, H. A., Ferrari, A. J., Degenhardt, L., Feigin, V., & Vos, T. (2015). The global burden of mental, neurological and substance use disorders: An analysis from the Global Burden of Disease Study 2010. *PLoS ONE, DOI:10.1371/journal.pone.0116820*(February), 1-14.

Willner, P., Muscat, R., & Papp, M. (1992). Chronic mild stress-induced anhedonia: A realistic animal model of depression. *Neuroscience and Biobehavioral Reviews, 16*, 525-534.

Winocur, G., Becker, S., Luu, P., Rosenzweig, S., & Wojtowicz, J. M. (2012). Adult hippocampal neurogenesis and memory interference. *Behavioral Brain Research, 277*(2 Special Issue S1 . doi:10.1016/j.bbr.2011.05.032), 464-469.

Wojtowicz, J. M., Askew, M. L., & Winocur, G. (2008). The effects of running and of inhibiting adult neurogenesis on learning and memory in rats. *European Journal of Neuroscience, 27*(6), 1494-1502.

World Health Organization. (2008). *The Global Burden of Disease: 2004 Update*. Geneva, Switzerland: World Health Organization.

World Health Organization. (2017). *Depression and Other Common Mental Disorders: Global Health Estimates*. Geneva, Switzerland.

Yassa, M. A., Lacy, J. W., Stark, S. M., Albert, M. S., Gallagher, M., & Stark, C. E. L. (2011). Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus, 21*, 968-979.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Beaulieu, S., Alda, M., et al. (2013). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disorders, 15*(1), 1-44.

Yoshihara, K., Hiramoto, T., Sudo, N., & Kubo, C. (2011). Profile of mood states and stress-related biochemical indices in long-term yoga practitioners. *BioPsychoSocial Medicine, 5*(6), doi:10.1186/1751-0759-1185-1186.

Zanier-Gomes, P. H., de Abreu Silva, T. E., Zanetti, G. C., Benati, E. R., Pinheiro, N. M., Murta, B. M., et al. (2015). Depressive behavior induced by social isolation of predisposed female rats. *Physiology and Behavior, 151*(November), 292-297.

Zimmerman, M., Martinez, J. A., Attiullah, N., Friedman, M., Toba, C., Boerescu, D. A., et al. (2012). Why do some depressed outpatients who are in remission according to the Hamilton Depression Rating Scale not consider themselves to be in remission? *Journal of Clinical Psychiatry, 73*(6), 790-795 doi: 710.4088/JCP.4011m07203.