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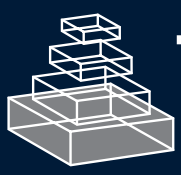
RESEARCH TOPICS

# PROGRESS IN PHYSICAL ACTIVITY AND EXERCISE AND AFFECTIVE AND ANXIETY DISORDERS: CURRENT VIEWS, PERSPECTIVES AND FUTURE DIRECTIONS

Topic Editors
Felipe Barreto Schuch, Neusa Rocha and Eduardo Lusa Cadore



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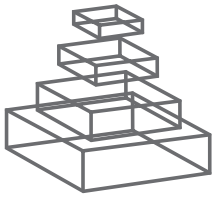

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# PROGRESS IN PHYSICAL ACTIVITY AND EXERCISE AND AFFECTIVE AND ANXIETY DISORDERS: CURRENT VIEWS, PERSPECTIVES AND FUTURE DIRECTIONS

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Physical activity and exercise were receiving a great attention as a strategy of prevention and treatment of affective and some anxiety disorders. Many studies have showed the efficacy of exercise in major depression and at depressed episode of bipolar patients, as well as, some authors shows the benefits of exercise in some anxiety disorders like Generalized Anxiety Disorder and Panic. Despite their efficacy, little is known concerning the main mechanisms related to the antidepressant and anxiolytic effects of exercise.

Several studies in an animal model using Neurotrophic Factors, Oxidative Stress, Immunologic response and other biological markers reveal promising results. However, few studies were conducted in clinical samples.

Additional to the antidepressant and anxiolytic effects, exercise appears improve QoL in major depressed, bipolar and anxiety patients. Theoretically, this increase may be associated with cognitive improvements, improvements at sleep quality, physical functioning, as well as other psychological issues as self-esteem, self-concept, and general well-being.

The propose of this topic is to address the novelty and most recent research, related to antidepressant and anxiolytic effects of physical activity and exercise in patients with affective and anxiety disorders, as well as the issues associated with QoL improvement.The topic is looking for:

– Clinical trials using exercise and physical activity as a treatment affective and anxiety disorders.
– Studies investigating the optimal prescription factors (dose, volume, intensity, setting, frequency) associated with antidepressant and anxiolytic effects of physical activity and exercise for affective and anxiety disorder patients.

– Original studies, comprehensive reviews, hypothesis and opinions concerning the mechanisms of antidepressant and anxiolytic effects of physical activity and exercise in affective and anxiety disorder patients.
– Original studies, comprehensive reviews, hypothesis and opinions concerning other benefits of physical activity and exercise like : cognition, weight gain prevention and QoL in affective and anxiety disorder patients.
– Translational research.
– Studies of cost-efficacy analysis.

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# Progress in the study of the effects of exercise on affective and anxiety disorders

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**Keywords: depression, anxiety, bipolar, quality of life, BDNF, galanin, meditative movement, genetic marker**

Exercise has received great attention as a treatment for affective and anxiety disorders, and several studies have highlighted its mental and physical health benefits for these populations. Despite the innumerous benefits, however, there are many issues in the literature that need further exploration.

In depression, exercise appears to moderately improve depressive symptoms. Blake (1) and Deslandes (2) reviewed the literature pointing to recent findings about the current use and efficacy of exercise in depression, and the challenges in treating depression with exercise. Some of these points, as the efficacy and effectiveness of exercise, and some potential factors related to its efficacy and effectiveness, were revisited in Schuch and Fleck (3). This paper highlighted the potential implications of the heterogeneity of depression diagnosis, the psychometric instruments, and other non-specific factors on the response rates found in clinical trials. In the same line, Stanton et al. (4) reviewed the effects of exercise, analyzing the guidelines that have discussed the prescription of exercise in major depression, bipolar disorder, and post-natal depression. Still related to prescription of exercise, Paine and Crane-Goodreau (5) reviewed studies using meditative movements on the treatment of depression and anxiety, suggesting its potential role in the treatment of depression and anxiety.

Quality of life (QoL) improvement is a major challenge in the depression treatment. Reinforcing the discussion of Blake (1) regarding QoL, a longitudinal study enrolling more than 15,000 participants showed that recreational activity improved some of the negative impact of depression on health-related QoL (6).

The mechanisms related to the antidepressant and anxiolytic effects of exercise remain unclear, though the literature reveals some insights in this regard. Anderson and Shivakumar (7) provided a review of the several potential physiological (hypothalamic–pituitary–adrenal axis, monoamines, opioids, and neurotrophic) and psychological (anxiety sensitivity and exposure, self-efficacy, and distraction) explanations to the anxiolytic effects of exercise. Similarly, Deslandes (2) discussed the potential role of brain-derived neurotrophic factor (BDNF) and neurogenesis in the antidepressant effects of exercise. Additionally, Holmes (8) analyzed the influence of Galanin and the interaction between Galanin and BDNF in the role of exercise-induced stress resilience. Genetic mechanisms, as pleiotropy, provide a possible explanation for some depressed populations' lack of response to exercise, as well as the association between inactivity and depression (9). The neuroimmune system appears to be implicated in the pathophysiology of depression. Meanwhile, exercise has shown effects on several immunological biomarkers. In this regard, Eyre et al. (10) provide an extensive review regarding some specific factors such as changes on some factors as interleukins (1 and 6), macrophage migration inhibitory factor, central nervous system-specific autoreactive CD4+ T cells, M2 microglia, quiescent astrocytes, CX3CL1, and insulin-like growth 35 factor-1, Th1/Th2 balance, pro-inflammatory cytokines, C-reactive protein, M1 microglia, and reactive astrocytes.

The topic presented several discussions regarding the current literature, the limitations of present studies, as well as several potential biological mediators of the relationship between exercise and depression/anxiety. The discussion may help researchers and other professionals of mental health form a broader comprehension of the exercise–depression relationship.

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# Physical activity and exercise in the treatment of depression

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Mental health problems continue to present a global challenge and contribute significantly to the global burden of human disease (DALYs). Depression is the most common psychiatric disorder and is thought to affect 121 million adults worldwide, and as such was rated as the fourth leading cause of disease burden in 2000 (Moussavi et al., 2007), projected to become the highest cause of disease burden by 2020. Antidepressant drugs are an effective and commonly used treatment for depression in primary care (Arroll et al., 2009), although almost half of those treated do not achieve full remission of their symptoms, and there remains a risk of residual symptoms, relapse/recurrence (Fava and Ruini, 2002). In those patients who do demonstrate improvements in depressive symptoms with antidepressant therapies, a time-lag in the onset of therapeutic effects is frequently reported. Antidepressant drugs are associated with adverse side effects (Agency for Health Research and Quality (AHRQ), 2012) and an increased risk of cardiovascular disease, particularly in those with pre-existing cardiovascular conditions or major cardiovascular risk factors (Waring, 2012). Furthermore, adherence to antidepressant medications is often poor and patients often prematurely discontinue their antidepressant therapy; it has been suggested that approximately 50% of psychiatric patients and 50% of primary care patients are non-adherent when assessed 6-months after the initiation of treatment (Sansone and Sansone, 2012).

Psychological treatments for depression have been recommended in the UK National Institute for Health and Clinical Excellence (NICE) guidelines (NICE, 2009) and are becoming more commonplace for helping to reduce symptoms in depressed adults (Ambresin et al., 2012; Brakemeier and Frase, 2012), with even brief psychosocial interventions showing promise for improving adherence to depression medication treatment in primary care settings (Sirey et al., 2010). However, attendance at psychological intervention sessions can be poor since many depressed adults who may benefit from such treatments choose not to attend mental health clinics due to the perceived stigma of psychological therapies.

As such there has been an increasing interest in the role of alternative interventions for depression. Physical exercise has been proposed as a complementary treatment which may help to improve residual symptoms of depression and prevent relapse (Trivedi et al., 2006). Exercise has been proposed by many as a potential treatment for depression and meta-analysis has demonstrated that effect sizes in intervention studies range from -0.80 to -1.1 (Rethorst et al., 2009). However, the evidence is not always consistent; recent research has shown that that provision of tailored advice and encouragement for physical activity did not improve depression outcome or antidepressant use in depressed adults when compared with usual care (Chalder et al., 2012). Other researchers have failed to find an antidepressant effect of exercise in patients with major depression but have found short term positive effects on physical outcomes, body composition and memory (Krogh et al., 2012). Others have argued that the nature of exercise delivery is an important factor, with exercise of preferred (rather than prescribed) intensity shown to improve psychological, physiological and social outcomes, and exercise participation rates in depressed individuals (Callaghan et al., 2011).

Research findings have been summarized by a recent Cochrane review which reported the findings of 32 randomized controlled trials in which exercise was compared to standard treatment, no treatment or a placebo treatment in adults (aged 18 and over) with depression (Rimer et al., 2012). This review concluded that exercise seems to improve depressive symptoms in people with a diagnosis of depression when compared with no treatment or control intervention, although highlighted that this should be interpreted with caution since the positive effects of exercise were smaller in methodologically robust trials. Similarly, a systematic review found that physical exercise programs obtain clinically relevant outcomes in the treatment of depressive symptoms in depressed older people (>60 years; Blake et al., 2009). Although the positive effects of exercise intervention on depressive symptoms are gaining more clarity, reviews suggest that there are currently insufficient high quality data to determine cost-benefit of exercise intervention in depression (Blake et al., 2009; Rimer et al., 2012). Many intervention studies with depressed populations are hampered by methodological weaknesses and small samples sizes. Further, comparisons between studies are often difficult due to variations in assessment or diagnosis of depression, level of severity of the condition, setting for delivery and size of the sample, outcomes of interest and the nature of the intervention delivered (type, frequency and duration of the intervention).

Despite some inconsistencies in research findings, in the UK, the value of exercise continues to be substantiated by current reports and guidelines which include exercise as a management strategy

for depression; NICE guidelines have recommended structured, supervised exercise programs, three times a week (45 min to 1 h) over 10–14 weeks, as a low-intensity Step 2 intervention for mild to moderate depression (NICE, 2009); Scottish Intercollegiate Guidelines Network (SIGN) for non-pharmaceutical management of depression in adults has recommended that structured exercise may be considered as a treatment option for patients with depression (SIGN, 2010); and exercise is specified as a treatment option for people with depression in a report for the National Service Framework for Mental Health (Donaghy and Durward, 2000). This is further substantiated by research which demonstrates that patients also find value in physical activity as an effective treatment for depression (Searle et al., 2011), although their perceptions of potential benefits and barriers to participation vary between individuals.

The relationship between exercise and improved physical and psychological health is very well established in both healthy populations and also in people with long-term conditions, and active lifestyles are generally promoted in all populations where physical activity can be safely undertaken. Depression has been clearly associated with low levels of physical activity (Biddle, 2000; Goodwin, 2003) although this does not necessarily infer causality—there are many reasons why individuals who are depressed may have a more sedentary lifestyle, not least recognizing the effects of depression on motivation to engage in healthy lifestyle behaviors.

We know that physical activity confers positive effects on mental well-being although the exact mechanisms which support this relationship are still poorly understood. Patients with depression have attributed this to a number of subjective benefits including biochemical pathways, and cognitive mechanisms include diversion from negative thinking, and a sense of purpose (Searle et al., 2011). Researchers have attempted to clarify this association and have identified a range of possible explanations. The potential role of the inflammatory response has been highlighted as a key mechanism in understanding the relationship between exercise and mood (Hamer et al., 2012). It has also been proposed that physiological changes associated with exercise including endorphin and monoamine levels, or reduction in the levels of the stress hormone cortisol (Duclos et al., 2003) may exert an influence on mood. Further, a growing body of research on the role of neurogenesis in the etiology and treatment of depression has indicated that exercise may alter neurotransmitter function, and promote growth of the hippocampus which is known to be reduced in depressed populations (Lucassen et al., 2010). Indeed, laboratory studies have shown that the neurogenic response to exercise has been found to be much stronger than the response to antidepressant medications (Marlatt et al., 2010). Whilst researchers continue to investigate the mechanisms for this relationship the fact remains that physical activity is good for physical and mental health and therefore important for all.

The social contact often derived from physical activity may play an important role in the relationship between physical activity or exercise and mood. Social support is known to be important for mental well-being, although early studies with older adults showed that exercise reduces depressive symptoms equally to social contact, with exercise also exerting a broader effect than social contact alone through reducing somatic symptoms (McNeil et al., 1991). Others have shown that physical activity intervention may improve mood and quality of life (QoL) equally to social contact in older adults, although this is yet to be tested in comparison with a "no-contact" control group (Kerse et al., 2010).

The focus on the relationship between QoL and exercise is increasingly evident although there are few well-designed studies which have examined the relationship between physical exercise and QoL in depressed individuals. Improvements in global functionality, depressive and general psychopathological symptoms have been observed in depressed patients who have undertaken a supervised exercise regimen adjunctive to standard therapy with antidepressant drugs, with concomitant improvements in perceived QoL although only in the "physical domain" (Carta et al., 2008). Current trials are including QoL as an important outcome variable in exercise interventions for patients with long-term conditions (e.g., Saxton et al., 2012). In fact, it has been argued that the promotion of exercise should now focus more heavily upon the benefits for QoL than focusing on the physical health benefits which have historically predominated in health promotion efforts (Stevens and Bryan, 2012).

QoL is an important outcome criterion for interventions with depressed patients, particularly since patients with depressive disorders and/or depressive symptoms have been shown to have substantial and long-lasting decrements in multiple domains of functioning and well-being that equal or exceed those of patients with chronic medical illnesses (Hays et al., 1995). Definitions of QoL vary in the literature with some definitions focusing on individuals' perceptions of their health status, whereas other definitions focus on individuals' levels of satisfaction with their health status. However, a commonly cited definition is "a state of well-being that is a composite of two components: (1) the ability to perform everyday activities that reflect physical, psychological, and social well-being and (2) patient satisfaction with levels of functioning and the control of disease and/or treatment-related symptoms" (Gotay et al., 1992). Exercise has been associated with QoL in epidemiological studies, and regular exercise has shown to substantially improve QoL in populations with serious long-term conditions such as cancer (Burnham and Wilcox, 2002), Stroke (Smith and Thompson, 2008) and chronic obstructive pulmonary disease (Emery et al., 1998). However, there is less evidence for exercise improving QoL in disease-free populations. Although QoL has been advocated as either a primary or secondary outcome in health research (Speight and Barendse, 2010), a recent systematic review revealed that very few exercise and depression trials have actually included QoL as an outcome (Schuch et al., 2011).

Largely due to the small number of intervention studies in this area, and methodological weaknesses within published studies, exercise intervention studies have not consistently demonstrated effects of exercise on QoL outcomes (Spirduso and Cronin, 2001; de Vreede et al., 2007), although in studies that *do* show positive

effects, exercise dose has been found to be a significant predictor of change in mental and physical aspects of QoL (Martin et al., 2009). However, assessing QoL continues to be challenging, particularly in depressed populations where there may be an overlap in measurement between QoL and psychopathology; depression is known to negatively impact on different aspects of an individual's life and this in turn can result in significant impairments in QoL (Ishak et al., 2012). The influence of depressive symptomatology on QoL scores may therefore invalidate research results (Aigner et al., 2006).

Overall, the evidence suggests that exercise can improve depressive symptoms and this is observed even in those suffering from major depressive disorder (Pilu et al., 2007) who have been shown to benefit more from physical exercise than other psychiatric groups (Tordeurs et al., 2011). Exercise, additionally, may exert a positive influence on QoL, although these benefits are subjective in nature and measurement can be difficult due to methodological concerns. In practice, clinicians may be somewhat hesitant to recommend lifestyle changes to depressed patients since they may lack the motivation to exercise. This may be hampered further by public media coverage of negative trial findings which can amplify the difficulties in persuading patients with depression to take exercise (Trueland, 2012). However, the magnitude of the known health benefits of exercise for all mean that researchers have proposed this as a "first-line therapy" in all patients (Nahas and Sheikh, 2011) where prescription should be tailored to patients' current level of activity, preferred type and intensity of activity.

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# Treating depression and depression-like behavior with physical activity: an immune perspective

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The increasing burden of major depressive disorder makes the search for an extended understanding of etiology, and for the development of additional treatments highly significant. Biological factors may be useful biomarkers for treatment with physical activity (PA), and neurobiological effects of PA may herald new therapeutic development in the future. This paper provides a thorough and up-to-date review of studies examining the neuroimmunomodulatory effects of PA on the brain in depression and depression-like behaviors. From a neuroimmune perspective, evidence suggests PA does enhance the beneficial and reduce the detrimental effects of the neuroimmune system. PA appears to increase the following factors: interleukin (IL)-10, IL-6 (acutely), macrophage migration inhibitory factor, central nervous system-specific autoreactive CD4+ T cells, M2 microglia, quiescent astrocytes, CX3CL1, and insulin-like growth factor-1. On the other hand, PA appears to reduce detrimental neuroimmune factors such as: Th1/Th2 balance, pro-inflammatory cytokines, C-reactive protein, M1 microglia, and reactive astrocytes. The effect of other mechanisms is unknown, such as: CD4+CD25+ T regulatory cells (T regs), CD200, chemokines, miRNA, M2-type blood-derived macrophages, and tumor necrosis factor (TNF)-α [via receptor 2 (R2)]. The beneficial effects of PA are likely to occur centrally and peripherally (e.g., in visceral fat reduction). The investigation of the neuroimmune effects of PA on depression and depression-like behavior is a rapidly developing and important field.

**Keywords: physical activity, exercise, depression, psychiatry, immune, neurobiology**

The increasing burden of major depressive disorder (MDD; WHO, 2008) makes the search for an extended understanding of etiology, and for the development of additional treatments highly significant. The global "pandemic" of physical inactivity (Lee et al., 2012) – a significant etiological factor for many non-communicable diseases, including depression (Garber et al., 2011; Kohl et al., 2012; Lee et al., 2012) – as well as the growing evidence supporting the clinical utility of physical activity (PA) in many psychiatric disorders, make the biological effects of PA highly relevant (Knochel et al., 2012; Lautenschlager et al., 2012; Rimer et al., 2012). Biological factors may be useful biomarkers for treatment with PA, and neurobiological effects of PA may herald new therapeutic developments in the future.

The neuroimmune system is important in the pathogenesis and pathophysiology of depression-like behaviors (Eyre and Baune, 2012c). Elevations in pro-inflammatory cytokines (PICs), causing neuroinflammation, are well known to be involved in the development of depression-like behaviors – e.g., sickness-like behavior, cognitive dysfunction, and anhedonia – in pre-clinical and clinical populations (Dantzer et al., 2008; McAfoose and Baune, 2009; Miller et al., 2009). The involvement of PICs in the development of depression-like behavior is often referred to as the cytokine model of depression (Dantzer et al., 2008; McAfoose and Baune, 2009; Miller et al., 2009).The neuroinflammatory state is associated with neurotransmitter dysfunction [e.g., reductions in serotonin (5-HT), as well as neurotoxic levels of glutamate (GLU) and tryptophan catabolites], reduced hippocampal (HC) neuroplasticity [e.g., neurogenesis, synaptic plasticity, and long-term potentiation (LTP)], oxidative stress, and glucocorticoid insensitivity (Dantzer et al., 2008; Miller et al., 2009; Eyre and Baune, 2012c; Leonard and Maes, 2012; Moylan et al., 2012).

A variety of novel neuroimmune mechanisms may also be involved in the development of depression-like behaviors (Eyre and Baune, 2012c; Littrell, 2012). Cellular immune factors include various T cells [e.g., CD4+CD25+ T regulatory cells (T regs), CNS-specific autoreactive CD4+ T cells] and macrophages (e.g., M2-type blood-derived macrophages) involved in the model of protective immunosurveillance (Schwartz and Shechter, 2010a,b; Martino et al., 2011; Ron-Harel et al., 2011). These neuroprotective immune cells – found to release neurotrophic factors and anti-inflammatory cytokines (AICs; Schwartz and Shechter, 2010a,b; Martino et al., 2011; Ron-Harel et al., 2011) – may be dysfunctional in the disease state (Schwartz and Shechter, 2010b). Moreover, the function of immunomodulatory proteins such as CX3CL1 (aka fractalkine; Rogers et al., 2011; Corona et al., 2012; Giunti et al., 2012), insulin-like growth factor-1 (IGF-1; Park et al., 2011a), and CD 200 (Lyons et al., 2007; Ojo et al., 2012) may be reduced.

In clinical studies, PA has shown efficacy in the treatment of MDD (Rimer et al., 2012), schizophrenia (SCZ; Knochel et al., 2012), anxiety-based disorders (Asmundson et al., 2013), and in

enhancing cognitive function in disorders of cognitive function (i.e., Alzheimer's disease, AD and mild cognitive impairment, MCI; Foster et al., 2011; Knochel et al., 2012; Lautenschlager et al., 2012). There are many reasons why PA is an attractive therapeutic option in psychiatry. It has a low side-effect profile and can be adapted according to a patient's medical co-morbidities and functional status (Garber et al., 2011; Knochel et al., 2012; Rimer et al., 2012). PA also enhances self-esteem (Salmon, 2001), has less stigmatization than psychotherapy, may reduce the use of pharmacotherapies in MDD (Deslandes et al., 2010) and has a positive effect on cardiometabolic risk factors relevant to many psychiatric diseases (e.g., chronic inflammation, visceral fat mass, glucocorticoid sensitivity, glucose control, and insulin sensitivity; Gleeson et al., 2011; Baune et al., 2012c; Hamer et al., 2012; Knochel et al., 2012; Stuart and Baune, 2012).

Physical activity has beneficial effects on depressive symptomatology in a variety of clinical contexts. It is found to have robust effects on the depressive phenotype found in MDD (Rimer et al., 2012), as well as beneficial effects on the depressive symptomatology involved in the negative symptoms of SCZ (Knochel et al., 2012). PA has also been shown to be effective in treating cognitive dysfunction-related depression (Knochel et al., 2012; i.e., in MCI and AD where a significant proportion of patients with AD suffer from co-morbid depression; Lee and Lyketsos, 2003). The clinical utility of PA in MDD is promising given most patients on antidepressants will not achieve remission following initial treatment (Trivedi et al., 2006), and nearly one-third will not achieve remission even following several treatment steps (Rush et al., 2006a,b). Encouragingly, a recent Cochrane meta-analysis of 28 trials (1101 participants) by Rimer et al. (2012) – comparing exercise with no treatment or control intervention – found a moderate clinical effect in MDD. Studies have found that whilst PA has an initial treatment effect equal to that of antidepressants (Rimer et al., 2012), its effects are slower (Blumenthal et al., 1999) with greater relapse prevention (Babyak et al., 2000). PA interventions have been shown to be efficacious as a stand-alone (Rethorst et al., 2009) and as an augmentation treatment for MDD (Trivedi et al., 2011). Adequate levels of PA are also found to have a role in the prevention of MDD (Pasco et al., 2011b).

Physical activity interventions are found to have a multitude of effects on neuroimmune processes (Eyre and Baune, 2012a). Most notably PA interventions are found to reduce PIC levels in the brain of rodents (Eyre and Baune, 2012a) and in the periphery in clinical studies (Beavers et al., 2010a; Rethorst et al., 2012). The anti-inflammatory effects of PA may be related to acute elevations in neuroprotective interleukin-6 (IL-6; Funk et al., 2011), and resultant downstream changes, e.g., increased IL-1ra and reduced neuronal death in the HC (Funk et al., 2011). Reductions in pro-inflammatory visceral fat mass may also play a role in the anti-inflammatory effect of PA (Gleeson et al., 2011).

The neuroimmune effects of PA were recently outlined in our review (Eyre and Baune, 2012a), however, there have been a large number of studies published in 2012 investigating other neuroimmune-related factors (Moon et al., 2012; Rethorst et al., 2012). Novel factors investigated include macrophage migration inhibitor factor (MIF; Moon et al., 2012), CX3CL1 (Vukovic et al., 2012), and IGF-1 (Duman et al., 2009). Taken together, there is a need for a review outlining and summarizing these recent studies in light of pre-existing literature with the intention of better understanding the neuroimmunological effects of PA. From this literature important questions arise: *Are there PA types which are more effective than others? Are there subpopulations of patients with MDD who would benefit more from PA than antidepressants or psychotherapy? Can the neuroimmune effects of PA inform therapeutic development in the future? Are immune biomarkers potentially useful in measuring a treatment effect for PA in depression?*

This paper provides a thorough and up-to-date review of studies examining the neuroimmunomodulatory effects of PA on the brain in depression and depression-like behaviors.

## METHODS

This review utilized an electronic search of databases such as PubMed, PsychInfo, OvidSP, and Science Direct. An initial search was conducted using the following keywords: (PA OR exercise) AND (immune OR inflammation OR cytokine OR anti-inflammatory OR immune cell OR glia OR neuroplasticity) AND/OR depression. Abstracts were selected based on the year of publication (between 1995 and December 2012), publication in the English language and of peer-reviewed type. They were excluded if they included anecdotal evidence. A total of 16,000 studies were found using these search terms. A total of 1000 articles remained after assessment of abstracts for relevance to the aims of this review. Of these, 770 studies were excluded after review of the full text if they did not examine the effect of the PA or depression on the immune system. A proportion of papers were found via the reference lists of the 1000 full text articles. Finally, 230 articles were utilized in this review.

## CLINICAL EFFICACY OF PHYSICAL ACTIVITY IN DEPRESSION

Evidence supporting the clinical efficacy of PA interventions with depression – and depression co-morbid with other diseases [MCI, coronary heart disease (CHD)] – is growing (Blumenthal et al., 2012a,b; Rimer et al., 2012). In the clinical setting, exercise interventions are defined as "planned, structured, and repetitive bodily movements done to improve or maintain one or more components of physical fitness" (Garber et al., 2011). Exercise types can include aerobic, resistance, neuromotor (involving balance, agility, and co-ordination), and flexibility types (Garber et al., 2011). The following section will outline clinical evidence supporting the use of exercise in depression.

A 2012 re-analysis of available clinical trials by the Cochrane Group (Rimer et al., 2012; 2009 version; Mead et al., 2008) revealed 28 trials (1101 participants) comparing exercise with no treatment or control intervention finding a moderate clinical effect in MDD (standardized mean difference, SMD; −0.67 95% CI −0.90 to −0.43). However, when the meta-analysis was conducted with more strict criteria – i.e., studies with adequate allocation concealment, intention-to-treat analysis, and blinded outcome assessment – there were only four trials (326 participants), the SMD indicated a small clinical effect (SMD −0.31 95% CI −0.63 to 0.01). Moreover, data from the seven trials (373 participants) that provided long-term follow-up also found a small effect for exercise interventions (SMD −0.39, 95% CI −0.69 to −0.09).

In comparison to cognitive behavioral therapy, six trials (152 participants) found no significant difference with exercise.

Further investigating the individual clinical trials analyzed in this field yields interesting information on the clinical effect of exercise regimens. A 16-week randomized controlled trial (RCT) study by Blumenthal et al. (1999) found aerobic exercise and antidepressant (sertraline) treatment were equally effective in reducing depressive symptom severity [as per both Hamilton Depression Rating Scale (HAM-D) and Beck Depression Inventory (BDI)], however, sertaline had a faster initial response (in the first 3 weeks). Shortly after, a paper by Babyak et al. (2000) was published on the same study participants showing – at 6 months follow-up – patients assigned to the exercise program were less likely to relapse (no longer diagnostic for MDD or HAM-D $< 8$) than patients assigned to antidepressant treatment. Self-initiated exercise after the study intervention was associated with a reduced probability of depression at the end of the follow-up period (OR $= 0.49$).

Treatment of depression in older people is often hampered by poor recognition and increased prevalence of medication side-effects, polypharmacy, and poor adherence to treatment; therefore, exercise is increasingly being evaluated as a possible treatment. A recent meta-analysis (Bridle et al., 2012) of seven trials of subjects $\geq$60 years found exercise was associated with significantly lower depression severity (SMD $-0.34$; 95% CI $-0.52$ to $-0.17$). These findings were irrespective of whether participant eligibility was determined by clinical diagnosis or symptom checklist. An RCT in elderly patients (>60 years) with MDD – non-responders to escitalopram – found a 10-week Tai Chi Chih (TCC) exercise intervention augmented antidepressant treatment (Lavretsky et al., 2011). TCC exercise was chosen given it can be readily implemented among older adults with physical limitations (due to chronic medical illnesses or poor balance) and its added stress reduction and mindful cognitive properties. Multiple studies have shown regular, moderate PA can have a positive influence on depressive symptomatology in subjects with AD (Knochel et al., 2012), however Mahendra and Arkin (2003) found this beneficial effect was only significant after >1 year of PA. Deslandes et al. (2010) reported patients with co-morbid MCI and MDD could significantly reduce their antidepressant dose when they underwent a PA program.

Exercise is shown to have some modest beneficial effects on certain aspects of neurocognitive disturbance in depression. An RCT study with patients who met MDD criteria found exercise (both supervised and home-based) performed better with exercise than sertraline on tests of executive functioning, but not on tests of verbal and working memory (Hoffman et al., 2008). A recent meta-analysis (Smith et al., 2010) examining the effects of aerobic exercise on neurocognitive performance found 29 studies (2049 participants) showing modest improvements in attention and processing speed ($g = 0.158$; 95% CI, 0.055–0.260), executive function ($g = 0.123$; 95% CI, 0.021–0.225), and memory ($g = 0.128$; 95% CI, 0.015–0.241).

Depression is a common co-morbidity with a variety of cardiac conditions. Depression affects as many as 40% of patients with heart failure (HF), with up to 75% of patients reporting elevated depressive symptoms (Blumenthal et al., 2012a). For CHD, MDD affects 15–20% of cardiac patients and an additional 20% report elevated depressive symptoms (Blumenthal et al., 2012b). Blumenthal et al. (2012a) recently published an RCT of 2322 stable HF patients who underwent an aerobic exercise program (supervised for 1–3 months followed by home exercise for 9 months) or education and usual guideline-based HF care. Compared with usual care, aerobic exercise resulted in lower mean BDI-II scores at 3 and 12 months (differences of $-0.76$ and $-0.68$, respectively). Another study by Blumenthal et al. (2012b) assessed efficacy of 4 months of aerobic exercise and antidepressant treatments (sertraline) in reducing depressive symptoms and improving cardiovascular biomarkers in depressed patients with CHD. At 4 months, exercise and sertraline were equally as effective at reducing depressive symptoms (HRSD) vs. placebo. Exercise tended to result in greater reductions in heart rate variability vs. sertraline.

When considering the anti-depressive effects of exercise – in addition to biological effects – we must consider psychosocial aspects. Studies have shown exercise regimens have a distraction effect (from negative thoughts and ruminations), provide a sense of mastery via the learning of new skills (Lepore, 1997), and hence enhance self-efficacy (Craft, 2005) and self-esteem (Salmon, 2001). A study by Craft (2005) found that those who experienced an increase in mood following exercise showed higher self-efficacy levels at 3 and 9 weeks post-exercise. Self-esteem is considered to be one of the strongest predictors of overall (Diener, 1984), subjective well-being and low self-esteem is considered to be closely related with mental illness (Fox, 2000). The abovementioned beneficial psychological effects may lead to the stress reducing and stress-resilience enhancing effects of exercise (Salmon, 2001). Additionally, exercise regimens in a group setting may have a beneficial effect via training social skill deficits (Rimer et al., 2012).Therefore, considering the immunomodulatory effects of social support, i.e., social isolation stress is repeatedly shown to enhance inflammation in clinical and pre-clinical models (Hafner et al., 2011), the social interaction effects of PA interventions must be considered as a confounder.

Whilst the vast majority of research using PA in psychiatry is positive and encouraging, it is important to also consider potential pre-cautions during PA interventions. Some studies report no effect for PA in depression (Rimer et al., 2012). This may be explained by inappropriate intensity of PA, or a too short duration of PA as a treatment (Rimer et al., 2012). In order to enhance the potential for antidepressant effects, multiple authors now recommend exercise of moderate-intensity and of at least 8 weeks duration (Mead et al., 2008; Trivedi et al., 2011; Rimer et al., 2012). PA regimens must be tailored according to the individual patient's functional status and other co-morbidities. Failing to do so can lead to further morbidity and/or mortality. In patients with social phobia-related symptoms, the approach to PA interventions should be tailored appropriately.

## NEUROIMMUNOLOGICAL EFFECTS OF PHYSICAL ACTIVITY IN DEPRESSION

When considering the neuroimmunological effects of PA in depression, it is important to first outline the current understanding on neuroimmunological mechanisms of the depression-like disease states. Therefore, the following section will outline these neuroimmunological mechanisms in detail; following, the neuroimmunological effects of PA will be examined.

## NEUROIMMUNOLOGICAL CHANGES IN DEPRESSION

The neuroimmunological changes found in depression involve humoral and cellular factors from both the innate and adaptive immune systems (Eyre and Baune, 2012c; Littrell, 2012). Humoral factors include PICs, AICs, C-reactive protein (CRP) as well as other immunomodulatory factors like CX3CL1, CD200, and IGF-1 (Eyre and Baune, 2012b). Cellular factors include resident glia (e.g., astrocytes, microglia) and centrally migrating immune cells involved in protective immunosurveillance (e.g., CD4+ T cells and macrophages; Eyre and Baune, 2012b).

### *Neuroinflammation and depression: a well recognized relationship*

The neuroinflammatory state is well known to be associated with the depressive phenotype (Dantzer et al., 2008; Dowlati et al., 2010). For example, a recent meta-analysis found a significant correlation between tumor necrosis factor (TNF-α), IL-6, and CRP with depression in humans (Dowlati et al., 2010). Neuroinflammation is characterized by elevations in PICs and reductions in AICs and can arise within the CNS itself, or peripheral inflammatory signals can be transferred into the CNS (Dantzer et al., 2008; see Quan and Banks, 2007; for a review of peripheral-CNS pathways, including: the neural route, circumventricular organs, BBB transport of cytokines, and secretions from BBB cells). The neuroinflammatory state is known to cause neurovegetative or sickness-like symptoms, depression- and anxiety-like behaviors, as well as cognitive dysfunction and symptoms of Chronic Fatigue Syndrome (Dantzer et al., 2008; McAfoose and Baune, 2009; Dowlati et al., 2010; Miller, 2010; Yirmiya and Goshen, 2011; Bansal et al., 2012), and the causation of these phenotypic states by PICs has been modeled in both rodent and human models and extensively reviewed (Dantzer et al., 2008; Miller, 2010).

Neuroinflammation-based models of depression have shown PICs to impact on other major neurobiological systems involved in depression. Neuroinflammation affects the neurotransmitter systems by activation if the tryphophan degrading enzyme, indoleamine 2,3 dioxygenase (IDO), altering metabolism of tryptophan into neurotoxic metabolites (3-hydroxykyurenin, 3-HK and quinolinic acid, QA) and depleting its availability for serotonin (5-HT) synthesis (Miller, 2010; Dantzer et al., 2011; Moylan et al., 2012). Inflammation also stimulates the reuptake of monoamines from the synapse by increasing the activity and the density of 5-HT, noradrenaline, and dopamine transporters (Moron et al., 2003; Nakajima et al., 2004; Zhu et al., 2006). Evidence suggests these immune mechanisms adversely affected glutamatergic neurotransmission causing GLU to rise to neurotoxic levels (McNally et al., 2008; Hashimoto, 2009; Popoli et al., 2012). In the neuroinflammatory state PICs may disrupt the capacity of the glucocorticoid receptor to translocate to the nucleus where it normally acts to suppress the activity of pro-inflammatory transcription factors such as nuclear factor-kappa B (NF-κB) – this is termed glucocorticoid resistance (Dantzer et al., 2008; Miller, 2010; Muller et al., 2011). High levels of PICs impair processes of neuroplasticity in the HC, such as neurogenesis, LTP, neurotrophin production (e.g., brain-derived neurotrophic factor, BDNF), and synaptic plasticity (Miller, 2010; Eyre and Baune, 2012c). In the context of reduced neuroplasticity, elevations in neurotoxic oxidative stress products and markers of apoptosis are found in the HC (Moylan et al., 2012). An in-depth assessment on the effects of inflammation on these systems is outside the scope of this review and have been outlined recently (see Dantzer et al., 2008, 2011; McAfoose and Baune, 2009; Muller et al., 2011; Moylan et al., 2012).

### *Rationale for examining immune mechanisms in addition to inflammation*

Whilst the cytokine and neuroinflammatory models of depression have been helpful in understanding the neurobiology behind the depressive phenotype, there are a number of clinical and biological reasons for investigating neuroimmune mechanisms in addition to inflammation. These factors include:

- A recent meta-analysis by Hannestad et al. (2011) found results arguing against the notion that resolution of a depressive episode is associated with normalization of levels of circulating PICs. This analysis of 22 studies (603 subjects) found – when all antidepressants were grouped – these medications reduced levels if IL-1β with a marginal effect on IL-6 (using less stringent fixed-effects models); there was no effect on TNF-α. However, a sub-group analysis of selective serotonin regulate inhibitors (SSRI) medication found a reduction in IL-6 and TNF-α. Other antidepressants did not reduce PIC levels.
- Recent evidence has emerged to suggest no effect or even an antagonistic effect for anti-inflammatory medications in depression. A large-scale prospective cohort study of treatment-resistant depression, the "sequenced treatment alternatives to relieve depression" (STAR∗D), found an antagonistic effect for anti-inflammatory compounds on ADs (Warner-Schmidt et al., 2011). Patients reporting concomitant non-steroidal anti-inflammatory drug (NSAID) or other analgesic treatment showed a reduced therapeutic response to citalopram, hence, the authors suggest concomitant use of NSAIDs may be an important reason for high SSRI treatment resistance rates (Warner-Schmidt et al., 2011). A recent re-analysis reached a similar conclusion, with more modest effects persisting after adjustment for potential confounding variables (Gallagher et al., 2012). Another recently published study shows no difference between infliximab, a TNF-α antagonist, and placebo in a recent 12-week double-blind, placebo-controlled RCT for treatment-resistant depression (Raison et al., 2012). There was a significant effect for infliximab in individuals who had a high baseline hs-CRP (>5 mg/L) and a significant effect for placebo-treated patients at a baseline hs-CRP of <5-mg/L. Schwartz and Shechter hypothesize anti-inflammatory drug compounds may block the production of brain-derived cytokines and chemokines which promote the migration of neuroprotective immune cells involved in protective immunosurveillance toward the CNS (Schwartz and Shechter, 2010b; Warner-Schmidt et al., 2011). Importantly, however, the use of NSAIDs may be most useful when used in the correct stage of neuroinflammatory diseases, i.e., administered early in the neuroinflammatory disease course when transmigratory immune cells have not come into effect (Schwartz and Shechter, 2010b).
- Evidence is emerging to suggest a neuroprotective and physiological role for "PICs." TNF-α and IL-6 have been shown to play an integral roles in processes of memory and learning in

both human and rodent studies, as well as having a physiological role in HC neuroplasticity (Carlson et al., 1999; Eyre and Baune, 2012c). The *TNF*-α gene (*rs1800629*) is correlated with enhanced cognitive processing speed in a healthy human population (Baune et al., 2008a). The *IL-6* gene (*rs1800795*) has been correlated with increased to HC volume in a healthy human population (Baune et al., 2012a). There are other studies outlining a neuroprotective effect of PICs in the brain (see below).

- From a clinical disease course perspective, there are other mechanisms in depression – in addition to inflammation – which may have a role in explaining the absence of correlation between the increase in neuroinflammation in aging and rates of depression. Since aging itself is related to higher levels of systemic inflammation and neuroinflammation (Hein and O'Banion, 2012), this should lead to higher rates of depression in old age, however, rates are highest in those aged 25–45 years, not in old age (Kessler et al., 2005). Other neuroimmune factors which may explain this scenario will be outlined below.

## DYSFUNCTION OF NEUROPROTECTIVE IMMUNE FACTORS IN DEPRESSION

When considering neuroimmunological factors in depression, historically the focus has mainly been on high levels of PICs and their detrimental effects on the brain. However, research is beginning to suggest a significant role for neuroprotective neuroimmune factors in depression and other neurobiological disorders (e.g., multiple sclerosis and AD; Martino et al., 2011; Kokaia et al., 2012). When considering these neuroprotective factors in depression, their loss of function may exacerbate the depression-like behaviors (Schwartz and Shechter, 2010b). The following section will outline evidence suggesting a possible beneficial role for a variety of neuroimmune factors.

### *Neuroprotective and physiological effects of cytokines*

There are a number of cytokines are found to have neuroprotective and physiological effects.

Interleukin-6 has been found to have neuroprotective effects via gp130 signaling and related pathways [i.e., Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT), Mitogen-activated Protein Kinase (MAPK)/cAMP Response Element-binding (CREB), Ras-MAPK, Phosphatidylinositol 3-kinases (PI3K); Baune et al., 2012a]. These mechanisms affect the production of neurotrophic factors, cellular survival, and apoptosis (Baune et al., 2012a). A recent imaging genetics study investigated the association between the *IL-6* gene and brain morphology in a large cohort of healthy adult participants in a whole-brain analysis approach (Baune et al., 2012a). Carriers of the G-allele of the *IL-6* genetic variant *rs1800795 (-174 C/G)* showed a significant association with larger HC volumes on the right side in healthy subjects. This genotype effect was remarkably specific to the HC, with no other structure surviving statistical threshold for the entire brain. The findings are suggestive of a neuroprotective role of the *IL-6* gene [*rs1800795 (-174 C/G)*] on HC morphology. Supporting a role of IL-6 in neuroproliferation is an *in vivo* study showing that IL-6 knockout mice have reduced proliferating NSCs specifically in the HC, hence underlining the importance of IL-6 in cell proliferation and cell survival (Bowen et al., 2011). However, other similar studies have shown no effect or a negative effect for IL-6 in neurogenesis processes (Eyre and Baune, 2012c). The difference between the pro- and anti-neurogenic effects of IL-6 may reflect differences in amounts and conditions used experimentally (Eyre and Baune, 2012c).

Tumor necrosis factor-α is thought to exert its protective and restorative effects primarily via TNFR2 (p75; primarily neuroprotective and neuroregenerative pathway) and related signaling pathways [i.e., IκB kinase (IKK)/Nuclear Factor κB (NF-kB), Transforming Growth factor β-activated Kinase 1 (TAK-1), PI3K-PKB-Akt, c-Jun N-terminal kinases (JNK), and IL-6), as opposed to the TNFR1 (p55; primarily neurodegenerative; Eyre and Baune, 2012a; Santello and Volterra, 2012). Importantly, whether the outcome of TNF-α signaling is protective or damaging may depend upon duration of NF-κB activation (Santello and Volterra, 2012). TNF-α has been found to exert beneficial effects in depression-related processes, e.g., cognitive function and HC neurogenesis (Eyre and Baune, 2012a; Santello and Volterra, 2012). During relatively health aging processes, it has been shown that the *TNF*-α gene (*rs1800629*) has protective effects on cognitive processing speed (Baune et al., 2008a) and has been associated with cognitive processes (e.g., response inhibition, error processing, attentional processes, and mental rotation) in young health individuals (Eyre and Baune, 2012a). In behavioral studies, TNF-α deficient mice exhibit impaired HC-dependent memory function in the Morris Water Maze suggesting that during early stages of brain development basal levels of TNF is required for memory and learning (Baune et al., 2008b).

Interleukin-4 has been found to have a beneficial role in depression-like behaviors and a neuroprotective effect. The release of IL-4 from CNS-specific autoreactive CD4+ T cells involved in protective immunosurveillance – in response to increased neurotoxicity (Ron-Harel et al., 2011) – binds to IL-4 receptor on the cytotoxic microglia (Kipnis et al., 2008) causing downregulation of PIC production, induction of BDNF and IGF-1, and an elevation in neurogenesis (Butovsky et al., 2005, 2006b; Lyons et al., 2009; Martino et al., 2011). Microglia under quiescent conditions, after exposure to IL-4 or low levels of IFN-γ (Butovsky et al., 2006b), have been shown to support neurogenesis and NSC differentiation and migration *in vitro* (Aarum et al., 2003; Butovsky et al., 2006b; Walton et al., 2006). IL-4 is also shown to promote the creation of neuroprotective M2-type microglial phenotype (Godbout et al., 2012). A recent study found central IL-4 administration increased microglial-specific M2a-type genes including *Arginase*, *IL-1R*α, and *BDNF* (Godbout et al., 2012). Microglia activated by IL-4 remain committed to their protective phenotype (M2-type) even when exposed to a threatening environment in the form of LPS, and, exposure of microglia, pre-activated to a cytotoxic phenotype, to IL-4 induces a phenotype switch toward neuroprotection (Butovsky et al., 2005; Schwartz et al., 2006). A study rodent by Derecki et al. (2010) shows T cell-derived IL-4 to have beneficial effects on the regulation of cognitive function in rodents via meningeal myeloid cell phenotypes producing BDNF. IL-4 knockout mice show greater sickness behavior (measured by exploratory behavior) than wildtype mice exposed to LPS (Lyons et al., 2009). Interestingly, Kim et al. (2011) proposes T-bet deficient mice may

have a neuroprotective effect by creating a predominance of Th2-derived IL-4, which may in turn stimulate meningeal myeloid cell BDNF production. T-bet is a Th1-specific T-box transcription factor which regulates CD4+ Th1 development by inducing endogenous Th1 cytokines, while simultaneously repressing Th2 development (Wong et al., 2008).

A role for IL-10 in neuroprotection and the prevention of depression-like behavior has been suggested. Central administration of IL-10 prevents the emergence of behavioral signs of depression in an LPS model of sickness behavior (Bluthe et al., 1999). IL-10 over-expression mice display less anxiety-like behaviors, while IL-10 knock-out rodents display greater anxiety and depression-like behavior (forced-swim test) with these effects more pronounced in females (Mesquita et al., 2008). In human studies, IL-10 is found to be reduced in the depressed state (Himmerich et al., 2010). Further papers examining the neuroprotective effects of IL-10 can be found in Raison and Miller (2011).

#### *Immunomodulatory factors*

Insulin-like growth factor-1 is a major neurotrophic factor involved in neuroplastic functions such as neurogenesis and is critical in normal memory and LTP functions (Trejo et al., 2007). Recent evidence suggests IGF-1 also has added immunomodulatory effects (Park et al., 2011a,b). In an LPS model of depression, central administration of IGF-1 is shown to prevent LPS-induced sickness- and depression-like behavior (Park et al., 2011a,b) in association with an induction of BDNF and a reduction of TNF-α, IL-1β, and iNOS in the pre-frontal cortex (PFC; Park et al., 2011b). Given the levels of IGF-1 have been found to be low in rodent models of depression (Mitschelen et al., 2011), the absence of this anti-inflammatory factor may exacerbate the neuroinflammatory and anti-neuroplastic state in depression.

CX3CL1 is a chemokine expressed by healthy neurons which has its receptor, CX3CR1, in membrane bound form or as soluble ligand (Rogers et al., 2011). It has an important role in inhibiting the activation of microglia (Rogers et al., 2011). A recent study with CX3CR1 knock-out mice and the LPS model of sickness behavior found a deficiency in the action of CX3CL1 resulted in protracted microglial activation, as measured by IL-1β and CD14 (Corona et al., 2010). These mice have extended LPS-induced depression-like behavior in association with the activated microglial phenotype described (Corona et al., 2010). In another study with CX3CR1 knock-out mice, a lack of the CX3CR1 receptor resulted in contextual fear conditioning (associative memory) and Morris Water Maze deficits (spatial memory), as well as impairment in LTP (Rogers et al., 2011). Disruption of the CX3CL1/CX3CR1-pathway in young rodents decreases both survival and proliferation of HC neural progenitor cells (Bachstetter et al., 2011).

CD200 is a membrane glycoprotein which has been identified as an immune-suppressive molecule (Cox et al., 2012). It is expressed in neurons and oligodendrocytes, but not on microglia (Cox et al., 2012). The receptor for CD200, CD200R, is also a membrane glycoprotein and is primarily restricted to cells of the myeloid lineage, hence being found on microglia, but not neurons or astrocytes (Cox et al., 2012). The interaction between CD200 and its receptor play a significant role in maintaining microglia in a quiescent state, therefore, a decrease in CD200 expression is associated with evidence of microglia activation (Cox et al., 2012). A rodent study by Frank et al. (2007) shows an inescapable shock model of stress over 24 h resulted in a downregulation of HC CD200 in association with enhanced LPS-induced cytokine production in HC microglia. This suggests stress can activate microglia via downregulation of CD200, enhancing the PIC production of microglia (Frank et al., 2007). A study by Cox et al. (2012) found a CD200 fusion protein (CD200Fc), activator of CD200R, attenuated age-related microglial immunoreactivity in the HC (indicated by MHCII, CD40, and iNOS). CD200Fc also attenuated LPS-induced microglial activation (indicated by elevated MHCII, CD40, CD11b, and CD68) and LTP deficits (Cox et al., 2012). Using CD200 knock-out mice and LPS-induced sickness behavior, Costello et al. (2011) found the neuroinflammatory changes resulting from CD200 deficiency have a negative impact on LTP in the CA1 region of the dentate gyrus. Interestingly, a study by Lyons et al. (2009) has shown IL-4 as a key inducer of CD200 expression.

#### *Dysfunction of protective immunosurveillance*

Emerging data suggests a role for CNS-specific autoreactive CD4+ T cells, blood-derived macrophages (in the form of M2 alternatively activated macrophages) in physiological, protective immunosurveillance functions of the brain (Derecki et al., 2010, 2011; Martino et al., 2011; Ron-Harel et al., 2011). Evidence suggests these cell types may have established a physiological connection between the immune system and the brain, and have assisted in explaining processes of HC-dependent neurogenesis and cognitive dysfunction (Kipnis et al., 2004b; Butovsky et al., 2006b, 2007; Ziv et al., 2006; Brynskikh et al., 2008; Derecki et al., 2010, 2011), anxiety- and depression-like behavior (Cohen et al., 2006; Lewitus et al., 2008; Cardon et al., 2010) due to an insufficient immune response (Derecki et al., 2010, 2011; Schwartz and Shechter, 2010a,b; Ron-Harel et al., 2011). The role of these cells in neuroprotection and higher neurocognitive functions has been reviewed in detail elsewhere (Martino et al., 2011; Yirmiya and Goshen, 2011); however, a brief summary will be given, below.

Immune cells involved in protective immunosurveillance can populate meningeal areas of the choroid plexus and the cerebrospinal fluid, hence gaining access to the healthy brain without entering the parenchyma (Ransohoff et al., 2003; Derecki et al., 2010, 2011; Schwartz and Shechter, 2010a). CNS-specific autoreactive CD4+ T cells are suggested to react to three signals, (1) T-cell receptor (TCR; Ron-Harel et al., 2011), (2) co-stimulatory signals (CD28/CD80,86; Jenkins and Johnson, 1993), and (3) PICs and reactive oxygen species (ROS; Curtsinger et al., 1999; Tse et al., 2007; Ron-Harel et al., 2011). The T cells in question, activated in response to increased neurotoxicity (Ron-Harel et al., 2011), are thought to secrete increased levels of IL-4 (Ron-Harel et al., 2011), where IL-4 penetrates the brain parenchyma and binds to IL-4R on the cytotoxic microglia (Kipnis et al., 2008). Exposure of cytotoxic microglia to IL-4 causes downregulation of PIC secretion, induction of BDNF and IGF-1 secretion, and an elevation in neurogenesis (Butovsky et al., 2005, 2006b; Martino et al., 2011). All of these signals support the restoration of brain homeostasis (Ron-Harel et al., 2011). Furthermore, the T cells boost infiltration

of neuroprotective blood-borne monocytes upon need (Shechter et al., 2009). A recent commentary by Ron-Harel et al. (2011) suggests any destabilization in brain homeostasis that cannot be locally contained by microglia and/or astrocytes will increase T cell recruitment as well as subsequent IL-4 release and recruitment of blood-derived macrophages.

According to the "protective immunosurveillance" model, increased susceptibility to mental illness may result from a deficiency in circulating T cells and the IL-4 they can produce, as the IL-4 mediates processes which are able to counteract neuroinflammation and restore brain homeostasis (Ron-Harel et al., 2011). Indeed, the brains of immune-deficient mice show accumulation of toxicity (i.e., increased glyoxalase-1, a compensatory mechanism against free radical and carbonyl levels; Ron-Harel et al., 2011).

According to the protective immunosurveillance model, activation of CNS-specific autoreactive CD4+ T cells (mentioned above) support the infiltration of neuroprotective, alternatively activated M2 macrophages to the sub-arachnoid meningeal spaces and choroid plexus, via IL-4 and IFN-γ secretion (Derecki et al., 2010, 2011; Ron-Harel et al., 2011). These infiltrating macrophages, together with the microglia they regulate, remove dead cells and cellular debris, buffer toxic compounds (such as GLU and ROS), and produce growth factors (i.e., BDNF and IGF-1), while down-regulating inflammation-associated compounds such as IL-1β, TNF-α, iNOS, and COX-2 (Hauben et al., 2000; Butovsky et al., 2005, 2006a,b, 2007; Shaked et al., 2005; Beers et al., 2008; Chiu et al., 2008; Rolls et al., 2008; Shimizu et al., 2008; Koronyo-Hamaoui et al., 2009; Shechter et al., 2009; Derecki et al., 2010, 2011; Prinz et al., 2011). These neurobiological functions are thought to contribute to blood-derived macrophages support of learning and memory (as determined via the Morris Water Maze and Barnes Maze; Derecki et al., 2010, 2011). Importantly, intravenous injection of M2 cells into immune-deficient mice can circumvent the need for CNS-specific autoreactive CD4+ T cells (Derecki et al., 2011). For a review of the role of blood-derived macrophages see recent papers (Derecki et al., 2010; Martino et al., 2011; Yirmiya and Goshen, 2011).

The type of macrophage – classical (M1), alternatively activated (M2), and deactivated types – determines the role in sickness behavior (for thorough review see Moon et al., 2011). Classical macrophages produce PICs and, hence, induce sickness behaviors (Dantzer et al., 2008; Moon et al., 2011). M2 macrophages which reduce PIC production, as outlined above, are associated with a reduction in sickness behavior (Derecki et al., 2010, 2011; Sherry et al., 2010). Deactivated macrophages which inhibit PIC production via IL-10 secretion are also thought to have beneficial effects of sickness behaviors, however, this finding has not been replicated (Moon et al., 2011).

It is important to mention a recent critique of the protective immunosurveillance concept recently produced by Rook et al. (2011). One important issue raised is that the phenotype of the neuroprotective, CNS-specific autoreactive CD4+ T cells is poorly understood (Rook et al., 2011). The authors suggest immune cells involved with the function of protective autoimmunity is likely from a regulatory cell – not always CD25+ – given the involvement of IL-4 and IL-10. Suggestions for potential cell types include Th3, Tr1, Th2, IL-10$^{+}$TH1, CD8+ reg cells, regulatory Foxp3+ NKT, IL-10$^{+}$CD56$^{bright}$NK, or various other IL-10-secreting cell types (Fujio et al., 2010; Rook et al., 2011). Another important consideration raised is the effect of T cell produced IL-4 on T reg differentiation. T cell differentiation into the T reg cell type can be enhanced or opposed by IL-4 depending on the context (Chapoval et al., 2010; Rook et al., 2011). Further, one study shows IL-4 increased certain chemokines (CCL1, CCL17, and CCL22) in an experimental autoimmune encephalitis (EAE) model capable of recruiting T regs (Butti et al., 2008). The above mentioned issues are relevant to the neuroimmune model of depression considering the dynamic relationship between T regs and effector T cells.

### *Glial cells*

The role of the immunocompetent glia, astrocytes, and microglia, in depression is complex and poorly understood (Beumer et al., 2012); importantly, however, there is a developing literature supporting a neuroprotective effect of these cells under certain conditions (Schwarz and Bilbo, 2011, 2012; Ekdahl, 2012). The follow section will summarize most recent evidence available in this field.

### *Microglia*

The function of microglia is dynamic even in the resting state whereby they continually survey their microenvironments by extending and contracting processes into nearly synapses (Bilbo et al., 2012). Microglia are the resident macrophages of the CNS and are recognized as the primary component of the neuroimmune system (Ekdahl, 2012). Once activated – by chronic stress conditions, or immune challenge with LPS or PICs – microglia are capable of producing PICs and neurotoxic mediators such as nitric oxide, PGE2, and superoxide anions (Liu et al., 2011; Bilbo et al., 2012; Ekdahl, 2012). A recent study by Walker and colleagues has shown a role for microglia in mediating the effects of stress on PFC neuronal function and PFC-regulated behavior (Hinwood et al., 2012). This study found restraint stress conditions caused a decline in working memory performance associated with increased microglial activity (measured by a 25% increase in Iba-1 labeling, ΔFosB, and a hyper-ramified state) in the medial PFC and no association was found with increased antigen presentation (MHCII) or apoptosis (caspase-3; Walker et al., 2011).

Given the pre-existing association with the inflammatory hypothesis of depression much research centers on reducing the PIC production of microglia (Liu et al., 2011). Recent evidence suggests a neuroprotective function of microglia under certain circumstances (Yirmiya and Goshen, 2011; Ekdahl, 2012). For example, microglia under quiescent conditions, after exposure to IL-4 or low levels of IFN-γ (Butovsky et al., 2006b), have been shown to support neurogenesis and NSC differentiation and migration *in vitro* (Aarum et al., 2003; Butovsky et al., 2006b; Walton et al., 2006). Microglia activated by IL-4 remain committed to their protective phenotype even when exposed to a threatening environment in the form of LPS, and, exposure of microglia pre-activated to a cytotoxic phenotype to IL-4 induces a phenotype switch toward neuroprotection (Butovsky et al., 2005; Schwartz et al., 2006). Exposure of rats to environmental enrichment (EE) increases neurogenesis alongside increased HC microglia proliferation (microglia assumed a neuroprotective phenotype expressing

MHC II and IGF-1; Ziv et al., 2006). As mentioned previously, the pro-neurogenic effects of microglia may be related to their interactions with CNS-specific autoreactive CD4+ T cells, this was further confirmed by a study showing transgenic mice with an excess of these T cells – and associated increases in neurogenesis – showed attenuated neurogenesis by chronic treatment with the microglial inhibitor, minocycline (Ziv et al., 2006). Furthermore, a rodent model of amyotrophic lateral sclerosis (ALS) illustrates the interaction between T cells and microglia whereby Th1 cytokines promote M1 microglia and Th2 or Treg cytokines promote M2 microglia (Chiu et al., 2008). Microglia were also shown to support neurogenesis in adrenalectomized rodents via TGF-β (Battista et al., 2006; Mathieu et al., 2010). Opposing the above neuroprotective findings is a rodent study demonstrating that PA-induced neurogenesis was not associated with microglial proliferation or activation, and no indication of T-cell-microglial interactions (i.e., no MHC II expression or T cells in the HC; Olah et al., 2009).

In summary, microglial function is closely intertwined with the immune system and neurogenesis (Ekdahl, 2012), with the cross-talk between these systems requiring further investigation. For instance, a recent review by Ekdahl (2012) suggests microglial activation patterns may by region-specific. Moreover, there appears to be a primarily beneficial interaction between microglia and new neurons in the intact brain, however, the cross-talk is complex and probably double-edged in pathological conditions, especially following long-term microglial activation (Ekdahl, 2012).

#### *Astrocytes*

Astrocytes are physically and functionally appositioned with most synapses, known as the "tripartite synapse" (Araque et al., 1999). They possess immune-like properties whereby they have an ability to respond to inflammatory cytokines (particularly IL-1β), to secrete PICs (i.e., TNF-α and IL-6) and to phagocytose cellular processes and debris (Yirmiya and Goshen, 2011). These cells play an important role in neural and synaptic functioning. For example, a rodent study by Bracchi-Ricard et al. (2008) shows female mice where the transcription factor NF-κB was inhibited specifically in astrocytes displayed deficits in learning, memory, and LTP. These cells were also found to mediate homeostatic synaptic scaling following prolonged inhibition of neuronal activity via TNF-α secretion, a known synaptic strength enhancer (Stellwagen and Malenka, 2006; Kaneko et al., 2008). The role of astrocytic IL-1 signaling in memory functioning and LTP was recently demonstrated by Ben Menachem-Zidon et al. (2011). In this study neural precursor cells (NPCs) derived from either WT or IL-1rKO neonatal mice were labeled with BrdU and transplanted into the HC of either IL-1rKO or WT adult host mice. Transplanted NPCs showed long-term survival and differentiated into astrocytes (expressing GFAP and S100β), but did not differentiate into neurons. Several weeks post-transplantation, IL-1rKO mice transplanted with IL-1rKO cells, or sham operated, displayed severe memory disturbances and a marked impairment in LTP. However, IL-1rKO mice transplanted with WT NPCs (expressing IL-1R) displayed complete rescue of the impaired memory functioning, as well as partial restoration of LTP. IL-4 is also found to be important in astrocyte functioning with the secretion of BDNF by *in vitro* astrocytes being markedly enhanced by this cytokine (Martino et al., 2011). Furthermore – and in fitting with the abovementioned model of protective immunosurveillance by Schwartz et al. – astrocytes also acquire a neuroprotective phenotype following their co-culture with T cells (Garg et al., 2008).

There is a paucity of evidence correlating the role of the abovementioned glial cells in models and tests of depression-like behavior. This is an important area for future research as these cells appear to be involved in depression-related pathophysiological processes.

#### *Additional cellular immune factors*

The role of T regs in depression is uncertain, and may be both positive and negative in depression pathophysiology depending on the surrounding environment (Cohen et al., 2006; Himmerich et al., 2010). In relation to the positive effects of T regs, some authors propose these cells may function to inhibit inappropriate or excessive immune responses, i.e., PIC production (Dantzer et al., 2008; Miller, 2010). Some human studies have found reduced IL-10 and TGF-β have been found in depressed patients, and are thought to be consistent with reduced T reg expression and/or function (Myint et al., 2005; Sutcigil et al., 2007; Dhabhar et al., 2009; Musil et al., 2011). One study found decreased T regs, alongside intracellular Foxp3, in association with IL-10 and TGF-β in depressed patients vs. controls (Li et al., 2010). A second study found 6 weeks of AD treatment led to increased T reg ($CD4+CD25^{hi}$) percentage in association with decreased IL-1β (Himmerich et al., 2010). A recent rodent study shows T reg cell depleted mice undergoing chronic immobilization stress displayed markedly increased anxiety in the Elevated Plus Maze and increased depression-like behavior in the Forced-Swim Test (Kim et al., 2012). These finds were found in correlation with elevated serum cytokines (i.e., IL-6, TNF-α, IL-2, IFN-γ, and IL-4) and reduced levels of HC 5-HT. In addition, a rodent model of cholestatic liver disease due to bile duct ligation found T regs suppress sickness-like behavior alongside inhibiting monocyte and hepatic IL-6 production, and subsequent signaling via circulating IL-6 acting (via p-STAT3 at the level of the cerebral endothelium; Nguyen et al., 2012). However, T regs have also been found to inhibit the beneficial effects of CNS-specific autoreactive CD4+ T cells on mitigating stress-induced anxiety-like behaviors in rodents (Cohen et al., 2006). This suggests T regs may inhibit the neuroprotective functions of these autoreactive T cells, a counterproductive effect. Interestingly, other studies with an optic nerve injury model have shown both Treg-free CD4+ T cells and T regs, respectively, can exhibit neuroprotective functions via preventing neuronal cell loss (Kipnis et al., 2004a). T regs exhibit significant plasticity and can lose regulatory activity, expressing effector cell function under certain circumstances (Zhou et al., 2009). Therefore, the balance of these two cells types may play a role in neuroprotective functions. Interestingly, T regs constitutively express CD25, a high affinity IL-2 receptor. The expression of CD25 is thought to be one of the ways by which T regs suppress proliferation of T effector cells, that is, by acting as a sink for IL-2 which is needed for T effector cell proliferation (Walsh and Kipnis, 2011). Interestingly, IL-2 is known to increase the suppressive abilities of T regs (Kohm et al., 2006), hence, the reduction of IL-2 which is seen in some studies of depression may

reduce the anti-inflammatory effects of T regs (Anisman et al., 1999; Blume et al., 2011). A recent review paper summarizes literature suggesting T reg phenotypes are flexible depending on background chemokine and cytokine levels (Rook et al., 2011). Flexibility of phenotype means these cells can change from anti- to pro-inflammatory functions (Rook et al., 2011); indeed, authors remark that T-cell phenotype may change from the start to the end of studies (Rook et al., 2011). Furthermore, gut microbiota may affect the immunosuppressive function of T regs as well as their effects on higher neurocognitive behaviors of the brain (Rook et al., 2011). Clearly, the effect of T regs in depression requires further research.

#### *Other T-cell subtypes in depression – Th1, Th2 cells, and T-bet*

The balance of Th1 vs. Th2 cytokines in depression is currently debated by prominent authors in the field (Capuron and Miller, 2011; Rook et al., 2011). The majority of evidence suggests a net Th1 production as a key feature of immune dysfunction in depression, however, some studies suggest increased Th2 production (Myint et al., 2005; Capuron and Miller, 2011; Rook et al., 2011; Leonard and Maes, 2012). Th1 cells can produce IFN-γ, IL-2, and TNF-α; Th2 cells can produce IL-4, IL-6, and IL-10. Recent evidence suggests T-bet is associated with depression-like behaviors (Wong et al., 2008; Kim et al., 2011). T-bet deficient mice, Th1/IFN-γ depleted, are shown to be resistant to stress-induced depression-like behavior and stress-induced neuroinflammation (i.e., IL-6 and TNF-α; Kim et al., 2011). A clinical study by Wong et al. (2008) in a sample of Mexican Americans with major depression, shows evidence that single nucleotide polymorphisms (SNPs) in the *T-bet* (*Tbx21*) gene, which is critical for helper T (Th) 1-cell function, are associated with susceptibility to major depression. Moreover, the same study showed T-cell involvement in AD treatment response of genes associated with T-cell development (T-cell antigen receptor-ε subunit of T3, CD3E; Wong et al., 2008).

## BALANCING BENEFICIAL AND DETRIMENTAL EFFECTS OF THE NEUROIMMUNE SYSTEM IN DEPRESSION

In the sections above we have outlined both the beneficial and detrimental effects of the neuroimmune system in depression. From this information, we suggest that depression-related pathophysiology and depression-like behaviors may be dictated by the balance between the beneficial and detrimental effects of neuroimmune factors. See **Figure 1** for a graphical representation of this balance. It is possible that when the balance is skewed toward the detrimental effects of the neuroimmune system, this leads to the development of depression-like behaviors, may prolong depressive episodes and lead to more severe symptomatology and behaviors. Alternatively, if the balance becomes skewed toward the beneficial effects of the neuroimmune system, this would reduce symptomatology and behavior and may drive the end of depressive episodes and prolong relapse remission.

## NEUROBIOLOGICAL EFFECTS OF PHYSICAL ACTIVITY IN DEPRESSION

The neurobiological effects of PA in depression include effects on neurotransmitter, neuroendocrine systems, effects on neuroplasticity, and effects on neuroimmunological factors. The following section will outline the effects of PA on these systems, below, with a focus on neuroimmunological factors.

#### *Neurobiological effects*

Physical activity has been shown to upregulate monoamine neurotransmitters in the brain (e.g., 5-HT, dopamine, and noradrenaline) as well as endorphins (Knochel et al., 2012; Lautenschlager et al., 2012; Sarris et al., 2012). Reductions in glucocorticoid stress hormones are also found alter PA interventions whereby PA appears to re-regulate the HPA axis (Eyre and Baune, 2012c). Oxidative stress is reduced in the hippocampus in pre-clinical populations (Marosi et al., 2012).

Hippocampal neuroplasticity (e.g., neurogenesis, HC volume, and neurotrophin production) is increased with PA interventions in both clinical and pre-clinical populations (Erickson et al., 2012; Knochel et al., 2012; Lautenschlager et al., 2012). Pereira et al. (2007) reported that aerobic exercise resulted in increased HC blood volume which correlated with improved aerobic capacity and neurogenesis in the dentate gyrus. A recent RCT by Erickson et al. (2011) found that an aerobic exercise program in older adults, for 3 days a week over 1 year, increased HC volume by 2%. This was associated with increased serum BDNF and improvements in spatial memory. Further work is required to investigate the effects of PA on neuroplasticity in the PFC and amygdala.

#### *Neuroimmunological effects in clinical populations*

A recent study by Rethorst et al. (2012) aimed to determine the extent to which inflammatory markers can be used to predict treatment response to exercise treatment, and if this effect was dependent upon the dose of exercise. This prospective study used participants who were incomplete responders to an SSRI and randomized them to two doses of aerobic exercise for 12 weeks [4 or 16 kilocalories per kilogram of body weight per week (KKW))] 16 KKW was designed to meet or exceed current PA guidelines for public health from professional associations. The study found participants with a high baseline TNF-α (>5.493 pg/ml) had a greater reduction in depressive symptoms (measured by IDS-C) than those with a low TNF-α level. Interestingly, this finding may suggest TNF-α as a moderator between SSRI and exercise treatment, and TNF-α levels could be used to recommend exercise rather than medication as part of a personalized treatment algorithm (Rethorst et al., 2012). This is given Eller et al. (2008) found high baseline TNF-α associated with non-response to an SSRI, and the Hannestad et al. (2011) meta-analysis also supports this association. There was a significant correlation between change in IL-1β and depression symptoms for the 16 KKW group, but not the 4 KKW group. The meta-analysis by Hannestad et al. (2011) also found a reduction in IL-1β correlated with better outcomes with SSRIs. Interestingly there was no change in cytokines levels following either exercise dosage. The authors suggest this may have occurred due to pre-treatment with SSRIs – a well known anti-inflammatory agent (Hannestad et al., 2011) – which obscured the ability to detect changes in cytokine levels. Indeed, many past studies have shown exercise to have a robust anti-inflammatory effect in both human and rodent studies (Rethorst et al., 2011; Eyre and Baune, 2012a).

Another recent study by Irwin and Olmstead (2012) utilized a 9-week TCC program in a healthy older adult population to investigate the effect of exercise on depression symptoms. This study

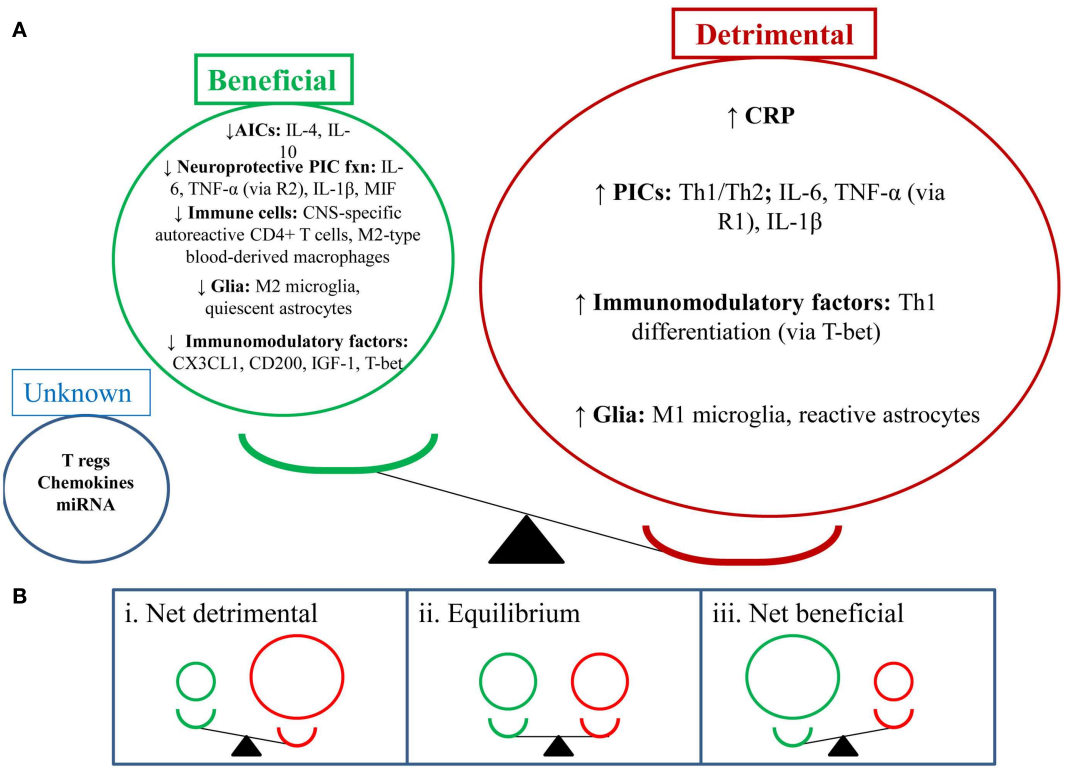


**FIGURE 1 | Depression-like behavior: balancing the beneficial and detrimental effects of the neuroimmune system. (A)** This section shows the balance of the detrimental (red) and beneficial (green) effects of neuroimmune factors in the depressed state (i.e., detrimental factors out way beneficial factors). NB: depression-like behavior includes sickness-like behavior, anhedonia, anxiety-, and cognition-like behaviors. **(B)** This section shows a number of potential outcomes for the balance between the abovementioned neuroimmune factors. (i) Shows a net detrimental effect which would lead to depression-like behaviors; clinically this could mean a depressive episode and could also increase relapse rates. (ii) Shows an equilibrium position which may suggest a stable/steady state in behavior; clinically this could mean a euthymic state. (iii) Shows a net beneficial effect which may attenuate depression-like behavior; clinically this could mean reduction or resolution of depressive symptoms and reduced relapse rates.

found TCC reduced depressive symptoms (BDI) in correlation with a reduction in IL-6 levels. TCC, however, had no effect on cellular markers of inflammation (i.e., sIL-1ra, sIL-6, sICAM, and IL-18). The authors suggest PA treatments may modulate IL-6 via decreasing sympathetic outflow. Aging and stress are associated with increases in circulating catecholamine levels, which are known to increase IL-6.

A study by Kohut et al. (2006) found aerobic exercise reduced pro-inflammatory factors (i.e., CRP, IL-5, TNF-α, and IL-18) more than a combination of flexibility and strength exercise over a 10-month period. These exercise types both reduced depressive symptoms in the Geriatric Depression Scale (GDS).

The robust lipolytic effects of PA are suggested to play a role in the antidepressant effects of PA in depression, via reducing the systemic pro-inflammatory state seen in obesity (Gleeson et al., 2011). A high visceral fat mass has been shown to cause a chronic inflammatory state, and this chronic inflammatory state may link depression and obesity (Stuart and Baune, 2012). Gleeson et al. (2011) also suggests physical inactivity is a risk factor for the accumulation of visceral fat which may predispose individuals to chronic illness like depression and heart disease via systemic PIC production by visceral fat mass.

See **Tables 1** and **2** for clinical studies examining the effects of exercise on neuroimmunological factors with and without depressive symptom correlations, respectively.

### *Neuroimmunological effects in pre-clinical populations*

As seen in **Tables 3** and **4**, there are a large number of studies investigating the neuroimmunological effects of PA. Studies have been variously conducted with and without behavioral correlates. The following section will summarize the salient studies in this field.

A recent study found a voluntary exercise regimen to be associated with increased HC MIF, as well as *Bdnf* and *Tph2* (tryphophan hydroxylase, involved in the synthesis of 5-HT) gene expression (Moon et al., 2012). These changes occurred in the context of reduced depression-like behavior (FST), and the effect of PA on these factors was mediated by the CD74-GTPase (MIF receptor) and RhoA-ERK1/2 pathway. MIF is a PIC expressed in the CNS whose deletion is associated with increased anxiety- and depression-like behaviors, as well as of impaired HC-dependent memory and HC neurogenesis (Conboy et al., 2011). Taken together, this information suggests a role of MIF in mediating the antidepressant action of exercise, probably by enhancing 5-HT neurotransmission and neurogenesis.

**Table 1 | Neuroimmune effects of physical activity in human populations with depressive symptom correlation.**

| Study | Study objective | Study details | Exercise details | Neuropsychological testing | Immune testing | Results |
|---|---|---|---|---|---|---|
| Rethorst et al. (2012) | To examine the extent to which inflammatory markers can be used to predict response to exercise treatment after an incomplete response to an SSRI | Prospective. Randomized. TREAD study | Randomized to either 16 or 4 KWW | Clinician: IDS-C30 | ELISA of serum at baseline and 12 weeks. IFN-γ, IL-1β, IL-6, and TNF-α | High baseline TNF-α (>5.493 pg/ml) α greater ↓ in depression sxs (IDS-C) over 12 weeks ($p < 0.0001$) |
| | To examine how the inflammatory markers change with exercise and if those changes are associated with dose of exercise or changes in symptom severity | Participants had MDD and were partial responders to an SSRI (i.e., ≥14 HRSD-17 following >6 weeks but <6 months of treatment)<br>Excluded if regularly engaging in PA<br>Age 18–70 years<br>73 participants<br>12-week | Aerobic EXC (treadmill or cycle ergometers)<br>Combination of supervised and home-based sessions | Self-rated: IDS-SR30 and HRSD-17 | | Sig pos α between Δ IL-1β and Δ depression sxs ($p = 0.04$). For 16KKW not 4 KKW<br>NS change in cytokine levels following 12 weeks of EXC. NS relationship between EXC dose and change in cytokine levels<br>High TNF-α may predict better outcomes with EXC vs. ADs<br>↓ IL-1β α positive depression treatment outcomes |
| Rethorst et al. (2011) | To determine whether the relationship between IL-6 and depressive symptoms is moderated by participation in moderate-intensity physical activity in a sample of primary care patients | Cross-sectional<br>97 participants. Family medicine clinic<br>≥40 years<br>CES-D > 15 | Moderate-intensity PA. Measured using modified Community Health Activities Model program for Seniors Activity Questionnaire for older adults | CES-D | ELISA of serum IL-6 | Correlation between IL-6 and depressive sxs NS ($r = 0.086$, $p = 0.40$)<br>Association between IL-6 and depressive symptoms was moderated by PA ($p = 0.02$)<br>Among those who did not engage in mod PA, higher depressive sxs α ↑ IL-6 ($r = 0.28$, $p = 0.05$)<br>Association was NS for moderate PA ($r = -0.13$, $p = 0.38$) |
| Irwin and Olmstead (2012) | To evaluate the effects of a behavioral intervention, TCC on circulating markers of inflammation in older adults | 83 healthy older adults (59–86 years)<br>RCT. Two arms – TCC, HE<br>16 weeks intervention + 9 weeks follow-up | TCC and HE<br>Groups of 7–10<br>TCC 20 min, 3/week | BDI<br>PSQI | ELISA of plasma for IL-6, CRP, sIL-1ra, sIL-6, sICAM, IL-18<br>NB *High IL-6 > 2.46 pg/ml* | High IL-6 at entry: TCC ↓ IL-6 comparable to those in TCC and HE who had low IL-6 at entry<br>IL-6 in HE remained higher than TCC and HE with low entry IL-6<br>TCC ns Δ cellular markers of inflammation<br>TCC = ↓ depressive sxs α ↓ IL-6 |

*(Continued)*

**Table 1 | Continued**

| Study | Study objective | Study details | Exercise details | Neuropsychological testing | Immune testing | Results |
|---|---|---|---|---|---|---|
| Kohut et al. (2006) | To determine if a long-term exercise intervention among older adults would reduce serum inflammatory cytokines, and if this reduction would be mediated, in part, by improvements in psychosocial factors and/or by β-adrenergic receptor mechanisms | Adults ≥ 64 years. Community-based Randomized to aerobic or flexibility/strength EXC. 10 months A sub-group of patients on non-selective β1β2-adrenergic antagonists were included | Aerobic (CARDIO) or flexibility/ strength EXC (FLEX) 3 days/week, 45 min/day, 10 months | GDS, PSS, CS, SPS, and LOT | ELISA of plasma: CRP, IL-6, TNF-α, and IL-18 | EXC = ↓ depressive symptoms, ↑ optimism CARDIO EXC = ↓ IL-6, IL-18, CRP, TNF-α vs. FLEX FLEX EXC = ↓ TNF-α, no change in IL-6, IL-18, CRP ↓ CRP α ↓ depressive symptoms No effect for non-selective β1β2-adrenergic antagonists |

*TREAD, treatment with exercise augmentation for depression; KKW, kilocalories per kilogram of body weight per weeks; HE, health education; PSQI, Pittsburgh Sleep Quality Index; GDS, Geriatric Depression Scale; PSS, Perceived Stress Scale; CS, Coherence Scale; SPS, Social Previsions Scale; LOT, Life Orientation Test; α, association with or correlation with; EXC, exercise; IDS-C30, Inventory of Depressive Symptomatology; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; CES-D, Center for Epidemiologic Studies Depression Scale; NS, non-significant; TCC, Tai Chi Chih.*

Other studies found investigating the effects of PA on neuroimmune-related factors suggest PA increases anti-inflammatory or immunomodulatory factors, e.g., IL-10, IGF-1, and CX3CL1. Sigwalt et al. (2011) shows that in a rat model of depression induced by repeated dexamethasone administration, swimming exercise reduces depression-like behavior in correlation with increased HC IL-10, BDNF, and DNA oxidation. Duman et al. (2009) and Kohman et al. (2012) show voluntary wheel running associated with increased IGF-1, a factor recently shown to have anti-inflammatory effects.

Physical activity has been found to have beneficial effects on immunocompetent glial cells. A study by Latimer et al. (2011) has shown PA to revise age-related astrocyte hypertrophic/reactivity and myelin dysregulation – changes associated with neuroinflammation, cognitive decline, and reduced vascular function. Kohman et al. (2012) recently published a study showing PA attenuates aging associated increases in the proportion of new microglia within the HC (Iba-1 labeled). Furthermore, they show PA increases the pro-neurogenic phenotype of microglia (i.e., IGF-1-releasing microglia) which may contribute to increased HC neurogenesis. Given the robust anti-inflammatory effect of PA, the authors suggest PA may reduce PIC protein production leading to impaired microglial proliferation. A recent study by Barrientos et al. (2011) shows access to a running wheel reduced PIC expression from cultured microglia of aged rats. A recent study by Vukovic et al. (2012) suggests PA enhances the immunomodulatory factor CX3CL1 in the HC, with this associated with enhanced microglia-dependent neural precursor activity, as per the *ex vivo* neurosphere assay.

A study by Funk et al. (2011) demonstrates that PA can offer significant protection to the HC in a chemical-induced injury model [via trimethyltin (TMT)] that involves TNF receptor signaling. PA attenuated TMT-induced changes such as loss of DG neurons and microglial activation. Furthermore, PA was accompanied by a significant elevation in IL-6 and IL-1ra mRNA levels and repressed elevations in PICs and chemokines (CCL2 and CCL3). Interestingly, the investigators identified a functional role for IL-6 in neuroprotection given mice deficient in IL-6 (IL-6 knock-out) were not responsive to the neuroprotective effects of PA on the HC. The effects of PA and TMT on IL-6 downstream signal events differed at the level of STAT3 activation. The beneficial effects of acute spikes in IL-6 with PA is clearly a significant factor in the anti-inflammatory effect of PA. In a human study by Starkie et al. (2003), 3 h of cycling blunted the endotoxin-induced increase in circulating TNF-α levels, and this effect was mimicked by an IL-6 infusion. Further, this regulatory role of IL-6 on TNF-α levels was demonstrated in anti-IL-6 treated mice and IL-6 knock-out mice (Mizuhara et al., 1994; Matthys et al., 1995). Whilst acute elevations in IL-6 are found throughout the body (Funk et al., 2011), a recent study shows a selective increase in IL-6 localized to the HC (Rasmussen et al., 2011).

Neuroimmune cells may also have a role in the beneficial effects of PA. A study by Ziv et al. (2006) found PA, a component of the EE protocol, was associated with enhanced HC neurogenesis alongside a neuroprotective microglia phenotype and in the presence of a T-cell population. The role of CNS-specific T cells in the neuroprotective effects of PA is suggested given severe combined

**Table 2 | Neuroimmune effects of physical activity in human populations without depressive symptom correlation.**

| Study | Study objective | Study details | Exercise details | Immune testing | Results |
|---|---|---|---|---|---|
| Nicklas et al. (2008) | To determine the effects of a long-term exercise intervention on two prominent biomarkers of Inflammation, CRP and IL-6, in elderly men and women | Single-blind, randomized, controlled trial<br><br>424 elderly (70–89 years), non-disabled, and community-dwelling men and women<br>12 months of moderate-intensity PA vs. successful aging (SA) health education intervention | Moderate-intensity PA. Combined aerobic, strength, balance, and flexibility exercise<br>Approx 1 h sessions, 3/week. Starting in center and transition to home-based exercise | ELISA of plasma: CRP and IL-6 | PA = ↓ IL-6 vs. SA. No ΔCRP |
| Donges et al. (2010) | To determine the effects of 10 weeks of resistance or aerobic exercise training on IL-6 and CRP. Further, to determine pre-training and post-training associations between alterations of IL-6 and CRP and alterations of total body fat mass (TB-FM), intra-abdominal fat mass (IA-FM), and total body lean mass (TB-LM) | 102 sedentary subjects<br>Resistance group (RG), aerobic group (AG), or control. 10 weeks<br><br>Subjects were involved in DEXA, muscle strength, aerobic fitness measures, and lipid profiling | Supervised exercise<br>Control group maintained sedentary lifestyle and dietary patterns | IL-6, CRP | RG and AG = ↓ CRP, no effect on IL-6 |
| Martins et al. (2010) | Effect of exercise on metabolic profile in a healthy elderly sample | RCT<br>$N = 63$<br>16 weeks | Aerobic: 40–80% HR max<br>Resistance: 8 exercises – 1set/8reps to 3sets/15reps | Total cholesterol, triglycerides – colorimetric end-point assay<br>HDL, LDL – two-point kinetic assay<br>Hs-CRP – immunoturbidometry<br>[@ baseline, 16 weeks] | Aerobic and resistance exercise = improvement in all measures |
| Stewart et al. (2007) | The purpose of this study was to examine the influence of a 12-week exercise training program on inflammatory cytokine and CRP concentrations. A secondary purpose was to determine whether training-induced changes in cytokines and CRP were influenced by age | 29 younger (18–35 years) and 31 old (65–85 years) subjects<br><br>Assigned to young physically active, young physically inactive, older physically active, older physically inactive groups | Inactive groups complete 12 weeks (3 days/week) of aerobic and resistance exc<br>Physically active control groups continue their normal exc programs | ELISA of serum: CRP<br><br>ELISA of plasma: IL-6, TNF-α, and IL-1β | Prescribed EXC = ↓ CRP, no change for IL-6, IL-1β, TNF-α for both young and older subjects |

*(Continued)*

**Table 2 | Continued**

| Study | Study objective | Study details | Exercise details | Immune testing | Results |
|---|---|---|---|---|---|
| Black et al. (2012) | To examine if a yogic meditation might alter the activity of inflammatory and antiviral transcription control pathways that shape immune cell gene expression | 45 family dementia caregivers Randomized to either Kirtan Kriya Meditation (KKM) or Relaxing Music (RM) | 8 weeks of KKM or RM. Both 12-min/day | Genome-wide transcriptional profiles collected from PBMC at baseline and 8 weeks follow-up. RNA extraction ◇ cRNA Transcript Origin Analysis | KKM = ↑ 19 gene's expression (immunoglobulin-related transcripts) KKM = ↓ 49 gene's expression (PIC, activation-related immediate-early genes). From plasmacytoid dendritic cells and B lymphocytes Effects may be due to ↓ NF-κB and IRF-1 |
| Santos et al. (2012) | To assess the effects of moderate exercise training on sleep in elderly people as well as their cytokine profiles | 22 male, sed, health, elderly<br>Polysomnography collected week – 1 and 6 Total body mass and% fat. Whole-body plethysmography | Mod training for 24 weeks. 60 min/day, 3 days/week Work rate equiv to ventilator aerobic threshold ($VO_{2max}$, VATI) | ELISA plasma: TNF-α, IL-6, IL-1, and IL-10 | EXC = ↑ aerobic fitness, ↓ REM latency, ↓ time awake EXC = ↓ IL-6, TNF-α, TNF-α/IL-10 EXC = ↑ IL-10 |
| Cordova et al. (2011) | To investigate the association between long-term RT and circulating levels of the pro-inflammatory mediators IL-6, TNF-α, and IFN-γ in elderly women | Cross-sectional<br>54 years. Women RT – $N = 28$ Sed – $N = 26$ | In RT group women underwent 8.6 ± 0.3 months of EXC. Mod-intensity (70% 1RM) 50 min, 3/week, 3 sets of 12 reps per exercise | ELISA plasma: TNF-α, IL-6, and IFN-γ | RT = ↓ IFN-γ, ↓ IL-6, ↓ TNF-α vs. sed RT = ↓ caloric intake, sBP FFM 1/α IL-6 |
| Libardi et al. (2012) | The aim of the present study was to evaluate the effects of 16 weeks of RT, ET, and CT on inflammatory markers, CRP, and functional capacity in sedentary middle-age men | Healthy inactive subjects. ∼ 49.5 years ± 5 Randomized to RT ($N = 11$), ET ($N = 12$), CT ($N = 11$), or ctrl ($N = 13$) BMI, waist-to-hip ration, DEXA for FFM Diet contents recorded | 3 weekly sessions for 60 min for 16 weeks Max strength (1RM) tested in bench press and leg press<br>$VO_{2peak}$ measured in incremental exc test | ELISA plasma: TNF-α, IL-6, and CRP | RT and CT = ↑ max strength ET and CT = ↑ $VO_{2peak}$<br>Ns Δ TNF-α, IL-6, CRP |
| Beavers et al. (2010b) | Effect of chronic exercise on inflammation in the elderly | RCT $N = 424$ | 12 months combined aerobics, strength, flexibility/balance training | CRP, IL-6, IL-6sR, IL-8, and IL-15, Adiponectin, Il-1rα, IL-2sRα, TNF-α, and sTNFRI and II ELISA | Exercise = ↓ IL-8, no Δ in others |

*(Continued)*

**Table 2 | Continued**

| Study | Study objective | Study details | Exercise details | Immune testing | Results |
|---|---|---|---|---|---|
| Colbert et al. (2004) | Effect of exercise on inflammation in the elderly | Cross-sectional<br>$N = 3075$ | Questionnaire | CRP, IL-6, and TNF-α (blood/serum) – ELISA | ↑ Exercise α ↓ CRP ($p < 0.01$), ↓ IL-6 ($p < 0.001$), ↓ TNF-α ($p = 0.02$) |
| Geffken et al. (2001) | Effect of physical activity on inflammation in healthy elderly | Cross-sectional<br>$N = 5201$ | Questionnaire | Blood: CRP, fibrinogen, Factor VIII activity, and WCC | ↑ Physical activity α ↓ Inflammatory markers |
| Nybo et al. (2002) | Is prolonged exercise associated with an altered cerebral IL-6 response? | Quasi-experimental $N = 8$, young men<br>Injected with radiotracer (133-Xe) | 2 min × 60 min bouts of cycle ergometer at 50% $VO_{2max}$ at different temperatures | Blood: IL-6 – ELISA | Prolonged exercise = ↑ IL-6 release |
| Kohut et al. (2006) | Effect of different exercise types on inflammation in the elderly | RCT $N = 87$ M34/F53<br><br>Subset administered non-selective β-adrenergic antagonists | 10 months: 45 min 3×/week<br><br>Cardio: 65–80% $VO_{2max}$<br><br>Strength/flexibility: 10–15 reps (moderate-intensity) | Blood: CRP, IL-6, TNF-α, and IL-18 | Cardio = ↓ all markers ($p < 0.05$)<br>Strength/flex = ↓ TNF-α ($p = 0.001$)<br>β-inhibitors made no effect |
| Reuben et al. (2003) | Effect of physical activity on inflammation in elderly | Cross-sectional<br>$N = 877$ | Sef-reported: Yale Physical activity survey | Blood: IL-6, CRP – ELISA | ↑ Physical activity α ↓ IL-6 and CRP |

*RT, resistance training; ET, endurance training; CT, concurrent training; FFM, free fat mass; VATI, ventilator anaerobic threshold; TCC, Tai Chi Chih; RCT, randomized controlled trial; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein.*

**Table 3 | Neuroimmunological effects of physical activity in rodent populations: with behavioral correlates.**

| Study | Study objective | Animal | Exercise type | Behavioral assessment | Immune measures | Results: behavioral | Results: neuroimmune |
|---|---|---|---|---|---|---|---|
| Moon et al. (2012) | To determine the underlying mechanism of MIF in HC neurogenesis and its role in exercise-induced antidepressant therapy | Rat MIF−/− and WT | Voluntary EXC vs. ECT | FST | *In vivo*: HC, RT-PCR, IB, IHC | *MIF−/−* = depression-like behavior | EXC = ↑ *Tph2 in vitro* and *in vivo* (*in vitro* α ↑ 5-HT) |
| | | *In vivo* component | 28 days of EXC or 10 days of ECT | | *In vitro*: PCR, RT-PCR | *MIF−/−* = blunted antidepressant effect of EXC in FST | EXC = ↑ *Bdnf in vitro* and *in vivo* |
| | | | ICV injection with MIF<br>*In vitro*: neuronal cell lines treated with MIF. Neuro 2A | | | Administration of MIF protein = antidepressant effect in FST | CD 74-GPTase (MIF receptor) and RhoA-ERK1/2 pathway mediated MIF-induced Tph2 and Bdnf gene expression and 5-HT content |
| | | | MIF −/− = ↓ *Dcx* and *Pax6* siRNAs, GTPase RhoA inhibitor CT04, MEK inhibitor U0126 | | | | EXC = ↑ MIF (HC) (IHC and IB) |
| Sigwalt et al. (2011) | The aim of the present study was to investigate the influence of swimming exercise training on behavior and neurochemical parameters in a rat model of depression induced by repeated dexamethasone administration | Adult Wistar rats. 60 days Daily s.c. dex (1.5 mg/kg) or saline administration | 4 groups: CTRL, EXC, DEX, and DEX + EXC | SPT | RIA blood corticosterone | DEX: ↓ sucrose consumption, ↑ immob time | DEX: ↑ HC DNA oxidation, ↑ IL-10, ↑ BDNF, ↓ blood corticosterone levels, ↓ adrenal weight, ↓ body mass |
| | | | EXC: swimming/aerobic. 1 h/day, 5 days/week for 3 weeks. Overload of 5% of rat body weight<br>CTRL: fluoxetine 10 mg/kg | FST | IHC HC: BDNF 8OHdG<br>RT-PCR HC: BDNF, IL-10 | EXC: ↑ sucrose consumption | EXC: normalization of BDNF and IL-10, ↑ blood testosterone, ↓ HC DNA oxidation |
| Duman et al. (2009) | To assess the role of peripheral IGF-I in mediating antidepressant-like behavior under resting physiological conditions | Mice. C57Bl/6 | Voluntary wheel running for 4 weeks | FST | PFC and HC | IGF-1 = ↓ immob time, ↑ sucrose consumption | Anti-IGF-1 blocked the BDNF producing effect of EXC |
| | To investigate the extent to which IGF-I might contribute to antidepressant-like behavior in exercising mice | uCMS | | NIH | ELISA for IGF-1 | Anti-IGF-1 blocked the antidepressant effect of EXC (FST) | EXC = ↑ IGF-1 mRNA |
| | | IGF-1 and anti-IGF-1 was administered s.c. | | SCT | ISH for IGF-1 and BDNF | | EXC ≠ PFC IGF-1 mRNA, nor HC and PFC BDNF |

*IHC, immunohistochemistry; IB, immunoblot; HC, hippocampus; PFC, pre-frontal cortex; SPT, sucrose preference test; dex, dexamethasone; FST, forced-swim test; MIF, macrophage migration inhibitory factor; RT-PCR, reverse transcription polymerase chain reaction; IB, immunoblot; ELISA, enzyme-linked immunosorbent assay; CTRL, control; BDNF, brain-derived neurotrophic factor; ISH, in situ hybridization.*

**Table 4 | Neuroimmune effects of physical activity in rodent populations: without behavioral correlates.**

| Study | Study objective | Animal | Exercise Type | Neuroimmune measures | Results: immune |
|---|---|---|---|---|---|
| Funk et al. (2011) | To examine the impact of voluntary exercise on a model of TNF receptor activation dependent neuronal apoptosis | Mice. Pathogen-free CD-1<br>WT and IL-6−/−<br>IP injection of TMT (2.4 mg/kg) or saline<br>Bone-marrow chimera mice used to confirm lack of infiltrating monocytes with TMT injury | Voluntary running wheel access for 2 weeks | Flow cytometry of CD11b, CD4, and GFP<br>IHC HC GFP+, Iba-1 cells; IL-6, IL-6 Rα, gp130, pAkt, p-STAT3<br>Mass spect: Tin (sn)<br>Fluorescent microscopy HC for cell death and microglia phenotyping<br>qPCR<br>Microarray analysis: cell death and IL-6 pathways | EXC = ↓ neuronal death, TNF-α, TNFr1, *MyD88*, TGF-β, CCL2, CCL3<br>EXC = ↑ IL-1α mRNA, IL-1RA mRNA, IL-6 (mRNA and protein), neuronal IL-6-Rα<br>TMT = ↑ IL-1α mRNA, IL-1RA mRNA, IL-6 (mRNA and protein), neuronal IL-6-Rα<br>EXC = ↓ TNF-α cell death signaling pathways with TMT. IL-6 pathway recruitment occurred in both EXC and TMT conditions – IL-6 downstream signal events differed in the level of STAT3 activation<br>EXC ≠ BDNF mRNA, NGF mRNA, GDNF mRNA<br>IL-6−/− mice: EXC showed ↓ neuroprotection against TMT-induced injury |
| Kohman et al. (2012) | To evaluate whether exercise modulates division and/or activation state of microglia in the dentate gyrus of the hippocampus | Adult (3.5 months) and aged (18 months) BALB/c mice | Vol running wheel for 8 weeks | IHC: BrdU HC<br>IF (confocal microscopy): HC: microglia (Iba-1 +), microglial division (Iba-1+ and BrdU +), co-expression of IGF-1, new neuron survival (BrdU × fraction displaying NeuN) | Aged mice = ↑ new microglia<br>EXC = ↓ new microglia in aged mice, ↑ microglial IGF-1 expression, ↑ survival of new neurons + proliferation<br>EXC ≠ microglial survival or proliferation in adult mice<br>[NB] *IGF-1-releasing microglia considered pro-neurogenic* |
| Yi et al. (2012) | To determine if regular treadmill running may blunt the effect of western diet on hypothalamic inflammation | Ldlr−/− (low-density lipoprotein receptor deficiency) and WT mice<br>High-fat diet exposure<br>Indirect calorimetry performed | Moderate, regular treadmill running exercise. Involuntary. 30 min/day, 5 days/week, 26 weeks<br>Exhaustion tests at weeks 0 and 25 | IP glucose tolerance test performed<br>Blood glucose levels measured<br>Plasma insulin via ELISA<br>Blood markers: TNF-α, IL-6, INF-g, IL-1α, PAI-1, and MCP-1<br>IHC: hypothalamus for iba-1 | EXC = ↓ hypothalamic inflammation, ↓ microglial activation<br>EXC = ↑ glucose tolerance<br>EXC ≠ circulating cytokines |
| Ehninger et al. (2011) | Effect of exercise on cell genesis in the adult amygdala | Female C57BL6/J mice, 2 mo | Exercise vs. 2 sedentary controls (environmental enrichment, standard housing) 10 days, voluntary wheel running | Iba-1, S100β, BrdU, NeuN, NG2, CNPase, GFAP, and ki67 (hippocampus) – immunofluorescence | Exercise and environmental enrichment = ↑ oligodendroglial precursor proliferation, ↓ microgliogenesis, ↑ neuroplasticity |

*(Continued)*

**Table 4 | Continued**

| Study | Study objective | Animal | Exercise Type | Neuroimmune measures | Results: immune |
|---|---|---|---|---|---|
| Latimer et al. (2011) | To test the hypothesis that exercise initiated at mid-age can slow the development of hippocampal glial and vascular biomarkers of early aging | C57BL/6 mice: young, middle and aged | Voluntary exercise for 6 weeks | BP monitoring<br><br>IHC HC: astrocyte (GFAP) and myelin staining (MBP)<br>ELISA HC: VEGF (angiogenesis marker)<br>Vascular casting: scanning electron micrographs of MCA were utilized | EXC = ↓ HC GFAP and MBP which were associated with aging<br>EXC = astrocytic changes, i.e., fewer branches, finer processes, less hypertrophied<br>EXC = ↑ VEGF which was associated with aging<br><br>EXC = improved endothelial functioning (less ragged and irregular, ↑ ECN) and ↓ BP |
| Jeon et al. (2012) | To examine the effects of aging vs. exercise on serum profiles of cytokines and chemokines in mice models | C57BL/6 mice. Young (2 months) and old (20 months) | Forced treadmill exc for 4 weeks. 30 min/day, 5 days/week | Multiplexed bead-based sandwich immunoassay of 50 serum cytokines/chemokines | Treadmill EXC ≠ Δ serum cytokines/chemokines significantly<br><br>Older mice = ↑ eotaxin, IL-9, TARC vs. young mice |
| Wu et al. (2012) | Effect of exercise on hippocampal neurogenesis in infection | Male/female IL-1β$^{XAT}$ (IL-1β over-expression) C57BL/6 mice, 8–12 months vs. WT | Exercise vs. sedentary control<br>Intra-hippocampal FIV (feline immunodeficiency virus) injection vs. vehicle<br>2 weeks, voluntary wheel running | MHCII DCX, BrdU, Iba-1 (HC) – immunohistochemistry | EXC ≠ normalized neurogenesis in presence of centrally mediated infection in IL-1β over-expression |
| Nichol et al. (2008) | Effect of exercise on amyloid load and neuroinflammation in AD mice | Male/female Tg2576 C57B16/SJL mice, 16–18 months vs. WT | Exercise vs. sedentary control 3 weeks, voluntary wheel running | HC and cortex<br>Pro-inflammatory: IL-1β, TNF-α – ELISA<br>Adaptive/alternate immune markers: IFN-γ, CD40, MHCII – Western blot<br>CD11c, MIP-1α – Immunohistochemistry<br>Aβ – ELISA, Dot-blot analysis<br>CD68, mannose receptor – Immunohistochemistry<br>Iba-1 – Western blot | EXC = ↓ TNF-α, IL-1β<br>EXC = ↑ IFN-γ, CD11c, MHCII, CD40, MIP-1α<br><br>EXC = ↑ CD68, mannose receptor<br><br>(↑ Perivascular MΦ infiltrate) |

*(Continued)*

**Table 4 | Continued**

| Study | Study objective | Animal | Exercise Type | Neuroimmune measures | Results: immune |
|---|---|---|---|---|---|
| Vukovic et al. (2012) | Effect of exercise on microglial-dependent hippocampal neurogenesis | Female TG-Csf1r-GFP C57BL/6J mice, 6–8-week old | Exercise vs. sedentary control *Ex vivo* neurospehere culture with/without microglia 2 weeks, voluntary wheel running | HC BrdU, DCX, Iba-1 – immunostaining CX3CL1 – ELISA MHCII – FACS | EXC = microglial-dependent ↑ neural precursor activity<br>EXC = ↓ MHCII+ve microglia,<br>EXC = ↑ CX3CL1 (neuroprotective phenotype) |
| Ziv et al. (2006) | Role of immune cells in neurogenesis | Male Sprague Dawley rats, 12-week old | EE vs. standard lab control Healthy rats vs. immune-deficient (SCID mice) | From HC: IHC: BrdU, MHCII, IB-4, IGF-1, NeuN, BDNF, and TCR | EE = ↑ neurogenesis and adaptive microglial profile in presence of function T-cell population |
| Leem et al. (2011) | Effect of exercise in neuroinflammation in AD mice | Male/Female Tg-Ad (NSE/htau23) C57BL/6 mice 16 months vs. WT | EXC vs. sedentary control Intermediate (12 m/min) vs. high intensity exercise (19 m/min) | From HC<br>RT-PCR: TNF-α, IL-6, and IL-1β<br><br>WB: iNOS, ERK, COX-2, p38<br>IHC: phosphoTau, GFAP, MAC-1, and p65 | High intensity EXC = ↓ phsophoTau ($p < 0.05$)<br>High intensity EXC = ↓ gliosis [MAC-1, GFAP] ($p < 005$)<br>High intensity EXC = ↓ μAPK-dependent signaling pathway [↓ iNOS, TNF-α, IL-6, IL-1β] ($p < 0.05$) |
| Herring et al. (2012) | Effect of exercise in pregnancy on AD pathology in offspring | Female Tg-AD APP695 CRND8 x C57BL/6-C3H-HeJ vs. WT | Exercise vs. sedentary control Duration of pregnancy, voluntary wheel running | From entire brain, except, cerebellum, brainstem<br>IHC: Aβ, A1F1, laminin, RELN<br>RT-PCR: Gapdh, APP, Lpap1, ApoE1, Clu, A2m, Mmp9, Mme<br>DC protein assay: $Aβ_{40}$, $Aβ_{42}$, sAPPα<br>WB: APP, CTFβ, RELn, APOER2, VLDR, ADC, CYP, IDE, IBA-1, PTGER2, SOD1, SOD2 | EXC = ↓ Aβ in offspring via altered APP processing ($p < 0.022$)<br>EXC = ↑ angiogenesis ($p < 0.022$)<br>EXC = ↑ neuroplasticity<br><br>EXC = ↓ microgliosis ($p = 0.002$), pro-inflammatory mediators, oxidative stress mediators ($p = 0.029$) |
| Carmichael et al. (2010) | Role of brain MΦ on central cytokines and fatigue post-exercise | Male C57Bl/6 mice, 8-week old | Exercise vs. sedentary control<br>MΦ depletion with clodronate injection or saline<br>Single bout of exercise, 22 m/min for 150 m | IL-1β (cerebrum) – ELISA | EXC = ↑ IL-1β from MΦs |

*ECN, endothelial cell nuclei; EE, environmental enrichment; IHC, immunohistochemistry; WB, western blot; TCR, T-cell receptor; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; EXC, exercise; APP, amyloid precursor protein; TMT, trimethyltin; NGF, nerve growth factor, BDNF, brain-derived neurotrophic factor; VEGF, vascular endothelial growth factor.*

immunodeficiency (SCID) mice exposed to EE did not show an increase in neurogenesis.

## MODEL OF NEUROIMMUNOLOGICAL EFFECTS OF PA IN DEPRESSION

Emerging evidence suggests the neuroimmune system is critical in both the development of depression-related pathophysiology and in the treatment of depression. From the evidence available in this field, PA has a multitude of beneficial neuroimmune effects which may lead to the improvement of depression-related neurobiological processes, hence leading to reduced depression-like behaviors.

From a neuroimmune perspective, evidence suggests PA does enhance the beneficial and reduce the detrimental effects of the neuroimmune system. **Figure 2** outlines these effects. PA appears to increase the following factors: IL-10, IL-6 (acutely), MIF, CNS-specific autoreactive CD4+ T cells, M2 microglia, quiescent astrocytes, CX3CL1, and IGF-1. On the other hand, PA appears to reduce detrimental neuroimmune factors such as: Th1/Th2 balance, PICs, CRP, M1 microglia, and reactive astrocytes. The effect of other factors is unknown, such as: T regs, CD200, chemokines, miRNA, M2-type blood-derived macrophages, and TNF-α (via R2). The beneficial effects of PA are likely to occur centrally and peripherally (e.g., in visceral fat reduction).

Based on the strong relationship between the neuroimmune system and other neurobiological systems (i.e., neuroplasticity, neuroendocrine function, and neurotransmission), we believe PA may exert beneficial behavioral effects via these neurobiological systems. PA's neuroimmune effects are likely involved in enhanced neuroplasticity, reduced oxidative stress, increases in 5-HT, dopamine, and noradrenaline, and enhanced glucocorticoid sensitivity.

The neurobiological effects of PA – mediated largely via the neuroimmune system – are likely involved with reduced depression-like behaviors in rodents (i.e., sickness-like behavior, anhedonia, anxiety-, and cognition-like behaviors) and positive clinical effects (i.e., reduced depressive symptoms, enhanced cognitive function, relapse reduction, and early intervention).

## DISCUSSION

Physical activity is increasingly investigated as a preventative, early intervention, and treatment option in depression. The interest in investigation of PA may have arisen for a number of reasons: the burden of depression is rising so novel therapeutic and preventative options are required (WHO, 2008; Berk and Jacka, 2012; Cuijpers et al., 2012; Southwick and Charney, 2012). Rates of physical inactivity are high and rising in modern society (Lee et al., 2012) with early evidence suggesting a link to the development of depression (Pasco et al., 2011a,b). Pharmacotherapy in depression is hampered by relatively high rates of resistance (Rush et al., 2006a,b) and considerable side-effects. Evidence is emerging to suggest co-morbid links between obesity, diabetes,

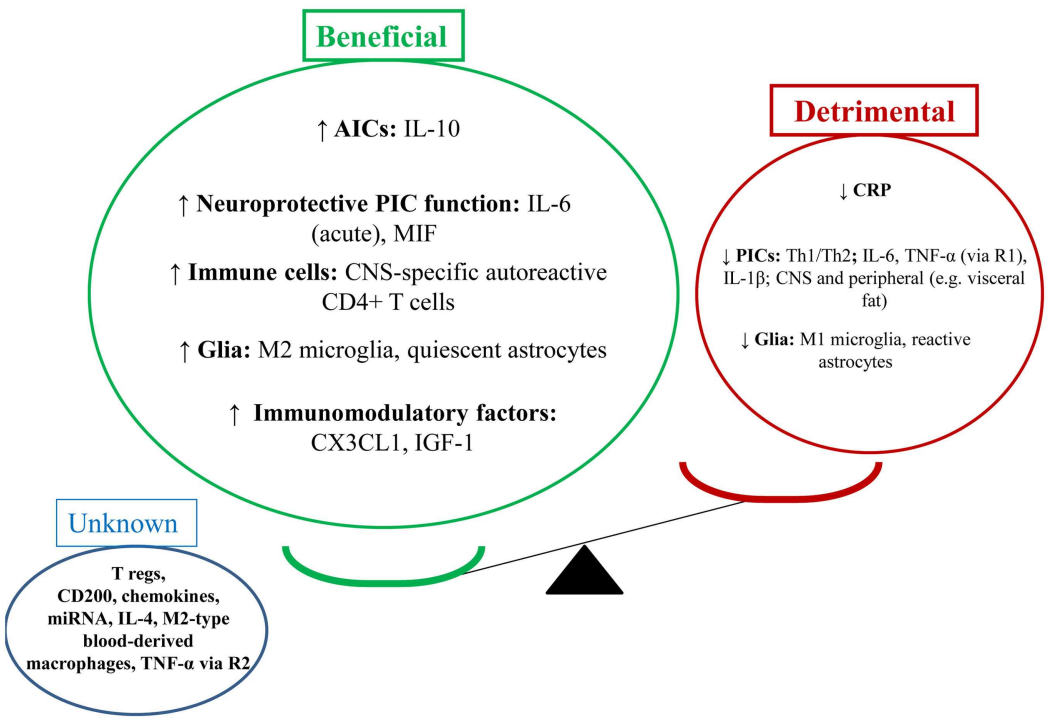


**FIGURE 2 | Physical activity in depression: antidepressant via enhancing the beneficial effects of the neuroimmune system.** This figure illustrates the effects of PA on the brain as per the balance between beneficial and detrimental effects of neuroimmune factors. PA appears to enhance the beneficial effects of the neuroimmune system and reduce the detrimental effects. From a behavioral perspective, this may lead to reduced depression-like behaviors. From a clinical perspective, this may lead to reduced depressive symptoms, depressive episode resolution, and reduced relapse rates (disease prevention).

heart disease, and depression (Baune and Thome, 2011; Stuart and Baune, 2012), and PA is a therapeutic option with beneficial cardio-metabolic effects (Gleeson et al., 2011; Baune et al., 2012c; Hamer et al., 2012; Knochel et al., 2012; Stuart and Baune, 2012).

Based on the abovementioned factors, research has been reviewed to better understand the clinical efficacy of different types of PA, to understand the mechanism of action of PA and to investigate for suitable biomarkers to measure the treatment effect of PA in depression. Further, a model has been suggested in order to assist in understanding the neuroimmune effects of PA in depression.

An important consideration in the field of exercise immunology includes understanding the mechanisms of treatment response in depression vs. other psychiatric disorders. At present the authors feel there is no enough data to address this issue systematically, with research evidence. Whilst it would appear that the effects of PA on the immune system in various disorders – in both clinical and pre-clinical studies – is quite similar, i.e., PICs are reduced (particularly in anxiety disorders and depression; Gleeson et al., 2011; Eyre and Baune, 2012a), this considers only a narrow range of neuroimmune factors. The authors speculate that the therapeutic difference in PA may occur due to subtle variations in the neuroimmune and neurobiological effect, dependent upon the CNS environment with each pathophysiological state. Studies investigating the effects of a standardized exposure to PA, in various psychiatric disorders in parallel, may assist in unraveling this complex issue.

When considering the balance between the beneficial and detrimental effects of immune system and the effect of PA tipping this balance toward beneficial effects, it is important to consider: *Is it possible to restore the balance of the immune system and still suffer from a low mood?* This is an interesting question and open to debate. It would seem that the majority of evidence suggests that as inflammation increases, mood worsens, and as inflammation reduces, mood appears to return to normal. For example, this is shown in meta-analysis by Dowlati et al. (2010) and a review by Maes (2011) whereby depressive symptoms are associated with elevations in PIC levels. Another meta-analysis shows inflammation reduces with the use of SSRIs in the treatment of depression (Hannestad et al., 2011). However, there are other therapies such as SNRIs which appear to improve mood, yet have no effect on levels of inflammation (Hannestad et al., 2011). Therefore, more work is required to understand the effect of various therapies (pharmacological and non-pharmacological) on a wider variety of immune-related factors such as cytokines (anti- and pro-inflammatory), anti-inflammatory factors like IGF-1, CD200, CX3CL1, MIF, neuroprotective systemic immune cells, etc. Interestingly, Walker (2012) suggests the concentration of antidepressant drug molecules in the CNS also alters the immunomodulatory effects.

### FUTURE DIRECTIONS

From current evidence, it is not possible to ascertain the type of PA which is most efficacious in the treatment of depression. Although, most evidence surrounds aerobic exercise. We suggest the need for head-to-head clinical trials comparing different types and intensities of PA to assist in making this issue clearer. Moreover, when considering the effects of distinct types of PA on neuroimmune factors, we also suggest the need for more head-to-head clinical trials (Baune and Eyre, 2012).

The most recent study examining the effects of PA on depressive symptoms was conducted by Rethorst et al. This study suggests that a high baseline TNF-α level was associated with a greater reduction in depressive symptomatology as opposed a high baseline TNF-α level being a negative factor for SSRI efficacy (Hannestad et al., 2011; Rethorst et al., 2012). The authors suggest TNF-α levels may be a moderator between SSRI and exercise treatment, and may have a role in personalized treatment algorithms. Whilst this is a promising suggestion, further research is needed to replicate these findings.

Our understanding of the neuroimmune effects of PA in depression will continue to develop as the understanding of the neuroimmune effects of PA develop. It is important to consider the use of multi-biomarker methods within this area in order to better understand potential biomarkers. For example, the use of neuroimaging, serum protein and genetic markers, and behavioral analysis. This type of methodology is increasingly employed in biological psychiatry (Baune et al., 2010, 2012a,b).

There are a number of neuroimmune-related factors which are yet to be considered in the effect of PA in depression. These factors include micro ribonucleic acid (miRNA), neuroimmune-related Positron Emission Tomography (PET) ligands, the neuroprotective effects of neuroimmune factors, and immune cells. Evidence is emerging to suggest a role for miRNAs, factors involved in regulating gene expression at the post-translational level, in modulating the effects of the immune system (Ponomarev et al., 2012). For example, various miRNAs such as miR-155 and miR-124 may have a role in polarizing microglia toward pro- or anti-inflammatory phenotypes, respectively (Ponomarev et al., 2012). The PET ligand, Translocator Protein (TPSO) ligand [(11)C]PBR28, a marker of microglial activation, was recently found to be elevated by LPS-induced systemic inflammation in non-human primates (Hannestad et al., 2012). This ligand has the potential to be utilized as a biomarker to investigate if activation of microglia may be a mechanism through which systemic inflammatory processes influence the disease course of depression. The biology of centrally migrating immune cells and CNS immune cells in depression is complex and far from understood. Regarding the debated issue of blood-derived macrophages can enter the brain parenchyma: research and development into novel methods for permanent differential labeling of circulating monocytes, as contrasted with resident microglia, is underway (Prinz et al., 2011). Studies are required to better understand the role of protective immunosurveillance in clinical and rodent models of depression.

## CONCLUSION

The investigation of the neuroimmune effects of PA on depression and depression-like behavior is a rapidly developing and important field. This paper summarizes the most recent findings in the area and proposes a model whereby PA enhances the beneficial effects of the neuroimmune system and reduces the detrimental effects of the neuroimmune system.

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# Recreational physical activity ameliorates some of the negative impact of major depression on health-related quality of life

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**Background:** Major depressive episodes have a negative effect on health-related quality of life (HRQoL). The objective of this study was to determine whether recreational physical activity can ameliorate some of this negative impact.

**Methods:** The data source for the study was the Canadian National Population Health Survey (NPHS). The NPHS is a longitudinal study that has collected data from a representative cohort of 15,254 community residents. Sixteen years of follow-up data are available. The NPHS included: an instrument to assess MDE (the Composite International Diagnostic Interview Short Form for Major Depression), an inventory of recreational activities (each associated with hours of participation and estimated metabolic expenditures), and a HRQoL instrument (the Health Utility Index, Mark 3, or HUI3). Proportional hazard and linear regression models were used in this study to determine whether MDE-related declines in HRQoL were lessened by participation in an active recreational lifestyle.

**Results:** Consistent with expectation, major depression was associated with a significant decline in HRQoL over time. While no statistical interactions were observed, the risk of diminished HRQoL in association with MDE was reduced by physical activity. In a proportional hazards model, the hazard ratio for transition to poor HRQoL was 0.7 (95% CI: 0.6–0.8, $p < 0.0001$). In linear regression models, physical activity was significantly associated with more positive HRQoL ($\beta = 0.019$, 95% CI 0.004 to −0.034, $p = 0.02$).

**Conclusion:** Recreational physical activity appears to ameliorate some of the decline in HRQoL seen in association with MDE. Physical activity may be an effective tertiary preventive strategy for this condition.

**Keywords: depressive disorders, quality of life, physical activity, recreation, epidemiologic studies, longitudinal studies**

## INTRODUCTION

Depressive disorders are among the most important contributors to disease burden in developed countries (World Health Organization, 2001; Wittchen et al., 2011). These disorders affect mortality (Wulsin et al., 1999; Lawrence et al., 2010; Patten et al., 2011), but their main impact is through diminished functioning and lower health-related quality of life (HRQoL). The most important depressive disorder, Major Depressive Disorder has an annual prevalence in North America of approximately 5% (Kessler et al., 2003; Patten et al., 2006). As these conditions are so common, effective strategies to reduce their impact will have a substantially positive effect on HRQoL at the population level. Physical activity is a candidate strategy.

It is not difficult to identify mechanisms by which physical activity may have a positive impact on outcomes of depressive disorders. Depressive disorders increase the risks of a variety of chronic physical conditions such as hypertension (Patten et al., 2009), diabetes (Brown et al., 2005), and heart disease (Gilmour, 2008). Physical activity may help to ameliorate these risks. Physical activity may also counteract negative dynamics that can perpetuate depression, such as the emergence of a lifestyle that is lacking in rewarding or enjoyable activity (Hopko et al., 2003). A growing literature has examined the role of exercise in treatment of depression. The clinical trial literature has been summarized in a recent Cochrane Review (Rimer et al., 2012). Only a few studies have examined quality of life as an outcome. Carta et al. reported that the physical subscale of the WHOQOL-Bref improved in a randomized trial among subjects receiving antidepressant treatment and adjunctive exercise, whereas this did not occur in a control group receiving only antidepressant treatment (Carta et al., 2008). Singh et al. also examined quality of life outcomes in a trial of high-intensity progressive resistance training in community dwelling adults >60 years old. Improvements were noted in several Medical Outcomes Study Short Form (SF-36) subscales, although only one of these, vitality, achieved statistical significance (Singh et al., 2005).

To our knowledge, no epidemiologic studies have examined the joint effects of physical activity and major depressive episode (MDE) on quality of life outcomes in major depression. The objective of this study was to examine these effects using a representative general population sample.

## MATERIALS AND METHODS

The data source for this study was a Canadian prospective cohort study called the National Population Health Survey (NPHS) (Swain et al., 1999). This is a longitudinal study based on a nationally representative community sample assembled by Statistics Canada (Canada's national statistical agency) in 1994/1995. Baseline interviews (mostly face to face) were carried out in 1994 and participants were re-interviewed every 2 years subsequently, usually by telephone. Statistics Canada reported a 69.7% rate of successful follow-up at completion of the project in 2010 (Statistics Canada, 2012).

The original NPHS longitudinal cohort included 17,276 participants in total, but the current analysis was restricted to 15,254 respondents who were over the age of 12 at the time of the initial 1994 interview. This subset was further restricted in specific analyses depending on the health transitions of interest to the study. For example, in the component of the analysis concerned with incidence of low HRQoL, those already having low HRQoL at the time of the baseline interview were excluded because they could not be considered at risk of developing this outcome.

The NPHS interview included the Composite International Diagnostic Interview Short Form (CIDI-SF) (Kessler et al., 1998) for Major Depression. This is a brief structured interview designed to identify people with a high probability of past year MDE. The CIDI-SF was developed using data from the National Comorbidity Survey in the US (Kessler et al., 1994), which used the DSM-III-R classification. The instrument consists of a modified subset of CIDI items and is scored using a predictive algorithm. For the current analysis, the 90% predictive cut-point was used. This scoring procedure requires endorsement of five symptom-based criteria (at least one of which must be depressed mood or loss of interest), providing face validity for the DSM-IV definition of MDE.

Each cycle of the NPHS also included items assessing participation in 21 recreational physical activities. Each activity was assigned a metabolic indicator (MET) value (Statistics Canada, 2004) representing an estimated metabolic energy cost (in kilocalories expended per kilogram of body weight per hour) which is expressed as a multiple of the resting metabolic rate. For example, the MET value for playing basketball is six, indicating that people playing basketball expend an estimated six times more energy per hour than people at rest. Daily estimated energy expenditure was then calculated from MET values based on the amount of time spent participating in each specified activity. A total estimated energy expenditure of 1.5 kcal/kg/day was used to categorize respondents into active or inactive categories. This level of activity corresponds approximately to 30 min of walking for exercise per day. The methodological approach to the assessment of leisure time physical activity was developed by the Canadian Fitness and Lifestyle Institute[1].

Health-related quality of life was assessed in the NPHS using the Health Utility Index, Mark 3 (HUI3). The Health Utilities Index (HUI) is a system for measuring HRQoL and for producing preference-weighted health utilities. The HUI3 system was originally developed for the 1990 Ontario Health Survey (Horsman et al., 2003). The HUI covers eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain. Each level of each attribute is associated with an attribute-specific utility score with values ranging from 1.0 (the highest of the five or six options) to zero (the lowest). However, most commonly, the various health states are used to compute a multi-attribute score using a multiplicative multi-attribute algorithm (Feeny et al., 2002). The preference weights used in this algorithm derive from data collected in a survey employing standard gamble methods (Feeny et al., 2002). In the version used by Statistics Canada, perfect HRQoL is associated with an HUI3 score of 1.0, a state equivalent to death is assigned a score of zero and health states of less than zero are viewed as being worse than death. Additional information is available at the instrument's website[2].

Various questionnaires that provide sufficient information to describe health status have been developed for use with the HUI3. The version used by Statistics Canada refers to "usual" experience of various impairments (some other versions use past month or past week ratings). The instrument used by Statistics Canada in its national surveys is called the Comprehensive Health Status Measurement System (CHSMS). This instrument was included in the NPHS. Eight domains are covered by the CHSMS: vision, hearing, speech, mobility, dexterity, emotion, cognition. As noted above, each of the individual health states is assessed at several different levels, which leads to 972,000 possible unique health states, each of which is associated with a HRQoL value.

We were interested in examining associations between major depression, physical activity, and HRQoL from several different perspectives. A commonly employed interpretation of HUI3 data is a nominal one, with scores $<0.70$ being considered indicative of low HRQoL (Horsman et al., 2003). However, it is also of interest to examine uncategorized ratings, so we also treated the HUI3 ratings as a continuous variable in some analyses.

In preliminary descriptive and stratified analyses we confirmed that major depression was associated in the longitudinal data with declines in HRQoL. In order to evaluate effect modification by physical activity, proportional hazards models were used. Because the NPHS collected data at specific time points (every 2 years), grouped time models were used. These models were fit as generalized linear models of the binomial family with a complementary log–log link function. Jenkins (1997) outlines procedures for implementation of such analyses in STATA (Stata Corporation, 2005), the data analysis software used in all analyses reported here. The proportional hazards assumption was evaluated using a likelihood ratio test for time by exposure (major depression, physical activity) interactions.

We extended this analysis to examine changes in HUI3 scores during the NPHS follow-up without categorization. To accomplish this we calculated a change score by subtracting the 2010

[1] http://www.cflri.ca

[2] http://www.healthutilities.com/hui3.htm

HUI3 rating from the 1994 rating. These differences were found to be normally distributed, so we were able to use linear regression to model these changes in terms of MDE and physical activity during the intervening cycles.

The target population for the NPHS consisted of household residents. Residents of institutions, certain remote areas, Indian reserves and the Armed Forces were excluded from the sampling frame. The NPHS used a multi-stage sampling procedure that resulted in unequal selection probabilities and clustering. To correct for these design effects, Statistics Canada recommends a bootstrap procedure that uses a set of 500 replicate sampling weights. The NPHS sampling weights also include a non-response adjustment. Respondents who were lost to follow-up, died, or were institutionalized were censored in the analysis. This project was approved by the University of Calgary Ethics Review Board.

## RESULTS

**Table 1** presents a description of the study sample. Demographic characteristics of the full baseline sample are presented, but also for those below the cut-point of 0.7 and those at or exceeding this threshold. The Table shows that 13% of the sample already had low HRQoL at their baseline time point. This group was older, more likely to be female, more likely to be divorced, widowed, or separated and more likely to have low education. They were also more likely to be depressed and more likely to be physically inactive.

We initially focused on the 12,398 respondents that did not have low HRQoL at baseline, and were therefore at risk of making this transition during follow-up (see the right-hand column in **Table 1**). We modeled their risk of developing low HRQoL during follow-up based on their MDE and physical activity status, each of which were allowed to vary with time during follow-up. Among those who were active, there was a diminished risk of transition into the low HRQoL group during NPHS follow-up (HR = 0.7, 95% CI: 0.6–0.8). Those with MDE had an elevated risk of this transition (HR = 2.3, 95% CI: 1.8–2.8). When both variables were included in a single model along with an interaction term, the HR associated with that interaction term was 1.1 (95% CI 0.7–1.8), which was non-significant according to a Wald test ($p = 0.57$). As this is a multiplicative model, the lack of an interaction suggests that physical inactivity and major depression have a multiplicative relationship – recreational physical activity diminishes the risk of transition to low HRQoL to about 70% of what it would have been in view of the strongly negative effects of MDE.

Another way to examine these results is to code the physical activity variable such that it represents physical inactivity rather than activity. Coded this way the hazard ratio for physical inactivity was 1.4 (95% CI 1.3–1.6), indicating that inactivity increases the risk of transition to low QoL by about 40%.

Additional covariates were explored in the modeling, including: age; sex; divorced, widowed, or separated marital status; and low (less than secondary level) educational attainment. These variables (except sex) all predicted low HRQoL during follow-up, but none of them confounded the opposing associations of major depression and physical activity with low HRQoL. A model that included each of these variables simultaneously along with a major depression by physical inactivity interaction term resulted in a non-significant interaction (HR = 1.1, 95% CI 0.7–1.8), $p = 0.60$. This model, with removal of the interaction term, is presented in **Table 2**. The adjusted HR for physical activity was nearly unchanged in this analysis (HR = 0.8, 95% CI 0.7–0.9).

As explained above, we also explored HUI3 as an uncategorized variable by examining the difference between baseline and end-point ratings. In this analysis, a slight negative change of 1.5% ($\alpha = -0.015$, 95% CI −0.02 to −0.01, $p < 0.0001$) was observed in respondents without MDE, apparently representing a slight age-related decline over the 16 years of follow-up. There was a significantly greater decline in those with MDE: 4% ($\beta = -0.025$, 95% CI −0.05 to −0.002, $p = 0.028$). Variables also associated with more rapid decline in HRQoL were explored by including them initially one at a time in a series of linear regression models. Female sex was associated with a more rapid decline in HRQoL ($\beta = -0.017$, 95% CI −0.02 to −0.004, $p = 0.008$). Age at baseline, which was treated as a continuous variable, was also associated with diminishing HRQoL ($\beta = -0.002$, 95% CI −0.003 to −0.002, $p < 0.0001$). Educational status and marital status were not significantly associated with change in HRQoL.

**Table 1 | Demographic features of study sample (NPHS) at baseline (1994).**

| | | NPHS; *N* = 15,254 [% (95% CI)] | HUI < 0.7; *N* = 2,250* [% (95% CI)] | HUI ≥ 0.7; *N* = 12,398* [% (95% CI)] |
|---|---|---|---|---|
| Gender | Male | 49.2 (49.1–49.2) | 42.9 (40.4–45.4) | 49.4 (49.0–49.9) |
| | Female | 50.8 (50.8–50.9) | 57.1 (54.6–59.6) | 50.6 (50.1–51.0) |
| Age (mean) | | 40.9 (40.8–41.0) | 49.7 (48.7–50.7) | 39.5 (39.2–39.7) |
| Marital status | Married/common law | 59.0 (58.2–59.7) | 54.6 (51.8–57.4) | 59.3 (58.4–60.2) |
| | Single | 28.9 (28.3–29.6) | 23.0 (20.6–25.4) | 30.1 (29.4–30.9) |
| | Widowed/separated/divorced | 12.1 (11.6–12.6) | 22.4 (20.3–24.4) | 10.6 (10.0–11.1) |
| Education | Less than secondary or secondary school graduation | 48.2 (47.2–49.3) | 57.5 (54.7–60.3) | 46.7 (45.6–47.8) |
| | Some post-secondary or post-secondary graduation | 51.8 (50.7–52.8) | 42.5 (39.7–45.3) | 53.3 (52.2–54.4) |
| Depressed | Yes | 5.6 (5.1–9.1) | 14.1 (12.1–16.0) | 4.3 (3.8–4.7) |
| | No | 94.4 (93.9–94.9) | 85.9 (84.0–87.9) | 95.7 (95.3–96.2) |
| Physically active | Yes | 41.6 (40.5–42.7) | 32.7 (29.8–35.5) | 43.1 (41.8–44.3) |
| | No | 58.4 (57.3–59.5) | 67.3 (64.5–70.2) | 56.9 (55.7–58.2) |

**The weighted proportion in the low HRQoL group at baseline was 13.4%, with 86.6% in the remaining "at risk" sample.*

In a separate analysis we identified respondents that were persistently physically active during follow-up (rather than treating this as a time-varying characteristic) and evaluated interactions between physical activity and MDE in another linear regression model. As with the previous analysis, a cross-product interaction term for depression and physical activity was not significant ($\beta = -0.014$, 95% CI −0.072 to 0.043, $p = 0.62$). When this variable was removed from the model the effect of MDE remained negative ($\beta = -0.024$, 95% CI −0.046 to −0.011, $p = 0.04$) and physical activity became associated with a significantly positive impact on HRQoL ($\beta = 0.019$, 95% CI 0.004 to −0.034, $p = 0.02$).

In a model containing the covariates listed in **Table 1**, the interaction term remained non-significant, as did marital status, sex, and education. Fitted values from a linear regression model including MDE, physical activity, and age are presented in **Figure 1**. The parallel nature of the regression lines reflects the removal of the non-significant interaction term from the model. Changes in HRQoL are positive in the youngest ages and then become negative at older ages. MDE is association with more negative changes, whereas this is partially offset by persistent physical activity.

In a final model, we categorized physical activity at two levels, sometimes physically active (i.e., in one or more of the 1–5 intervening NPHS cycles) or persistently physically active. After adjustment for age, which was again the only significant predictor of HRQoL changes, being sometimes physically active was associated with a small and non-significant positive effect ($\beta = 0.011$, 95% CI −0.009 to 0.033, $p = 0.27$), whereas the effect of persistent physical activity remained significant in this analysis ($\beta = 0.027$, 95% CI 0.003–0.050, $p = 0.03$).

**Table 2 | Proportional hazards model predicting HRQoL < 0.7 in the NPHS.**

| Variable | | HR (95% CI) | *p*-Value |
|---|---|---|---|
| Physical activity | | 0.8 (0.7–0.9) | $p < 0.001$ |
| Major depression | | 2.9 (2.3–3.7) | $p < 0.001$ |
| Female sex | | 1.1 (1.0–1.2) | $p = 0.25$ |
| Age* | | 1.0 (1.0–1.0) | $p < 0.001$ |
| Marital status | Single | 1.4 (1.2–1.6) | $p < 0.001$ |
| | Divorced, widowed, separated | 1.3 (1.1–1. 4) | $p = 0.001$ |
| Education < secondary level | | 1.4 (1.3–1.6) | $p < 0.001$ |

**Age was treated as a continuous variable in this analysis. The unrounded HR was 1.03, indicating a 3% increase in risk of the transition to low HRQoL with each increasing year of age.*

## DISCUSSION

There has been much discussion in the literature about the role of physical activity as a treatment or clinical management strategy for depression. A recent Cochrane review concluded that the evidence from high quality studies is generally positive, but that the effect on depression was small (Rimer et al., 2012). A possibility that has received much less attention is the possibility that participation in physically active recreational activities may lead to better quality of life outcomes. The epidemiologic data presented here suggests that it does.

There are several mechanisms that may explain this association. When people become depressed they often diminish their participation in recreational activities due to the anhedonia and

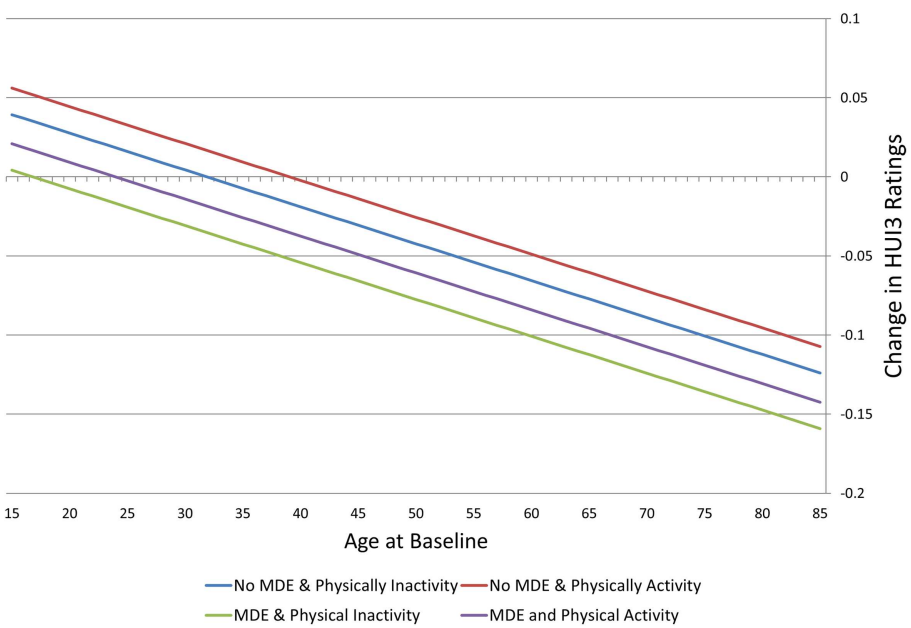


**FIGURE 1 | Linear regression model for change in HRQoL.**

fatigue that often accompanies depressive disorders. This may lead to lifestyle changes that become habitual and do not recover after the episode. On the other hand, people that maintain their participation in physical activity may derive benefits from this. Many other mechanisms are possible. For example, chronic disease incidence is elevated in MDE, and as chronic conditions are likely to contribute to declining HRQoL, physical activity may protect against declining HRQoL by diminishing chronic disease incidence. It should be acknowledged, however, that once a medical condition emerges participation in physical activity may be affected by that condition. Whereas it may appear that HRQoL declined to a greater extent as a result of MDE combined with physical inactivity, in reality the physical inactivity may have resulted from some other factor (such as an emerging medical condition) having a subsequent effect on HRQoL.

One of the limitations of the epidemiological data source used in this is study is that the interviews were spaced 2 years apart. As a result, the exact timing of changes within NPHS cycles cannot be discerned. For this reason, temporal relationships between depressive episodes, physical activity, associated factors such as medical conditions, and HRQoL changes cannot be clarified with certainty. It is therefore prudent to regard the findings as being suggestive, but not confirmatory, of a causal effect. Randomized controlled trials provide an appropriate vehicle for confirming these results. Future trials of exercise in MDE should including HRQoL measures in their assessment of outcome.

This study has several additional limitations. One is that the epidemiologic data set employed in the analysis was a general health survey that did not include sophisticated assessments either of MDE or of physical fitness. Instead, there was a reliance on abbreviated survey instruments to measure these variables. A related limitation is that it was not possible to make detailed adjustments for confounding variables, except for some fairly basic demographic variables. If replicated, however, these results highlight the potential of physical activity to diminish some of the negative impact of depressive disorders. This is potentially a valuable avenue for reducing the burden of depressive disorders on population health.

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# Is exercise an efficacious treatment for depression? A comment upon recent negative findings

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Exercise is receiving substantial and increasing attention as a potential treatment for depression. Despite the many positive meta-analytical findings and recommendations of some guidelines to incorporate exercise as a treatment for depression (National Institute for Health and Clinical Excellence, 2009), most clinical trials have significant methodological flaws that limit the generalizability of their findings (Daley, 2008; Rethorst et al., 2009). Furthermore, recent meta-analyses show that, when only robust clinical trials are included, the effects of exercise are "moderate at best" or statistically insignificant (Rimer et al., 2012).

Similarly, four recent, robust, randomized controlled trials (RCTs) have failed to find any antidepressant effects of exercise: the DEMO (Krogh et al., 2009), DEMO II (Krogh et al., 2012), TReatment with Exercise Augmentation for Depression (TREAD) (Trivedi et al., 2011), and TREAD-UK (Chalder et al., 2012). The DEMO trial (Krogh et al., 2009) compared aerobic exercise, anaerobic exercise, and relaxation (control) groups; after 4 months of intervention, no differences in depressive symptoms, as assessed by the Hamilton scale for depression (HAM-D17) (Hamilton, 1967), were found between the groups. Subsequently, the DEMO II trial (Krogh et al., 2012) compared aerobic exercise and stretching (control) groups; after 3 months, the authors found reductions in HAM-D17 scores in both groups but failed to find differences between the groups. In both studies, the authors concluded that exercise was as effective as placebo and had no biological antidepressant effects.

Corroborating the DEMO and DEMO II findings, the TREAD (Trivedi et al., 2011) found a non-significant trend ($p < 0.06$) toward a remission rate of 16 kcal/kg/week for aerobic exercise versus 4 kcal/kg/week for aerobic exercise (control) after 3 months of intervention. Lastly, the TREAting Depression with physical activity (TREAD-UK) (Chalder et al., 2012) evaluated the cost-effectiveness of a strategy for promoting and increasing the physical activity levels of depressed patients in primary care. After 8 months, physical activity was shown to be an ineffective and more costly strategy than conventional primary care assistance and resulted in a non-cost-effective strategy according to willingness-to-pay thresholds.

Considering these recent results, the answer to the question "is exercise an efficacious treatment for depression?" appears to be "No." However, before this question is answered, some issues must be highlighted.

Similar to the findings regarding exercise, several meta-analyses have shown that the benefits of antidepressants are "minimal or non-existent," as they are as effective as placebo. Other meta-analyses have shown that antidepressants are effective only in severe, but not in moderate or mild depression (Kirsch et al., 2008; Fournier et al., 2010; Khan et al., 2012). On the other hand, clinical practice and some qualitative studies have revealed that both exercise and antidepressants are effective in the opinion of patients (Searle et al., 2011) and mental health professionals (Martinsen, 1994; Kirsch, 2008); these findings reveal a discrepancy between the views of health professionals and patients and the clinical findings.

There are some possible explanations for this discrepancy: (1) the heterogeneity of "depression" as a construct; (2) the psychometric pitfalls of depression assessment scales; and (3) the possible interference of unspecific factors that could mask the biological effects of exercise.

Parker (2005) argued that the "major depression" concept classifies a heterogeneous group of patients who may have different, and sometimes opposite, clinical features and symptoms (e.g., insomnia or hypersomnia, weight loss or weight gain, and psychomotor retardation or psychomotor agitation) into on diagnosis. In the words of Parker, the major depression construct "circumscribes a range of heterogeneous conditions, homogenizes them, and has come to be viewed as an entity." This quote exemplifies the diagnoses of individuals with "clinical dyspnea" because such diagnoses are not informative because the individual may have asthma, pneumonia, or a pulmonary embolus, and each condition requires a different treatment. Similarly, major depression may need a more finely focused diagnosis that requires greater explanatory power. The proposal of Parker is a new categorical-dimensional model that classifies three more finely focused diagnostic subgroups: psychotic depression, melancholic depression, and non-melancholic depression; these subgroups possibly have different biological backgrounds and may be responsive to different treatments. For more detailed information, see Parker's works concerning a new categorical-dimensional construct of depression.

Another possible explanation for this discrepancy may be the low "effectivity" of the HAM-D17, which is the most used instrument in RCTs and was used in three of the recent studies of exercise (DEMO, DEMO II, and TREAD). Some studies have shown that this scale has several flaws, as assessed by classical (Bagby et al., 2004; Fleck et al., 2004) and modern psychometric techniques, including Item response theory and Rasch analyses (Bagby et al., 2004). Based upon these studies, the HAM-D17 lacks unidimensionality; furthermore, some items appear to be insufficiently discriminative of different levels of depression, particularly within the mild and moderate levels, although the HAM-D17s work for severe

levels of depression (Santor and Coyne, 2001). According Salum et al. (2011), the HAM-D17 is like an "industrial thermometer being used to measure a temperature of a baby." Interestingly, antidepressants have higher efficacy in severe, compared to low or moderate, depression (Kirsch et al., 2008; Fournier et al., 2010). Furthermore, some preliminary results show that exercise is also effective as a complementary treatment of severely depressed inpatients (Knubben et al., 2007; Schuch et al., 2011).

Finally, exercise has many factors that "compose" the exercise session but are not exercise *per se*. For example, when a patient exercises in a group setting, or even in the company of health professionals, the resultant social support and attention may have an important role, especially in light depression. A similar effect occurs in structured psychotherapies studies, in which non-structured interventions (placebos) efficacies similar to structured interventions (Jakobsen et al., 2011).

Before a final judgment is made, clinical trials using exercise as a treatment for depression must be carefully analyzed. Furthermore, meta-analyses show that exercise has similar efficacy as other standardized treatments for depression including some antidepressants and some psychotherapies. Thus, exercise may not be more efficacious than conventional treatments; however, it is not less efficacious.

On the other hand, exercise has other issues that deserve more attention: the initial acceptance and compliance/adherence. Two of the major difficulties of the use of exercise as a treatment for depressed patients are the initial acceptance of and compliance/adherence to exercise regimens. For example, two weaknesses of the DEMO II trial are the limited number of patients included and the low compliance with the exercise sessions.

In the DEMO trial, of 390 possible patients recruited, 100 refused to participate. In the DEMO II trial, the patients' inclusion had to stop due to "lower referral than anticipated." Second, the authors' initial sample size tests showed that 85 subjects in each group were necessary, but after the recruitment phase and an additional 12 months of recruitment, they had just 56 subjects in the aerobic exercise group and 59 in the stretching group. Lastly, in our study (unpublished data), 46 of 96 severely depressed inpatients refused to participate in the study, and, of these 46, 40 stated they had low interest in exercise.

Moreover, the in DEMO II trial, patients attended a mean 13.5 and 12.5 of 36 sessions of aerobic exercise and stretching, respectively. In an attempt to increase adherence/compliance, Trivedi et al. (2006b) suggested that a more flexible program based upon energetic expenditure, without a fixed intensity (e.g., 70% maximum heart rate), may be more suitable and increase compliance. For example, in the DOSE study (Trivedi et al., 2006a), patients in the exercise groups completed 72% of the sessions. In another recent study, Callaghan et al. (2011) showed that women that exercised "as recommended by national guidelines" attended 6 of 12 sessions (50%), while the group that had exercised at the "preferred intensity" attended 8 of 12 sessions (66%), resulting in a mean increase of 2/12 sessions. In the TREAD (Trivedi et al., 2011) study, the low and high dose groups had mean adherences of 99.4 and 63.8%, respectively. These three studies show that more flexible strategies may be an interesting alternative that may increase adherence and compliance compared to conventional strategies (e.g., 30 min at 70% of maximal heart rate).

Two interesting papers propose some practical suggestions to initiate and sustain exercise and physical activity in depressed patients. One is a paper from Seime and Vickers (2006) that suggests some practical strategies including the following: promote discussions related to what activities "would benefit your patient most based upon his/her symptoms" in terms of pre-preferences and personal barriers that prevent the patient from beginning or maintaining exercise, and share with patients an easily accessible brief overview of recommendations for physical activity that could include the guideline recommendations for public health and the dose-response relationship demonstrated by Dunn et al. (2005). Moreover, Blumenthal et al. (2012) suggested that exercise professionals should become more familiar with the principles of motivational interviewing, a well-researched approach to promoting behavioral change, and the "seven tips" for patients.

In summary, recent negative findings concerning the use of exercise as a treatment for depressed patients must be interpreted with caution. Exercise, along with other treatments for depression, has some issues because the instrument used to assess depression and the diagnoses of depression may lead to misunderstandings. Thus, the DSM-V will most likely open new perspectives concerning diagnoses of depression, and subsequently, the instruments used to assess depression. Although the initial adherence and compliance with exercise programs are a great challenge, the use of cognitive and motivational approaches and more flexible and comprehensive strategies of exercise may be useful in increasing and maintaining a the exercise of depressed patients.

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# Effects of exercise and physical activity on anxiety

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## INTRODUCTION

The beneficial effects of regular physical activity on health are indisputable in the field of modern medicine. Exercise is often the first step in lifestyle modifications for the prevention and management of chronic diseases. According to a US Department of Health and Human Services report on physical activity, regular exercise significantly reduced causes of mortality by up to 30% for men and women (DHHS, 2002). These health benefits are seen consistently across all age groups and racial/ethnic categories. The Centers for Disease Control and Prevention currently recommends 30 min of moderate- to high-intensity exercise for at least 5 days a week for all healthy individuals (DHHS, 2002).

In addition to significantly lowering causes of mortality, regular exercise and physical activity lowers prevalence of chronic disease(s). There is a strong evidence to support that 2–2.5 h of moderate- to high-intensity exercise per week is sufficient to reduce one's risk for the occurrence of a chronic disease(s). Numerous epidemiological studies have shown that exercise improves one's self-esteem, and a sense of wellbeing. Individuals who exercise regularly exhibit slower rates of age-related memory and cognitive decline in comparison to those who are more sedentary. Such observations have provided the basis for using exercise to improve memory and cognition in cognitive disorders such as Alzheimer's Dementia. Adults who engage in regular physical activity experience fewer depressive and anxiety symptoms, thus supporting the notion that exercise offers a protective effect against the development of mental disorders (van Minnen et al., 2010).

Anxiety disorders are common psychiatric conditions with a lifetime prevalence of nearly 29% in the United States (Kessler et al., 2005). These disorders are chronic, debilitating, and impact multiple aspects of one's life. The economic burden of anxiety disorders in the US was estimated to be $42.3 billion in the 1990s (Greenberg et al., 1999). The prominent anxiety disorders defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are General Anxiety Disorder (GAD), Panic Disorder (PD), Posttraumatic Stress Disorder (PTSD), Obsessive Compulsive Disorder (OCD), Social Anxiety Disorder, and Specific Phobia (APA, 2000). The exact etiology and pathophysiology of these conditions is not fully understood. Comprehending the effects of exercise and physical activity on the mechanisms of anxiety disorders might further our knowledge of these psychiatric disorders. The purpose of this article is to highlight the known and emerging mechanisms that may result in the anxiolytic effects of exercise.

## PHYSIOLOGICAL MECHANISMS

Broadly, regular exercise results in physiological changes and adaptations in the human body. Studies have shown that regular aerobic exercise is associated with lower sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis reactivity (Crews and Landers, 1987; Åstrand, 2003; Jackson and Dishman, 2006; Rimmele et al., 2007).

## HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

The HPA axis plays a critical role in developing adaptive responses to physical and psychological stressors (De Kloet et al., 2005). Dysregulations in the HPA axis have long been implicated in the manifestations of depressive and anxiety symptoms (Landgraf et al., 1999; Steckler et al., 1999). Acute stress leads to alterations in adrenocorticotropic hormone (ACTH) and excess levels of glucocorticoids. Chronic stress, as seen in PTSD, has been associated with lower concentrations of peripheral cortisol and upregulation of the glucocorticoid receptors resulting in increased central feedback sensitivity. Depending on the experimental paradigm used for chronic stress, some studies have shown decreased plasma ACTH and corticosterone levels while other studies have shown increased corticosterone secretion (Irwin et al., 1986; Kant et al., 1987). In preclinical studies, voluntary exercise alters the releases of corticotrophin-releasing factor (CRF) from the hypothalamus and ACTH from the anterior pituitary (Salmon, 2001; Droste et al., 2003). These findings suggest that exercise induced changes in the HPA axis modulates stress reactivity and anxiety in humans.

## MONOAMINE SYSTEM

Abnormalities in monoamine function in the brain have been implicated in the pathophysiology of anxiety spectrum disorders. In animal studies, learned helplessness resulting from chronic electric shock was associated with a reduced release of serotonin in the frontal cortex (Miller et al., 1975; Petty et al., 1992). Learned helplessness is also associated with a depletion of norepinephrine (Petty et al., 1993). It is postulated that the reductions in serotonergic and noradrenergic levels reflects synthesis not being able to keep up with demand (Charney et al., 2004). Animal models also provide evidence that regular aerobic exercise increases serotonergic and noradrenergic levels in the brain, similar to the effects of antidepressants (Praag, 1982; Veale, 1987; Chaouloff, 1989; Meeusen and De Meirleir, 1995). Researchers have observed increased extraneuronal uptake of norepinephrine and increased levels of norepinephrine in the hippocampus and frontal cortex of rodents after treadmill training and wheel running (Dunn et al., 1996; Dishman, 1997). Increases in serotonin

synthesis, metabolism, and release have been noted following exercise (Dunn and Dishman, 1991; Meeusen and De Meirleir, 1995; Wilson and Marsden, 1996; Chaouloff, 1997). Animal models utilizing chronic voluntary wheel running have also shown small increases in serotonergic neural activity in the dorsal raphe nucleus, an area of brain that is abundant in serotonergic neurons, during uncontrollable stress (Greenwood et al., 2003). Treadmill exercise training also increases levels of prepro-galanin mRNA, suggesting that gene expression for galanin is sensitive to the stress from exercise training and may have a "neuromodulating role" in the noradrenergic response in the locus ceruleus, an area of brain rich in noradrenergic neurons (O'Neal et al., 2001).

## OPIOID SYSTEM

Another possible mechanism for the anxiolytic effects of exercise is via mediation by the endogenous opioid system. Endogenous opioids have a role in the regulation of mood and emotional responses (Bodnar and Klein, 2005). For example, abnormal levels of both central and peripheral β-endorphins have been discovered in individuals diagnosed with depression (Scarone et al., 1990; Darko et al., 1992). The endorphin hypothesis posits that the mood elevations and reduced anxiety following acute exercise is due to the release and binding of β-endorphins (endogenous opioids) to their receptor sites in the brain. Studies demonstrate that exercise increases endogenous opioid activity in the central and peripheral nervous system and may induce a euphoric state and reduce pain (Harber and Sutton, 1984; Morgan, 1985; North et al., 1990; Thorén et al., 1990). When opioid antagonists were administered following regular exercise, the endorphin produced analgesic effects were attenuated, but there were no changes in the mental health benefits suggesting that the exercise-related surge in endorphins may not completely account for mental health benefits in these studies (Carr et al., 1981; Moore, 1982; Howlett et al., 1984; Thorén et al., 1990; Yeung, 1996).

## NEUROTROPIC FACTORS

Brain-derived neurotrophic factor (BDNF), the most abundant neurotrophin in the brain has been linked to both anxiety and depression. Stress-induced depressive and anxious behaviors are correlated with decreased BDNF levels especially in the hippocampus (Duman and Monteggia, 2006). Furthermore, infusions of BDNF into the dorsal raphe nucleus have been shown to have an a antidepressant effect (Altar, 1999). Evidence also suggests that BDNF may be a mediator of the anxiety reducing effects of antidepressant medications (Chen et al., 2006). Increases in BDNF following physical activity have also been observed. Following 20 days of voluntary wheel running compared to non-wheel running rats, BDNF mRNA levels increased in the hippocampus and caudal neocortex (Meeusen and De Meirleir, 1995; Russo-Neustadt et al., 1999). These changes in BDNF increases functioning in the serotonergic system and may promote neuronal growth (Altar, 1999).

## EVIDENCE FOR NEUROGENESIS

New neuronal growth in the adult brain, particularly in the hippocampus, has been implicated in the treatment of psychiatric conditions including depression and anxiety (Eisch, 2002). Detection and evaluation of hippocampal neurogenesis is an active area of investigation in recent years (Eisch, 2002). In primate models of chronic stress, the hippocampus has been shown to be highly sensitive to the toxic effects of excessive glucocorticoids, thus impairing the process of neurogenesis (Uno et al., 1989). Neuroplasticity is further supported by the stress-related changes found in studies of hippocampus function. Animal studies have shown exercise up regulates hippocampal neurogenesis (Duman et al., 2001). Exercise is also believed to positively influence surrogate measures of adult hippocampal neurogenesis such as β-endorphins, vascular endothelial growth factor, BDNF, and serotonin, all of which are thought be common pathophysiologic mechanisms for anxiety disorders.

## PSYCHOLOGICAL MECHANISMS

### ANXIETY SENSITIVITY AND EXPOSURE

Anxiety sensitivity is a term for the tendency to misinterpret and catastrophize anxiety-related sensations based on the belief that they will result in disastrous physical, psychological, and/or social outcomes (Broman-Fulks and Storey, 2008; Smits et al., 2008). McWilliams and Asmundson (2001) found an inverse relationship between anxiety sensitivity and exercise frequency and suggested that this relationship was due to avoidance of the physiological sensations of exercise that may be interpreted as anxiety and panic. A number of research studies have pointed to the effectiveness of short-term aerobic exercise to reduce anxiety sensitivity (Broman-Fulks and Storey, 2008; Smits et al., 2008; Ströhle et al., 2009). Exposing someone with high anxiety sensitivity to the physiological symptoms they fear, such as rapid heartbeat, in the context of physical exercise increases their tolerance for such symptoms (McWilliams and Asmundson, 2001). This exposure reveals that the feared physiological sensations may be uncomfortable, but do not pose a serious threat (Ströhle et al., 2009). Repeated exposures through regular aerobic exercise may also facilitate habituation to the feared sensations (Beck and Shipherd, 1997).

### SELF-EFFICACY

According to social cognitive theory, one's sense of self-efficacy regarding their ability to exert control over potential threats has an important relationship to anxiety arousal. Individuals who trust their ability to manage potential threats (high self-efficacy) are not plagued by thoughts of worry and experience lower levels of anxiety arousal. Based on the theory of self-efficacy, Bandura posited that a treatment will be successful if it is able to rebuild a sense of self-efficacy by supplying experiences of self-mastery. It has been debated that exercise can increase self-efficacy by supplying experiences of successfully coping with the stress of exercising (Petruzzello et al., 1991). As fitness improves, the individual receives feedback of greater endurance, less pain, greater duration capabilities, etc. As a result, self-efficacy should increase (Petruzzello et al., 1991). In fact, one study suggested that exercise with an emphasis on increasing self-efficacy, in this case, martial arts, was more effective in reducing state anxiety than exercise such as riding a stationary bike (Bodin and Martinsen, 2004). In a study examining the relationship between exercise intensity and self-efficacy effects on anxiety reduction in a non-clinical population, researchers found that the influence of self-efficacy on decreased anxiety was exhibited in the moderate intensity exercise group, but not in the light- and high-intensity exercise groups (Katula et al., 1999). These two studies suggest that exercise providing an optimal level of challenge best utilizes the power of self-efficacy.

### DISTRACTION

Distraction or "time out" has been proposed as another reason why exercise is effective at reducing anxiety. Based on their study that found that distraction techniques such as meditation, and quiet rest were as effective as a single session of exercise in reducing state anxiety, Bahrke and Morgan (1978) suggested that the anxiolytic benefits of exercise may result from it being a distraction from stressors and a "time out" from daily activities. The results of meta-analyses supporting this hypothesis are mixed. Exercise and cognitively based distraction techniques were shown to have equal effectiveness at reducing state anxiety, however exercise was more effective in reducing trait anxiety (Petruzzello et al., 1991). In addition, the anxiolytic effects of exercise have been shown to last for a longer period of time than those produced by therapies based on distraction techniques (Raglin and Morgan, 1985).

## CONCLUSION

There is strong evidence from animal studies that exercise and regular activity positively impacts the pathophysiological processes of anxiety. Numerous studies and meta-analyses show that exercise is also associated with reduced anxiety in clinical settings. Similar to the heterogenic nature of the anxiety, no single mechanism sufficiently accounts for the anxiolytic nature of exercise. Physical activity positively impacts a number of biological, as well as psychological, mechanisms. The role of exercise in the enhancement of neurogenesis in humans has drawn significant attention in recent years and its implications for anxiety disorders are an exciting area of investigation. Future studies are needed to further this type of work, as well as studies specifically exploring clinical applications of exercise in anxiety disorders.

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REVIEW ARTICLE
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# Meditative movement for depression and anxiety

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This review focuses on Meditative Movement (MM) and its effects on anxiety, depression, and other affective states. MM is a term identifying forms of exercise that use movement in conjunction with meditative attention to body sensations, including proprioception, interoception, and kinesthesis. MM includes the traditional Chinese methods of Qigong (Chi Kung) and Taijiquan (Tai Chi), some forms of Yoga, and other Asian practices, as well as Western Somatic practices; however this review focuses primarily on Qigong and Taijiquan. We clarify the differences between MM and conventional exercise, present descriptions of several of the key methodologies of MM, and suggest how research into these practices may be approached in a systematic way. We also present evidence for possible mechanisms of the effects of MM on affective states, including the roles of posture, rhythm, coherent breathing, and the involvement of specific cortical and subcortical structures. We survey research outcomes summarized in reviews published since 2007. Results suggest that MM may be at least as effective as conventional exercise or other interventions in ameliorating anxiety and depression; however, study quality is generally poor and there are many confounding factors. This makes it difficult to draw definitive conclusions at this time. We suggest, however, that more research is warranted, and we offer specific suggestions for ensuring high-quality and productive future studies.

**Keywords: Qigong, Chi Kung, Taijiquan, Tai Chi, exercise, basal ganglia, default mode network, interoception**

## INTRODUCTION

While both exercise and meditation have been acknowledged as having health benefits, the category of exercise that combines meditative focus with movement is often ignored or misunderstood. As a class of exercise it lacks a broadly accepted name. We refer to the group of practices including the traditional Chinese practices of Taijiquan (1), Qigong (2), and Hatha (postural) Yoga (3), as well as Western methods such as the Alexander Technique (4) and Feldenkrais (5). It has been proposed that this form of exercise be called "Meditative Movement" (MM), which is defined by Larkey et al. as a practice involving movement, a meditative state of mind, attention to the breath, and deep relaxation (6). We will use the designation MM except when referring to a specific discipline.

We address MM because of the proliferation of publications, some scholarly, some in the popular press, that claim physical or psychological benefit from one or more of these practices, including reduced anxiety and depression, a more positive affective state, greater calmness of mind, greater physical relaxation, improved general health, better balance, lower blood pressure (BP), and improved biomarkers for inflammation and immune function [such as C-reactive protein (CRP) and cortisol] (7–13).

Conventional exercise has been shown to improve depression and anxiety (14, 15), but it is not clear whether these results also apply to MM, or whether the mechanisms of MM are similar or different to those of conventional exercise. Likewise there is a substantial body of literature on (seated) meditation; it is likely MM shares many of the same mechanisms as meditation, but they are distinct practices. The objective of this review is to define MM and to clarify how it differs from conventional exercise and from seated meditation, to examine the evidence for its ability to ameliorate depression and anxiety, and to suggest possible mechanisms for these effects.

## METHODS

To gather preliminary information for the survey of the current state of research into the effects of MM on anxiety and depression, we performed searches in PubMed, Ovid, and Google Scholar, using the key words Qigong, Taijiquan, Tai Chi, Chi Kung, exercise, Yoga, mindful, movement, meditative, meditation, Somatics, Alexander Technique, and Feldenkrais, combining these terms with psychological, health, psychosocial, stress, well-being, depression, and anxiety. We confined our search to publications in English, and prioritized reviews later than 2006. We found 14 review papers focusing solely or substantially on MM in relation to anxiety or depression (16–29), all of them relating to meditation, Yoga, Qigong, and/or Taijiquan, and used these as our principal source of information. In some cases we included general reviews of MM as long as they included a substantial focus on affective states (18, 19, 29).

For the purpose of this study we excluded Yoga, as well as studies focusing solely on seated meditation. Due to the many systems covered by the word "Yoga" (explained in, see Yoga below) we chose to substantially limit our use of studies of Yoga. Future studies of MM could include Yoga as long as care is taken to separate the more

religious or philosophical aspects from the MM components and to examine carefully the specific techniques to determine whether they meet the definition of MM. We also chose not to explore the literature on seated meditation in detail, except in specific cases where it directly illuminates MM, for the reasons explained in Section "Seated Meditation." Some academic reviews of MM practices have, however, included seated meditation (16, 30). The traditional Chinese practices of Taijiquan and Qigong conform well to the proposed definition of MM (6), therefore our study focuses principally on them.

We found no relevant reviews of Somatics, Feldenkrais, or Alexander Technique. For further information on aspects of MM not mentioned in the scientific literature, we relied on the authors' extensive libraries of books and articles on the subject, supplemented when necessary by searches on Amazon.com and the Library of Congress.

Limitations of these methods were that we did not include reviews in languages other than English; however, because several of the reviews we included did not have this limitation, we nevertheless were able to take into account much of the work published in China and Korea. We were however unable to access directly research papers in languages other than English, which is a significant limitation of this study. Also, we focused mainly on Qigong and Taijiquan, excluding the literature on Yoga and much of the literature on meditation for the reasons explained above. A deeper investigation of the specific nature of the techniques of Yoga and meditation studied in specific papers might allow a more inclusive approach in the future, and might lead to changes in the definition of MM. In addition we chose not to search for every possible kind of practice that might be a form of MM. Some initial exploration found no relevant references in the scientific literature to several names of Somatics or Asian MM systems (for example, Alexander Technique, Feldenkrais, Baguazhang), and we concluded that continuing this search would be unfruitful and would take too much time, besides necessarily being incomplete as the authors are not familiar with all forms of practice that might be considered MM. Nevertheless, this is an acknowledged limitation of this study. A more thorough search using more terms might well discover more information of value.

## DEFINING THE TERMS

"Qigong" and "Taijiquan" often appear in Western literature with multiple spellings. There are two systems of transliteration, the earlier Wade–Giles system, and the contemporary (and official) Pinyin. By way of introducing these alternative spellings, we will use the Pinyin form, with the Wade–Giles and other alternate spellings in parentheses, and a phonetic approximation in italics in our definitions below.

### QIGONG

"Qi" (Ch'i, *chee*) means "life energy" or "breath." It is a core concept throughout Chinese culture. "Qigong" (Ch'i Kung, Chi Kung, *chee goong*) means "work on the life energy," and is a broad term including methods that simultaneously "regulate the body, the breath, and the mind" (1). There are four main branches of Qigong: health-maintenance Qigong, medical Qigong, martial Qigong, and spiritual Qigong; all share the same basics, but use different techniques relevant to their specific aims.

### TAIJIQUAN

Taijiquan (T'ai Chi Ch'uan, Tai Chi Chuan, Tai Chi, *tie jee chwahn*) is a Chinese martial art based on the same principles as Qigong; basic or modified Taijiquan is also used as a health and meditative exercise. Opinions differ as to whether Taijiquan should be regarded as a form of Qigong or as a separate category (16, 30); here, we consider both Qigong and Taijiquan as forms of MM.

### SEATED MEDITATION

Seated meditation uses a mostly static posture, and involves the exploration of various mental states. Many different form of seated meditation are practiced throughout the world. There is substantial overlap between the techniques of MM and some forms of seated meditation, in that they may use similar mental strategies. However the term MM implies that movement or the intention of movement is involved (6), which is not true of many forms of meditation. There is a large literature on seated meditation, especially the style called "mindfulness," and comparatively little on MM *per se*.

### YOGA

The Sanskrit word "Yoga" means "to join," and refers to the individual's union with God; traditionally, Yoga is the practical side of the diverse Hindu religious systems. Different forms of Yoga use differing methods to achieve union with God. Some forms of Yoga may be forms of MM as defined in Section "Characteristics of MM" below, such as Hatha Yoga asanas and pranayama (3) and Yantra Yoga (31); others, such as Bhakti, Jnana, and Raja Yoga (32), are specialized forms of devotional practice, philosophical inquiry, or sitting meditation, and often involve moral and dietary observances.

### OTHER ASIAN SYSTEMS

Meditative movement includes more Asian systems than those mentioned above; a full enumeration would not be useful here as the numbers run into the hundreds, but Aikido (33), Shin Tai Do (34), Baguazhang (35), Sufi Dance (36), and Buddhist walking meditation (37) are other exemplars.

### SOMATICS

Over the past century, a number of MM practices have developed in the West. These have been referred to by the name "Somatics" (38). This term includes a wide variety of practices that, in general, share the defining characteristics of MM; in addition to the Alexander Technique (4) and Feldenkrais (5), examples of Somatic practices are: Eutony (39), Mensendieck (40), Focusing (41), Sensory Awareness (42), Aston Patterning (43), Rolfing Movement (44), Continuum (45), and Authentic Movement (46). Somatic Experiencing® (47) uses the principles of MM as a therapy for trauma. At this point there are very few scientific studies of these methods, and we found none focusing on affective states.

## WHY "MEDITATIVE MOVEMENT?"

In the past 5 years, the number of research studies of MM has increased considerably (47); however, these practices have often

been treated by researchers as forms of exercise comparable to ordinary aerobics, stretching, or relaxation techniques. As Catherine Kerr pointed out (48), the understanding of the biomedical researcher as to what is happening in MM is often at variance with that of the MM teacher. A researcher might understand the MM practices as a form of exercise for generalized stress reduction, not much different in principle from going for a walk. The MM instructor, however, thinks of it as a more sophisticated process, in which the awareness of the practitioner is placed in specific regions of the body to make specific changes. This disjunction of views can lead to problems in designing experiments that ask and answer relevant scientific questions (49).

The use of the term "MM," suggested by Larkey (6), is an important step in recognizing the special features of these practices. Larkey proposed the following essential characteristics of MM: first, a meditative state of mind, usually involving a focus of awareness on the body; second, some form of prescribed (or sometimes spontaneous) movement; third, explicit attention to the breathing; and fourth, a state of deep relaxation. Larkey based his definition on his familiarity with Qigong, Taijiquan, and similar practices, in an attempt to bring attention to these forms of exercise as distinct from conventional exercise. We will expand somewhat on these in order to define more precisely the features of MM, and to make it clear how radically it differs from most other exercise. We believe that, for future research, it is important to have a full and precise understanding of MM on its own terms, so that it can be accurately evaluated.

## CHARACTERISTICS OF MM

### MIND

"Mind" in this context means "awareness" and not "conceptual thought." In MM the mind is neither engaged in conceptual activity nor focused on a future goal, nor is it in the "default mode" of mind-wandering (50), but instead is focused on direct bodily experience. We view this spatial/interoceptive/proprioceptive/kinesthetic focus of awareness as the principal defining characteristic of MM. The practitioner's awareness is on the kinesthetic sensations of the whole body moving through space; the flow of breath and blood and other visceral sensations; the experience of balance, orientation, and posture; and the felt sense of space – quite different from physical awareness in conventional exercise (51). Kerr (49) has referred to this focus as "mind-in-body," to distinguish it from the more familiar concept of "mind-body" practices. This way of using the attention is similar to that used in some forms of seated meditation (52); but MM often involves additional specific mental techniques. For example, practitioners may be instructed to "feel the air as heavy" (53), as if they were moving underwater. This may be difficult at first, but with practice one can develop a vivid tactile/kinesthetic sense of viscous, almost hydraulic air movement, accompanied by a pleasurable sense of lightness, warmth, smoothness, and power (53). This indicates progress in the exercise and may be predictive of positive objective effects. In MM practices, the mind is also used to "direct the movement of Qi" (54). Since this is a core aim of most MM, it is important to understand this in a way that is compatible with a scientific approach. Section "Imagery" below explores this in more detail.

### MOVEMENT

Meditative movement may use either prescribed movement (where the required motion is specific and must be learned and practiced) or spontaneous free-form movement (where the practitioner allows their body to move spontaneously on its own). In some cases, the movement used may be extremely subtle, to the point of being invisible (55). In order to move the Qi (cause certain sensations in the body), physical movement is useful but not necessary. A practitioner may begin by making a large and obvious motion, then make it smaller and smaller until it is imperceptible. In this process the interoceptive/proprioceptive sensations become progressively more intense. This increased intensity may correlate with the objective effectiveness of the practice. A common saying in Qigong is, "Small movement is better than large movement; no movement is better than small movement" (56). In traditional Qigong practice, quiescent seated meditation is considered to be a part of Qigong, as is quiet standing. Although the distinction between "static" and "moving" practice is acknowledged, it is not a major distinction; in traditional Qigong, they were usually practiced together, with each supporting the other (57). In many apparently static forms of Qigong, the mind is actively employed in imagining movement, which produces certain internal sensations of motion; such a practice may alternate between overt and imperceptible "movement." In this context, it becomes hard to define exactly what is meant by the distinction between movement and stillness. We wonder whether, logical as it seems at first, making overt movement an essential element in MM is appropriate. One possibility would be to refine this part of the definition of MM to refer to the intention of movement, or to include the movement of internal sensations in the body in the definition of "movement."

### BREATHING

Awareness and control of the breath are central in Qigong and Taijiquan (58), Hatha Yoga (59), and Somatics (8). In Chinese and in many other languages, the same word can refer to both "breath" and "life energy." "Attending to or moving the Qi" can refer either to the physical breathing, or to certain bodily, emotional, or spatial sensations (58). These multi-level meanings of key terms must not be ignored in approaching MM. Altering the breathing pattern may alter the functioning of the autonomic nervous system (60). Various breathing practices are said to enable emotional release (61), to calm the mind (62), or to enhance physical power (63). A central practice in most forms of Qigong is to pass the awareness through the body in synchrony with the breathing rhythm (64). Depending on the desired result, the breath may be slow or fast, felt in various parts of the body, imagined as having different qualities (such as warmth or coolness), or held for various lengths of time (65). In MM, the breath is described as a bridge between unconscious and conscious functions, a way for the conscious mind to influence the unconsciously controlled functions of the autonomic nervous system (66). The mutual influence of the breath, the autonomic nervous system, and the emotions is well recognized in the scientific literature (60, 67–76), and numerous studies have been made of the effects of specific MM breathing techniques (77–83), but as far as the present authors are aware there has been no systematic review of these studies.

### DEEP STATE OF RELAXATION (BALANCED TONE)

In English "deep relaxation" conjures images of a floppy slackness. On the other hand, we can talk of a jaguar walking through the jungle as "deeply relaxed"; these are two different states. The Chinese word usually translated "relax" is "song" (*soong*) 鬆 (84). However, this word does not mean limpness (84), but rather a state of completely balanced tone, "eutonis" (39, 85), in which every muscle is doing exactly what it should. This state is experienced as light, free, open, and effortless; but at the same time stable, powerful, and well-rooted. Tension is a state of hypertonus, slackness a state of hypotonus, and the outcome of successful MM practice is a state of eutonis. There are practices that involve a hypotonic state, like Hatha Yoga's Shavasana, or "corpse posture" (3); some practices use brief maximal hypertonus. Neither of these is typical of MM, which always aims at the balanced state described above.

Biological systems are "complex systems"; this is a technical term implying spontaneous self-organization (86, 87). Complex systems organize themselves to preserve optimal, rather than minimal or maximal, levels of any number of variables (such as temperature or chemical composition). This is known as "homeostasis," a term coined by Cannon (88). Cortisol levels, for instance, can be an indicator of stress, a presumptively negative condition; too little cortisol, however, is as bad as too much (89, 90). Great care is needed in pharmacological interventions to avoid unwanted side effects due to "overshoot." The aim of MM is to restore the body's innate mechanisms for establishing homeostasis or dynamic equilibrium (58). Keeping this simple point in mind could change a research hypothesis from "does this intervention reduce cortisol levels?" to "does this intervention move cortisol levels toward a normal range?"

A complex system that is poorly self-regulated may fail to maintain a variable (such as the level of hormones or other signaling agents) within a normal range; or the level of concentration may oscillate over time, between too low and too high. Increased self-regulation will reduce the magnitude of oscillations so they no longer leave the normal range; more refined regulation results in smaller oscillations (91). Investigations of body sway suggest that MM may also improve postural self-regulation (92).

In studying MM it should be kept in mind that the desired outcome is a state of increasingly refined dynamic balance, and not a state characterized by maxima or minima, tension, or slackness. The word "relaxation" should be used with caution due to its ambiguity, and the concepts from the theory of complex systems may prove useful in describing the outcomes and processes of MM.

## RESEARCH

### BENEFITS OF MM

Meditative movement has positive effects on a wide range of mental and physical measures, although results are far from unambiguous. There have been a number of publications on the effects of MM practices on: depression (23), anxiety (17), cognitive ability (93), inflammation (94), immune function (95), arthritis (96), supportive cancer care (97), cardiac and pulmonary health (78, 98, 99), balance (98, 100), aerobic capacity (101), strength (102), bone density (103), fibromyalgia (104), and diabetes (105). Overall, MM seems to have positive effects on a broad range of health conditions. An equally consistent finding is that the vast majority of studies have serious limitations, and much more high quality research is needed to be able to draw definitive conclusions (11, 19, 20, 48).

### REVIEWS OF MM's EFFECTS ON AFFECTIVE STATES

A number of reviews have looked specifically at the effects of Taijiquan, Qigong, Yoga, and seated meditation on improving anxiety, depression, and other affective measures (16–29). A relatively small number of studies have focused on the use of MM for improving anxiety and depression, whereas a larger number of studies have investigated the effects of seated meditation (106, 107). Here we focus principally on MM rather than seated meditation.

Ospina (29) reviewed the scientific quality of studies of meditation, defined as including Yoga, Taijiquan, and Qigong as well as seated meditation (30), and, applying the rigorous CONSORT standards (108, 109), concluded that most studies were of poor quality. Further scientific research into meditation required better attention to study quality as well as a more unified theoretical perspective on meditation. She stated that no firm conclusions about the effects of meditation could be drawn from the available research (30).

A more recent review and meta-analysis by Chen at al. focusing on MM for anxiety (16), examined 36 adequate randomized controlled trials (RCTs). This study used the classical Chinese definition of Qigong as "the skill of mind-body exercises that integrate body, breath, and mind adjustments into one" (16), and thus included sitting meditation practices. In evaluating studies for inclusion, Chen advocated the use of the Boutron modification (110) of the rigorous CONSORT standards. The CONSORT standards (108, 109) were designed to apply to the evaluation of design quality of pharmaceutical trials, where rigorous double-blinding is easy. In studying MM however, the same level of blinding is more problematic; the Boutron modification gives guidelines specifically for non-pharmaceutical studies.

Twenty-five of the 36 RCTs investigated by Chen (16) found meditation (seated or moving) significantly more effective than control interventions in improving the symptoms of anxiety. Control groups included standard of care only (no intervention), attention controls (using another activity unrelated to MM), and active interventions other than MM (16). Comparing Standard Mean Difference (SMD), there were two statistically significant differences between different groups of studies: outcomes of poorer quality studies tended to be more positive, and studies from Asian countries also tended to more positive outcomes. There were also indications (although not statistically significant) that movement-oriented methods were more effective than static meditation, and that group delivery was better than individual. Most studies did not focus on clinically diagnosed anxiety disorders, but used anxiety questionnaires as one among several measures, leaving it unclear how effective these interventions would be for clinically significant levels of anxiety. No adverse effects were reported in any of the studies (16).

Jahnke selected 67 RCTs for review (out of 576 considered) (19). His criteria were that the study appeared in a peer-reviewed English-language journal between 1993 and 12/2007; that it had been cited in the academic literature; and that it was designed to test the effects of Taijiquan or Qigong (exclusive of seated

meditation). Twenty-seven of the 67 studies focused on psychological outcomes, and 6 on immune and inflammatory outcomes. In most cases MM demonstrated improvement in measures of anxiety and depression; these changes were generally significant compared with inactive controls, but did not usually reach significance when compared to an exercise or other active therapeutic control. In six other studies, MM reduced stress markers such as cortisol, adrenaline, and noradrenaline, and inflammation markers such as cytokines, CRP, and immunoglobulin-G (Ig-G). These results gave a biochemical confirmation that MM may reduce the secretion of stress-related and inflammation-related biomarkers. Jahnke noted that MM rarely produced less change than active therapeutic controls, which was significant in view of the simplicity, safety, cost-effectiveness, and gentle exertion of MM practice. Jahnke's conclusion was that "this category shows promise for examining (MM's) potential mechanisms of action for the change of psychological states." Jahnke made a case for considering Taijiquan and Qigong as substantially identical: his study revealed no significant differences in outcomes between Taijiquan and Qigong over a wide range of variables.

A review by Oh (21) on Qigong and depression found 10 acceptable RCT studies between 2009 and 2011. Oh excluded Taijiquan and meditation, including only moving Qigong practices. Only two of the studies focused specifically on depression as a primary outcome; the rest used a measure of depression as one among others. Of the 10 studies, 4 found that Qigong had significant positive effects on depression; 2 found that Qigong had the same positive effectiveness as conventional exercise, and 1 found that Qigong was as effective as conventional rehabilitation treatment. This latter study by Tsang (23) involved both a pilot study and a follow-up with a larger sample size, comparing Qigong to a specific rehabilitation program targeted at depression. Qigong had significantly better results than the rehabilitation group. Oh's evaluation was that these results were inconclusive: he cited widespread problems with poor experimental design, lack of specificity in description of the intervention, small sample size, brief length of study, lack of investigation of biomarkers, lack of studies involving clinical cases, lack of three-arm studies, and inadequate blinding. While many studies indicate that Qigong may effectively reduce stress, the litany of experimental short-comings outlined above highlights the need for greater rigor in the design of future studies.

A 2013 review of the effects of Qigong on anxiety, depression, and well-being by Wang et al. (28) drew from both Chinese and English-language studies, since 2000 for the former and 2003 for the latter. One hundred and fifty-eight studies were identified, of which 15 were finally selected for inclusion. This review excluded Yoga and seated meditation, focusing exclusively on standard Qigong exercises involving obvious movement, and applied rigorous standards for study selection. In all but one study, subjects were healthy or had a non-psychiatric chronic illness; one study involved depressed patients. In seven of the studies, mood and depression scores improved significantly (using a variety of scales such as the Hamilton Depression Severity Index, the Self-Rating Depression Scale, and the CES Depression Scale). Compared to usual care, psychosocial support, and active stretching, Qigong did better in two studies, while in two studies Qigong did as well as the active control. Anxiety scores also decreased significantly in seven studies, two of these compared to an active control. One study looked at stress-related biomarkers (cortisol, catecholamines) and found significant reductions compared to a wait-list control. Quality of life (a general measure of well-being based on a questionnaire) and self-efficacy (a measure of how capable and confident the subject feels in relation to daily demands) also showed significant improvement, both compared to wait-list controls and to a traditional rehabilitation group (one study); in another study, Qigong trended toward being more effective than conventional exercise but not significantly so. A meta-analysis of three studies of diabetic patients demonstrated that Qigong was effective at reducing depression and anxiety and improving quality of life. The authors comment on the poor quality of most studies and the need for more careful study design, larger samples, and better controls. They suggested using a convincing "sham" Qigong control to reduce "frustrebo" effects (the possible negative effect on controls from not receiving the intervention they want).

The use of sham MM controls is rare in MM studies, and designing such a study presents challenges (111), however a RCT by Lee et al. (9) used an effective sham Qigong control. They found significant reduction of anxiety (as measured by Spielberg's state-trait anxiety inventory, STA1-X1), as well as cortisol and aldosterone levels, in a Qigong ("Qi-training") group as compared to sham Qigong controls. The control group learned exactly the same movements, but participants were not instructed how "to gather and move the Qi" (the process of intentional manipulation of interoceptive sensation). Lee states that after the 1-h training, the intervention subjects "could gather and move Qi with conscious effort" and that "[t]he control group learned to perform the same external motions as the Qigong training group, but without any conscious effort to gather or move Qi." Measures were taken shortly before and shortly after each training session; sessions lasted 1 h, and were repeated three times, separated by at least 2 days. Care was taken to blind the randomization as well as the collection of outcome data. This study is one of the few that give adequate details about the intervention, including the subtle factors alluded to above, as well as providing a valid double blind in the assessment of outcomes. The results suggest a contribution to anxiety reduction by factors specific to MM ("gathering and moving the Qi").

In a 2010 review focusing on Taijiquan, Fields (18) mentioned three studies showing the positive effects of Taijiquan on the autonomic nervous system as measured by heart rate (HR) variability frequency analysis; in two of these studies, Taijiquan was shown to have better results than brisk walking or slow movement, which has interesting implications for the comparison between conventional exercise and MM. Fields also mentioned four studies in which Taijiquan has been shown to decrease a variety of negative emotional states, as well as two of her own studies combining Taijiquan and Yoga practice for pregnant women, in which significant alteration in EEG measurements was shown. Like all the other reviewers, she pointed out the many methodological flaws in these studies, including a wide range of dosages, target populations, diagnostic instruments, and the frequent use of pre-post measurements rather than controls. A limitation of her review is that she does not give details of how she selected the studies to include.

Another 2010 review by Saeed (22) looked at conventional exercise and Yoga as well as Taijiquan, Qigong, and meditation. Saeed focused on studies of clinically diagnosed affective disorders. Although Yoga is not within the scope of the present study, it is interesting to note that there appear to be a number of studies of the effects of Yoga on clinical anxiety, depression, and other psychiatric diseases, in contrast to the literature on Qigong and Taijiquan where there are very few such studies. Saeed's conclusion was that there was not enough evidence to support using Qigong or Taijiquan as a treatment for clinical affective disorders. Saeed's survey excluded most of the studies included in other reviews, which measured changes in anxiety, depression, and mood among non-clinical populations. Saeed also found little evidence for the effectiveness of conventional exercise in these populations.

Yet another review in 2010 by Wang et al. (26) searched English and Chinese databases through 2009 for references to Taijiquan (not Qigong) in relation to anxiety, depression, mood, self-esteem, and psychological stress. Randomized, non-randomized, and observational studies were considered. Randomized controlled studies were assessed for inclusion using the Jadad criteria (112). Wang performed a meta-analysis (using a bias-corrected Hedges g-score to compensate for small sample size), and discussed the non-randomized studies, separately for each of the five affective measures (anxiety, depression, mood, self-esteem, and psychological stress). Overall results included significant support for the positive effect of Taijiquan on all five measures. He noted that, despite the use of exercise control groups in several studies, it was not possible to say whether Taijiquan had equal or superior effects compared to conventional exercise. He also noted the limitations in conducting a meta-analysis due to heterogeneity of population and dosage. The present authors note that very few of the studies tested the effects of daily practice of Taijiquan; most studies involved practice two or three times a week, which is generally regarded among Taijiquan teachers as inadequate for achieving significant results (113).

A recent 2013 review by Wang et al. (27) looked at Qigong (not Taijiquan). An extensive search of English and Chinese databases was done, inclusive of Chinese dissertations and doctoral theses. The selection of studies for inclusion in the review used narrowly focused criteria: only RCTs were included; subjects had to have a diagnosis of anxiety or depressive illness; studies of mood, self-esteem, or stress were not included; studies had to use instruments validated for the measurement of depressive or anxiety states. The Wayne checklist (103) was used to evaluate study quality; this is a checklist developed specifically for use in studies of Qigong. It includes several items clearly required by the nature of the Qigong intervention, such as a complete description of the intervention and details of the qualifications of the instructors, as well as appropriate blinding requirements. Following data extraction, the effect sizes were calculated using Hedges g-score, and SMD was calculated for pooled effects. Out of 503 studies, 12 RCTs met inclusion criteria. Three of these used conventional exercise as a control. All studies measured depressive symptoms, whereas only four evaluated anxiety. Pooled effects were calculated for each type of control group used. Compared with conventional exercise, Qigong showed a moderate positive effect on measures of depression; compared with Cognitive-Behavioral Therapy, Qigong was equal in effect; compared with a newspaper reading control, Qigong showed a large effect; and compared with waitlist, a moderate effect. Among the four studies investigating anxiety, only one showed Qigong superior to controls. Wang cautioned that home practice was not monitored, thus dosage is hard to ascertain. Also, the Qigong intervention was always provided in a group context whereas the control groups often did not have this social exposure. Since social engagement may have a significant effect on depressive symptoms it is necessary in future studies to provide equal social engagement for all groups. Wang's overall conclusion is that evidence for the effectiveness of Qigong in treating anxiety and depression is positive but limited by numerous factors.

A speculative 2008 review by Tsang (25) moved forwards from his earlier studies on the effects of Qigong on depression in the elderly (114, 115) to reflect on the possible neurobiological basis for these effects. His earlier studies investigated the psychological basis for improved depression. Qigong practice increased the sense of self-efficacy and mastery by enabling elders to master a physical task as well as to improve competence through increased balance and strength; in addition Qigong practice provided them with increased social support and improved interpersonal relationships. These psychological factors may cause decreased depression (116). Tsang offered three possible neurobiological explanations for Qigong's anti-depressive effect. First, he suggested that Qigong may act by increasing brain levels of monoamine neurotransmitters, as has been claimed for selective serotonin reuptake inhibitors (SSRIs). He noted that studies have shown that conventional exercise has this effect (117), as well as increasing the concentration of tryptophan in the brain (tryptophan is a serotonin precursor). He pointed out that the time course of Qigong's effect is similar to that of SSRIs: the antidepressant effect takes a couple of weeks to initiate, then fades away a few weeks after ceasing the intervention. Tsang's second explanation involved the hypothalamic-pituitary-adrenal (HPA) axis which secretes cortisol and adrenaline in response to stress, and which has been implicated in depression. Tsang pointed out that, since the hypothalamus is under control of the limbic system, the mental calming effects of Qigong may reduce limbic activation of the HPA axis, thus reducing plasma cortisol and ACTH and possible lessening depression. Tsang cited studies showing that Qigong practice may reduce cortisol and ACTH (9). Tsang's third explanation invoked the relation between decreased neurogenesis in the hippocampus and depression. Stress and the resultant increase in plasma cortisol may downregulate brain derived neurogenesis factor (BDNF) and reduce neurogenesis. He noted that animal studies suggest that exercise upregulates BDNF and increases neurogenesis (118), and that conventional exercise in humans may have the same effects (119, 120).

Many reviews of MM have noted its effects on biomarkers of inflammation such as CRP, tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) (19, 62, 93, 94). As Tsang pointed out, this is potentially relevant to some of the effects of MM on depression, as it appears that depression is linked to inflammatory processes in the brain (in particular the hippocampus), which interfere with the generation or survival of new neurons in the hippocampus (neurogenesis). In a recent review of the connection between depression and inflammation, Krishnadas pointed out that a third of patients with major depressive disorder (MDD),

without any other major illness, have elevated inflammatory biomarkers; in particular, CRP, TNF-α, and IL-6. Moreover, MDD is epidemiologically associated with inflammatory medical conditions (121), and patients treated with cytokines are at increased risk of developing MDD. Neuroinflammation is linked with a number of psychiatric and neurological disorders in addition to depression (122). Since peripheral inflammation and central nervous system (CNS) inflammation involve somewhat different conditions, it is not possible to conclude from blood and salivary markers that MM might affect CNS inflammation. However melatonin may protect the brain against inflammation and promote neurogenesis (123), and meditation produced both short-term and long-term increases in melatonin levels (80, 124, 125).

### CONCLUSION

Overall, these reviews invite the following tentative conclusions: MM consistently produced reductions in measures of anxiety and depression when compared with non-active controls in studies of anxiety or depression. When matched to an exercise or other active therapeutic intervention control, MM usually performed about the same, rarely any worse, and sometimes better than the control. MM generally produced less reduction in measures of anxiety and depression in seriously ill patients and more reduction in healthy or slightly compromised subjects. However, the forms of MM used in such studies are invariably health-maintenance Qigong, and not the much more specifically targeted medical Qigong. It would be surprising if an intervention designed for mild ill health were to be effective for severe clinical conditions.

Review papers usually investigate multiple studies of pharmaceuticals or other well-defined treatments. Since the administration of a specific dosage of a particular drug is easy to standardize, variation of results between different studies is assumed to reflect random or uncontrolled factors not related to the drug itself; therefore a statistical averaging of many studies is assumed to give more accurate results as to the true effectiveness of the drug. However, the situation with MM is quite different. Given the complete lack of standardization or taxonomy of MM, divergent results in studies of MM may reflect in part the differential effectiveness of the interventions used rather than uncontrolled factors. For this reason, although we agree with several of the reviewers that the results are inconclusive, we feel that the remarkably positive results obtained in some studies, even when MM was compared to an active targeted intervention (23), warrant continued exploration of MM along the scientifically more rigorous lines we suggest below.

### SHORTCOMINGS OF STUDIES OF MM

All the reviewers mentioned above (16, 18, 19, 21, 22, 25–29) come to similar conclusions about the shortcomings of most of the studies of MM to date. These short-comings fall into two broad categories.

The first category has to do with general experimental design (16, 19, 28, 126). This includes first, disagreement about the necessity of certain aspects of experimental design, such as blinding of the participants; and second, the clearly necessary and often inadequate aspects of the studies, such as small sample size, inadequate description of procedures, inadequate blinding of data collection, and inadequate controls. The former issue involves the nature of the MM intervention itself. Because an important part of most MM practices is the cognitive/affective state of positive belief and expectation, controlling for this variable could be seen as inappropriate, irrelevant, or unnecessary (111). Further complicating experimental design, in MM the placebo effect is not necessarily regarded as a confounding factor; rather, the factors on which the placebo effect is based are being harnessed to produce positive outcomes (111). It is possible to tease out the cognitive, affective, and motor aspects components of the effects of MM by good experimental design; however, MM might achieve some of its effects through the interaction of its component factors, rather than a simple addition.

The second category involves difficulties in experimental design specific to the study of MM (21, 49, 127). The study of MM presents issues such as difficulties with blinding and the selection of appropriate sham control activities. Studies present a wide range of interventions, often poorly specified; they use diverse doses and durations; and there is usually a mixture of possible active factors in a single intervention (such as expectation, psychosocial support, skill levels, training methodology, movement, mental focus, belief, and expectation). Much of this confusion stems from the lack of a systematic and complete taxonomy of these methods, which should be based on accurate understanding of MM. The various complex processes of gathering, storing, purifying, and circulating Qi should be understood, operationalized, and brought out of the realm of apparent superstition. We do not mean to suggest that the traditional concepts of Qi should be imported into the realm of science; this cannot and should not be done. But both the subjective and the objective phenomena associated with descriptions of Qi can be identified in a scientific way.

We note in the reviews cited above the lack of complete agreement as to the requirements of adequate study design. Whereas some apply the rigorous CONSORT (109) standards in evaluating the acceptability of studies, others suggest more moderate standards such as the Boutron modifications (110) or the Jadad criteria (112), or standards specifically designed for this particular field such as the Wayne checklist (103). Some consensus needs to be reached on this issue to further research in this field.

## POSSIBLE MECHANISMS OF THE EFFECTS OF MM ON AFFECTIVE DISORDERS

There are two broad categories of mechanisms proposed for the effects of MM: first, well-recognized mechanisms shared by ordinary physical exercise, such as muscular or cardio-vascular loading; and second, complex neurological mechanisms relating either to neuronal plasticity (128–130) or neurohormonal and neuroimmunological modulation (25, 95). We think the latter offers the most productive avenue for future research, and we make several speculations along these lines below.

### METABOLIC EXPENDITURE

Meditative movement exercises are of mild to moderate intensity, are easily controlled, need no equipment, and little space, can be done indoors in inclement weather, and involve no sudden movements. The level of exertion is not much more than that of a gentle walk, and it may be hard to understand how MM can have such a range of powerful effects. MM involves smooth coordinated

movements of all parts of the body, which gently challenge the range of motion of essential joints. In keeping with its philosophy of balance, MM avoids extremes of stretch or exertion and cautions against any feelings of strain or effort (131).

Studies comparing the effects of MM on physical measures such as balance, bone density, HR, heart rate variability (HRV), BP, aerobic capacity, and strength to a no-intervention control generally found significant improvement in these indices (increased balance and bone density, reduced HR and BP, increased HRV, aerobic capacity, and strength) with MM, whereas comparisons to conventional exercise interventions often showed MM to have equally positive effects as conventional exercise. However in the case of the MM intervention, the degree of exertion appeared to be substantially less than that used in the conventional exercise intervention. Jahnke mentions that the relatively mild leg flexion and low intensity movements typical of MM nevertheless produced significant effects on bone density (19, 103). Jahnke speculated that some of the positive physical effects of MM might not be due to the same mechanisms as those of conventional exercise. More precise measurements of the metabolic equivalent (MET) and other objective measures of exertion will be necessary for clear conclusions. Chao has measured the MET of modified Taijiquan to be three METs, a moderately low intensity level (132). MET is a measure of the energy consumption during exercise, expressed as a ratio to a standard level of energy consumption approximately equivalent to that during a resting state. Thus one MET is a resting state, three METs is three times the energy consumption of the resting state. Maximal exertion would be about 23 METs. Some comparisons of MM to conventional exercise demonstrate greater effects on regulating the autonomic nervous system for MM (18), again suggesting a different mechanism from that of conventional exercise.

## RHYTHM

The smooth rhythmic motions of MM are usually experienced as quite pleasurable. Shin Lin (102) suggests that moderate rhythmic movement may increase parasympathetic tone, whereas intense exertion causes more sympathetic activation (102). Both in the elderly and in infants, regular rhythmic motion has been shown to be calming (133). In animal behavior, moderate rhythmic motion is very common in grooming behavior, which has been observed to have a calming effect on the animal. Cats have been shown to release elevated levels of serotonin while grooming (134); it is possible something similar happens in humans when activities mimic grooming behaviors.

The speed with which one performs MM is around six times a minute (0.1 Hz); this appears to be a frequency at which the breath and heart beat have the greatest tendency to come into coherence (135); in other words, at this frequency respiratory sinus arrhythmia (RSA) is enhanced. During MM practice there is a feeling of "being in the groove," of moving in a strong, slow rhythm. When RSA is strongly established, blood circulation becomes more efficient; the heart rate increases during inhalation, as the blood volume moves relatively more into the lungs, and slows during exhalation, as the blood volume moves into the peripheral circulation. This alteration in blood volume may be part of the basis for the suggestion in MM that one "breathes into the arms and legs" – an obvious physical impossibility, but perhaps a good description of the experience of a regular oscillation of blood volume (136). This promotes efficiency in the cardio-respiratory system, and may enhance parasympathetic tone when such tone is low. In states of excess vagal tone and insufficient sympathetic arousal (vaso-vagal syndrome), this rhythmic breathing could bring the ANS back toward balance by elevating sympathetic activity (137) and possibly reducing vagal tone. This restoration of autonomic balance is likely to have a moderating effect on affective symptoms, and might reduce conscious fear and anxiety by reducing the intensity of the somatic markers (the interoceptive awareness of visceral/affective states on which subjective affective experience may be based) (138). This synchronized breathing will affect measures HRV (139); a frequency analysis of HRV will tend to show a strong narrow spike in the high frequency (HF) range, which is regarded as the most reliable indicator of healthy increase in vagal tone (72), and will show reduced power through the rest of the range. This has been referred to as "coherent breathing" (140), and it may be associated with strong positive feelings and a more balanced mental state (135). Interestingly, the one outcome for which there is the greatest evidence for the effectiveness of Qigong is reduced BP; hypertension can be significantly associated with increased anxiety and stress.

## GROUNDING AND POSTURE

Many MM practices involve a regular shifting of the weight form one foot to the other, or a rhythmical activity of the whole body with the weight firmly planted on both slightly bent legs. Great attention is paid to correct postural alignment and to using the body as a whole. Although the degree of exertion is low, the muscles are being used in a well-coordinated and conscious way, possibly re-patterning the motor nervous system. This aspect of the practice is held to enhance "grounding," which is the subjective feeling and objective state of being more stably connected to the ground. It seems likely that this experience would help increase the sense of self-efficacy, balance, and confidence, all of which have been shown to be improved by MM (23, 98), and might help to stabilize mood swings and reduce depression and anxiety.

A recent study of posture (141) showed that when subjects adopted a "low-power" or a "high-power" posture for a few minutes, there were significant shifts in behavior as well as in testosterone and cortisol levels. The authors stated that their results indicate the reality of "cognitive embodiment," in which voluntary physical posture can produce not only changes in cognitive and affective experience, but neurohormonal shifts as well. This suggests that the emphasis on posture in MM may have a scientific basis (142). Carney et al. used typical postures of the kind one might see in a boardroom; from the viewpoint of MM, the postures were unbalanced and poorly integrated (although they do clearly express power or lack thereof). The neurochemical and behavioral shifts that occurred through adopting a "high-power" posture involved increased testosterone and a shift toward risk-taking behavior; this is no more a shift toward balance than the increased cortisol observed in the "low-power" postures. The very precise posture used in almost all MM movements is well aligned and balanced between the extremes. We speculate that just the act of holding a balanced posture for a period of time may induce behavioral, affective, and neurochemical shifts in the direction of

balance. A study by Yeh et al. (143) demonstrated a significant decrease in leukopenia in breast cancer patients using a 3-week Standing Meditation Qigong intervention (Zhan Zhuang); this practice involved simply standing for 15 min in a precisely aligned, relaxed, and well-balanced posture. In seated meditation too, the correct posture is seen as a central part of the practice (144).

## INTEROCEPTION

A central aspect of MM is the attention to interoceptive and proprioceptive sensations. MM practitioners become significantly more sensitive to tactile (129), interoceptive (128), and kinesthetic perceptions, and regularly experience a variety of positive and complex inner sensations. Damasio's recent theory of somatic markers (145) has clarified how important interoception is to affective and cognitive function; he has shown that what are called intuitions or hunches may be due to this system. Information about the state of the viscera comes up lamina 1 of the spinal cord, via the brainstem parabrachial nucleus to the ventromedial thalamus, and thence through the posterior insular cortex (the primary interoceptive cortex) to the anterior insula where the information is integrated with higher order contextual information and becomes accessible to consciousness. Damasio suggests that the integrity of this pathway is necessary for many affective, interpersonal, and cognitive processes, since it is the basis for a clear sense of one's own affective and autonomic state (146). Information received through this interoceptive system is the basis on which the anterior insula (as well as the anterior cingulate gyrus and the ventromedial prefrontal cortex) generate an attentional bias, which organizes the brain to pay attention to the outer world in particular ways. This system is implicated in the capacity for empathy and compassion, as well as addiction, anxiety, and depression. Farb (147) found that improved conscious access to the interoceptive cues associated with sadness was associated with decreased depressive symptoms. Meditation and MM have been shown to enhance interoception, even to the point of altering the neuronal connections between the posterior and anterior insula, the crucial bridge through which interoceptive sensations reach consciousness (128).We speculate that positive affective changes from MM may be due in part to this process of enhanced interoception.

## IMAGERY

Qigong uses phrases such as "direct the Qi," "gather the Qi," "move the Qi," which may be problematic to understand from a biomedical point of view. This capacity is a principal goal of Qigong (148) and other forms of MM (where the term "Energy" is often used instead of "Qi"). A useful way of understanding these terms is to think of "Qi" as a dynamic interoceptive/proprioceptive/kinesthetic/tactile sensation of tingling, vibration, warmth, pressure, or flow. Thus "moving the Qi" translates as the intentional use of imagery to modify the practitioner's inner experience. A typical MM instruction might be: "While you are performing a certain coordinated movement, imagine the sensation of a flow of warm liquid from your pelvis up through your spine and out your arm." Or: "place your attention in the center of your chest and imagine a flower gently opening." After a period of practice, such procedures can result in vivid physical sensations; not an abstract mental picture, but an embodied "felt sense" of interoceptive/kinesthetic experience, usually with a clear hedonic component. These subjectively experienced interoceptive shifts are believed to correspond to actual changes in the physiology of the body and nervous system (58, 131). For instance a spread of pleasant warmth may indicate increased capillary dilation; a soft feeling in the heart may involve reduced BP and increased HRV; a feeling of weightlessness in the limbs may indicate improved control of muscle tone via the reticular activating system in the brain stem.

This process is similar to an athlete's use of motor imagery for the rehearsal of a sport (149). Visual, interoceptive, and kinesthetic imagery can produce significant, widespread, and lasting changes in the brain. Motor imagery is known to activate areas of the brain responsible for generating internal sensations, such as the posterior parietal cortex and the pre-motor and supplementary motor areas (150–152). Visualization can improve motor performance significantly (149, 153), and increase muscle strength (154). Imagined movement activates many of the same areas of the brain as actual motion, although the patterns of activation are not identical (155). The posterior parietal cortex, where the body image is constructed (156), as well as the supplementary motor area, where motor plans are elaborated, are preferentially activated by imagined movement (151, 157). The effects of imagined movement extend to the autonomic system; cardio-vascular and skin resistance changes accompany imagined exertion (150, 158), and it is possible that other autonomic changes can be triggered as well, such as altered parasympathetic regulation of the heart (140), improved autonomic regulation of the enteric nervous system, and increased capacity for social engagement through activation of the supra-diaphragmatic portion of the parasympathetic system – Porges' ventro-vagal system (159). The positive effects of motor imagery can be predicted from the degree of autonomic responsiveness during the imagery (160).

## THE BASAL GANGLIA

The principle functional circuits of the brain: affective, interoceptive, motivational, attentional, executive, associative, memory, and sensorimotor all need to coordinate with each other in relation to the challenges from the environment. One needs to be able to notice and orient to a relevant stimulus, identify its meaning, adopt an appropriate physical, affective, and cognitive preparatory stance (posture), then choose and execute appropriate action. Recent research into the basal ganglia (BG) suggests that they are a major center for this functional integration. All cortical regions have semi-independent parallel loop circuits going down to the striatum (the input nucleus of the BG), to the globus pallidus, substantia nigra, and sub-thalamic nucleus, and returning via the thalamus to the same area of the cortex (161). This enables the BG to selectively inhibit or stimulate particular parts of the cortex, as well as to coordinate their actions. This applies to both voluntary and involuntary or habitual actions (162). The BG have a similar set of loop circuits descending to the pontine and medullary areas, extending the process of selection and coordination to brainstem functions (163). The symptoms of Parkinson's disease (PD; which is caused by a deficit in the dopamine circuits of the BG), as well as other diseases possibly related to the BG, such as Tourette's syndrome and attention deficit hyperactivity disorder (ADHD), have associated behavioral, cognitive, and affective symptoms (161). PD

is known for restrained movement, contracted posture, depression, and cognitive limitations; ADHD presents an opposite picture. The terms hypophrenia and hyperphrenia have been coined to refer to the cognitive/affective dimensions of hypo- and hyperkinetic disorders, indicating the interaction of motor, affective, and cognitive dimensions in the BG (161).

We speculate that the focus of MM on the intentional cultivation of balanced posture, enhanced interoception, and kinesthesis, the conscious focus on smooth and balanced movement, rhythmic breathing and positive affect, and the explicit use of intention, all acting together, may affect the whole brain via the BG and move it toward more balanced functioning. Hyperphrenia (anxiety, ADHD) calms down and hypophrenia (depression, apathy) is energized. Excess activation in the HPA axis diminishes, and the neurochemical environment becomes well regulated. In this process posture and movement play a central and fundamental role; the process of "adopting a posture toward something" (164) is a central and unifying function of the entire nervous system. Llinas (165) has argued that motor function is the principle reason for the existence of the CNS.

### DUAL DEFAULT MODES OF THE BRAIN

Recent research has identified rumination or mind-wandering (the chronic semi-conscious churning of thoughts) (166) as a significant factor in anxiety and depression (167–169). The "default mode" of the brain (50, 166) involves activity of the posterior cingulate cortex and the precuneus, as well as the superior and medial temporal gyri; these are both involved with internal "self-talk," the "autobiographical" self with all its stressful stories (170). Brewer (166) has shown in a study of experienced meditators that in meditative states these regions become less active, and the dorso-lateral and medial prefrontal cortex, the dorsal anterior cingulate cortex, and posterior insular cortex become more active. These are areas involved with cognitive control and attention to the present, particularly to interoceptive stimuli. Long-term meditation practice brings about permanent restructuring of these pats of the brain, resulting for instance in increased gray matter in areas of the cortex involved in interoception (171, 172). We suggest that MM may be effective in the short term at changing the default mode of brain activity away from rumination toward present-oriented awareness, and in the long term at changing the wiring of the brain (128). If this is the case, MM could be of immense help in the therapy of depression and anxiety.

## PITFALLS IN STUDYING MM AND SUGGESTIONS FOR FUTURE RESEARCH

We have emphasized above the importance of an adequate understanding of the core principles of MM, as well as the development of a systematic taxonomy. We believe this is necessary for significant progress. Research should be carried out in populations with clinical diagnoses of depression or anxiety; however when dealing with clinical illness, an MM intervention should be matched to the condition it is designed to treat. This requires the help of an appropriately qualified practitioner. A confounding factor could be that the diagnosis of the patients in the research group from an MM point of view might not be congruent with that of Western medicine.

### RESEARCH DESIGN

As noted in Section "Reviews of MM's Effects on Affective States" above, consensus needs to be reached as to the appropriate standards for conducting and evaluating studies of MM. Recommendations for the design of future research include: adequate sample size, the correct use of blinding procedures, ideally use of a double blind; the use of control groups, ideally three-arm studies using an inactive and an active attention, treatment, or sham intervention control. In reporting outcomes blinding and randomized selection procedures should be fully described. The great majority of studies of the effect of MM on depression or anxiety are limited to about 3 months of intervention. In many cases, this may not be enough time to even begin to achieve mastery; one could say that the real "dose" does not begin until there is a reasonable degree of skill in performing the practices. Trials should be long enough to ensure subjects achieve an adequate level of skill. Skill levels attained by subjects should be measured and taken into account in analysis of the outcomes. We suggest defining certain reported subjective experiences – such as sensations of lightness, flow, warmth, wholeness – as indices of skill levels. Traditional Qigong teachings describe the experiences indicative of various degrees of achievement (113). Objective measures could also be made that might correlate with skill, such as analysis of postural sway or stride variation (173). Measures based on the theory of complex systems could prove productive (111, 173–176).

Since MM uses many variables in intervention, studies need detailed descriptions not only of physical movements, but also of the nature of instructions in terms of use of mind as well as the social context. One shortcoming for all current research is the lack of some sort of taxonomy to break down elements into recognizable categories; until such a system is developed and adopted, it will remain difficult to compare studies and gain significant understanding of MM and disciplines like Qigong.

### FUTURE DIRECTIONS

As the above factors are implemented, clear and solid results should begin to accumulate as to the effects of MM practices. Should these results confirm the suggestions from current research, then it will be appropriate to begin to deconstruct the role of the different aspects of MM: what proportion of the results are due to the movement, the breathing, the mental focus; how much is due to social interaction, positive expectation, cultural belief, and so on. Specific elements of MM should be used in isolation to examine the exact mechanisms of action, and in combination to determine whether the components have an additive or a synergistic effect. As the definition of MM becomes clearly established, more forms of MM should be studied in depth, including specific forms of Yoga and Western Somatics. Care should be taken to discriminate between MM and other factors such as religious belief, devotional practices, and philosophical or moral practices. As more forms of MM are studied the definition of MM should be evaluated and refined to make sure that it remains valid and useful.

## CONCLUSION

Meditative movement is a system of considerable scope, sophistication, complexity, and potential power. At this early stage it is necessary to consider, with appropriate discrimination, a wide range of explanatory mechanisms of its effects, from

ordinary physiological and psychological processes, through higher brain functions, to electrical, and electromagnetic field phenomena.

Meditative movement uses techniques that are quite different from those of conventional exercise, and there are sound possible explanations for their mechanisms of action on affective and autonomic states. Investigation into these putative mechanisms could lead to significant breakthroughs in the development of new forms of intervention for anxiety, depression, and related conditions. We have shown that culturally unfamiliar explanations of the therapeutic effects of MM (such as "moving the Qi") can be translated into scientifically meaningful terms, allowing for a significantly more thorough and effective investigation of MM disciplines than has been possible hitherto. In particular we believe that is necessary to consider actions via the higher centers of the brain when studying MM.

Given the lack of adverse outcomes in studies that employed various forms of MM, the low costs involved in delivering MM therapies and that the outcomes of most studies are encouraging, we believe that continued research in this area could prove to be highly beneficial in the field of anxiety and depression disorder treatment.

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# Exercise interventions for the treatment of affective disorders – research to practice

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## INTRODUCTION

Mental illness presents a growing disease burden, with worldwide prevalence estimates between 18 and 36% (1). In the USA, the prevalence of affective disorders including unipolar depression and bipolar disorder (BD) is around 20% (2, 3). While psychotropic medications remain at the front line of treatment for affective disorders, a growing body of research evidence strongly supports the role of exercise in the treatment of these affective disorders. Although remaining to be elucidated, there are a number of potential mechanisms by which exercise may be beneficial including neurobiological (4, 5) and pharmacological-like mechanisms (6). In the present paper, we shall discuss recent findings from systematic reviews and make recommendations for structured exercise, as distinct from unstructured or incidental physical activity, in the treatment of both depression and BD. This review also examines the role of exercise in the treatment of post-natal depression (PND) since this often transient but prevalent condition is rarely examined.

## EXERCISE FOR DEPRESSION

Three recent systematic reviews (7–9) confirm the potential benefit of exercise for people with depression. Rethorst et al. (7) reviewed 75 RCTs comparing exercise versus no treatment or wait-list control. Fifty-eight of the 75 studies were included in a meta-analysis, which showed a clinically significant effect of exercise on depressive symptoms (ES: −0.80, 95% CI −0.90 to −0.67). More recently, Rimer et al. (8) reported that both aerobic exercise and muscle strengthening exercises are effective in reducing depressive symptoms with resistance exercise (ES: −0.85, 95% CI −1.85 to −0.15) or combined aerobic and resistance exercise programs (ES: −0.82, 95% CI −1.39 to −0.25) showing larger effect sizes, albeit with wide confidence intervals. In further support of the role of aerobic exercise in the treatment of depressive symptoms, Robertson et al. (9) also reported a significant, large effect (ES: −0.86, 95% CI −1.12 to −0.61) of walking on symptoms of depression.

In contrast, not all reviews support the role of exercise in the treatment of depression. Krogh et al. (10) reported only limited benefit [Standardized Mean Difference (SMD): −0.40, 95% CI −0.66 to −0.14)] for exercise in a population diagnosed with clinical depression. When only studies with long-term follow-up data were analyzed, this effect disappeared (SMD: −0.01, 95% CI −0.28 to 0.26) suggesting no long-term benefits of exercise for people with depression. More recently, Cooney et al. (11) concluded that while exercise is more effective in the treatment of depression compared to no treatment (SMD: −0.62, 95% CI −0.81 to −0.42), it is no more effective than antidepressant medications (SMD: −0.11, 95% CI −0.34 to 0.12) or psychological treatment (SMD: −0.03, 95% CI −0.32 to 0.26). When the analysis was limited to high quality studies with long-term follow-up, the positive effects of exercise were markedly diminished.

Despite recent systematic reviews and meta-analyses producing contrasting outcomes, it would appear that exercise may be as effective as other treatment strategies and better than no intervention at all. Importantly, people with mental illness, including those with depression, view exercise as a valuable yet underutilized treatment strategy, and this acceptance of exercise treatment may lead to better long-term adherence (12).

As far as we are aware, only three reviews have examined the exercise program variables (frequency, intensity, duration, and type of exercise) for the treatment of depression (7, 13, 14). These are highlighted in **Table 1**. The most recent of these reviews examined exercise program variables from studies reporting positive mental health outcomes for people with depression. Stanton and Reaburn (14) reported that supervised aerobic exercise, performed in either group or individual formats, undertaken 3–4 days per week, at low to moderate or self-selected intensity, for 30–40 min per session for at least 9 weeks, is likely to provide positive benefits in the treatment of depression. This is not substantially different to the exercise recommendations for healthy populations (15). Therefore, clinicians should be confident that public health exercise guidelines represent an excellent starting point when prescribing exercise for people with depression.

## EXERCISE FOR POST-NATAL DEPRESSION

Two recent reviews offer support for exercise in the treatment of PND (16, 17). Lewis et al. (16) reviewed nine studies, including four 12-week RCTs investigating the effect of exercise on PND. Three of the four RCTs reported an improvement in PND symptoms (18–20) and one reported no effect of exercise (21).

Most recently, Blamey et al. (17) reported a moderate (SMD: 0·73, 95% CI 0.35–1.11) but not clinically significant (<4 points on Edinburgh PND Scale)

**Table 1 | Summary of exercise prescription guidelines**.

| Author | Frequency (per week) | Intensity | Session duration | Mode of exercise |
|---|---|---|---|---|
| **DEPRESSION** | | | | |
| Rethorst et al. (7) | 3 | Not reported | 45–60 min | Not reported |
| Perraton et al. (13) | 3 | 60–80% $HR_{max}$ | 30 min | Individualized according to preference |
| Stanton and Reaburn (14) | 3–4 | Low-moderate or patient preferred | 30–40 min | Any aerobic activity |
| **HEALTHY POPULATIONS** | | | | |
| Garber et al. (15) | ≥5<br>≥3 | Moderate<br>Vigorous | Min 30 min/session or ≥150 min/week<br>Min 20 min/session or ≥75 min/week<br>Or a combination to achieve ≥500–1000 kCal/week | Individualized according to preference |
| **POST-NATAL DEPRESSION** | | | | |
| Lewis and Kennedy (16) | 3 | Moderate | 40 min | Pram-walking |
| **BIPOLAR DISORDERS** | | | | |
| Alsuwaidan and McIntyre (29) | 5–7 | Moderate | 30 min | Not reported |

effect of exercise in the treatment of PND. The authors also reported that structured exercise classes were more effective than tailored advice. However, the high risk of bias, poor reporting of data, and substantial study heterogeneity limits the interpretation of these findings.

Not all reviews support the effectiveness of exercise in the treatment of PND. Daley et al. (22) reviewed five RCTs comparing exercise of any type, with any other treatment, or no treatment and reported no significant effect of exercise as a stand-alone intervention, compared to no exercise in women with PND (SMD: −0.42, 95% CI −0.90 to 0.05). However, based on the limited available evidence, exercise appears to be beneficial in the treatment of PND (23) and has been included in clinical practice guidelines for the treatment of PND (24). However, this recommendation is based on two small, low quality trials (18, 19) and does not offer detailed guidance on exercise prescription. Possibly due to the lack of high quality RCTs and the significant heterogeneity in intervention design, no systematic reviews have examined the exercise program variables for the treatment of PND. From the review of Lewis et al. (16), a 12-week program of pram-walking including social support may be valuable for the treatment of PND as outlined in **Table 1**. Until more high quality RCTs are conducted to examine the appropriate program variables for exercise in the treatment of PND, the recommendations of Stanton and Reaburn (14), or the exercise program variables used for healthy populations, might be considered valuable.

## EXERCISE FOR BIPOLAR DISORDER

Compared to other affective disorders such as depression, there is considerably less research examining the effect of exercise in the treatment of BD. However, from the findings of studies undertaken to date, it would appear that exercise may reduce both depression and anxiety (25), improve acute wellbeing (26), and reduce stress (25, 27) in people with BD. As with other studies of exercise in the treatment of mental illness, the limited number of studies on exercise intervention and BD are typically underpowered, have poor adherence and poor reporting of program variables. This makes replication and interpretation of study outcomes difficult.

To our knowledge, only one systematic review has been conducted on the effect of physical activity and exercise in people with BD (28). From the six studies included, the authors concluded that, while exercise may be feasible, more research is necessary before recommendations can be made for appropriate exercise prescription in individuals with BD. In a review of the neurobiological correlates to BD, Alsuwaidan and McIntyre (29) concluded that a program of exercise consistent with the public health dose of 30 min of moderate intensity exercise on most days of the week may be effective for individuals with BD (see **Table 1**). This recommendation was based on the findings from both animal and human studies, which show exercise may mediate the neurobiological dysfunction seen in people with BD.

Despite the research limitations, people with BD report that exercise assists with managing symptoms, except during periods of mania or severe depression (30). Experiences from people with BD suggest a need for flexibility to tailor exercise to the mood state (e.g., more rhythmic exercise during periods of mania) since exercise may exacerbate manic symptoms or result in injury due to overexertion (30). A more recent study (31) has confirmed these views, showing lower levels of exercise were associated with higher levels of depression, while higher levels of exercise were associated with more symptoms of mania. Supervised individualized exercise delivered by experienced exercise specialists may minimize the risk of adverse events during these times.

## LIMITATIONS ASSOCIATED WITH INTERPRETATION OF THE LITERATURE

A number of systematic reviews and meta-analyses have highlighted significant methodological weaknesses in many of the previously published studies including a lack of blinding to treatment, lack

of blinding of assessors, poor reporting of program variables, inconsistent use of assessment tools and high dropout (10, 32). More specifically, questions arise regarding the lack of comparison groups (7), lack of long-term data (10), significant heterogeneity (8, 16), and low sample sizes (9, 16). These limitations should be considered when interpreting the outcomes of systematic reviews and meta-analyses. Importantly, future studies should ensure these limitations are addressed in the design, implementation, and analysis of exercise interventions for people with affective disorders.

## RESEARCH TO PRACTICE

At present, the findings from systematic reviews reporting the effect of exercise on depression, PND and BD are somewhat conflicting. However, from the available evidence, exercise prescription based on current public health recommendations (15), the reviews of Lewis et al. (16), and Alsuwaidan and McIntyre (29), or the recommendations for people with depression (14), are likely to offer positive benefits with few adverse events.

In summary, supervised, individual, or group cardiovascular exercise, performed at low to moderate or self-selected intensity, for 30–40 min per session, with three to four sessions per week, over at least 9–12 weeks, is likely to be beneficial for people with affective disorders. The mode of cardiovascular exercise should be individualized according preference and access to resources. Walking or cycle exercise, pram-walking or other supervised group or individual cardiovascular exercise, is likely to be effective. The unique states of hypo- and hyper-mania should be considered when prescribing exercise for people with BD. It is our conclusion and recommendation that for effective exercise prescription, interdisciplinary care teams, comprising accredited exercise physiologists, physical therapists, mental health nurses, case managers, psychologists, and psychiatrists should strive to implement these guidelines to improve the mental and physical health of this vulnerable population.

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# Genetic modification of the effects of exercise behavior on mental health

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Anxiety and depressive disorders are a major contributor to the global disease burden (1). Although these disorders differ in duration and intensity, they are often chronic and treatment options include medication, psychotherapy, or a combination of both. In addition, regular exercise is argued to be effective in reducing anxious and depressive symptoms. Results from several meta-analyses indicate that exercise has a moderate to large antidepressant effect in clinical populations (2–6). Based on these studies, one might easily conclude that exercise consistently has beneficial causal effects on anxious and depressive symptoms (7).

The question remains whether this conclusion is also valid with regard to the general population as, despite these beneficial psychological effects, the majority of the population is not engaging in leisure-time exercise activities (8, 9) and population studies on the association between exercise and mental health are scarce. Secondly, there may be mechanisms that only mimic causal effects. The observed association between exercise and anxious–depressive symptoms might be due to underlying factors that influence both exercise behavior and symptoms of anxiety and depression. These factors can reside in the environment or in our genes. Underlying genetic factors might for instance have a detrimental effect on regular exercise behavior while simultaneously increasing the risk for depression, a mechanism known as genetic pleiotropy. The effect of these genetic factors on exercise behavior could even precede their effects on depression, thereby nearly perfectly mimicking a causal association. Only a few research groups have the optimal resources to investigate these possible effects in a genetically informative design, which requires large population-based longitudinal datasets with family data, but preferably twin data.

Results from population-based twin studies that have tested the nature of the association between a lack of exercise and anxious–depressive symptoms conclude that the association is best explained by underlying genetic effects. De Moor et al. (10) showed that within genetically identical twins, a twin who exercised more did not have fewer symptoms than his or her less exercising co-twin. This suggests that genetic factors independently cause low levels of exercise behavior as well as anxious and depressive symptoms. In addition, there is no evidence for causal influences of exercise behavior on feelings of psychological wellbeing, a phenotype presumably at the other end of the emotional scale, i.e., the absence of anxious or depressive symptoms (11, 12). Taken together, these studies conclude that the association between regular exercise and psychological wellbeing as well as the association between a lack of regular exercise and anxiety and depressive disorders largely reflect the effects of common genetic factors.

In an effort to explain the mechanisms that contribute to the association between exercise activities and mental health in the general population, a model was proposed that accommodates genetic pleiotropic effects, but still allows exercise to causally increase wellbeing in specific subgroups of the population (13). As with any other behavior, for exercise behavior to be repeated regularly, the net appetitive effects of exercise would need to outweigh the net aversive effects. Individuals who experience greater exercise induced mood enhancement are likely to repeat the behavior and become regular lifetime exercisers. This assumption is supported by several studies, which show that a more positive affective response during exercise was associated with greater participation in (voluntary) moderate to vigorous exercise (14, 15) or the intention to engage in voluntary exercise (16). Individual differences in these acute mood effects of exercise could be strongly co-determined by genetic factors.

In addition to differential acute mood effects, there could be a social-psychological mechanism that makes some individuals more attracted to exercise than others. Individuals with higher innate exercise capacities will gain more in exercise performance than others at comparable levels of training. The higher trainability and the superior exercise performance will lead to feelings of competence and mastery. This increased confidence, or self-efficacy, may not only enhance the frequency of exercise in individuals (17), but will also lead to higher self-esteem and in turn, in feelings of wellbeing. Vice versa, low trainability and lower levels of performance will lead to disappointment and particularly in adolescents to shame and lowered self-esteem. Genetic variation among people influencing exercise ability will therefore become associated with experiencing psychological beneficial effects of exercise activities and, as a consequence, with an increase in the frequency of exercising.

Major future challenges are to test the association between the level of voluntary exercise behavior and the acute and longer term psychological responses to exercise, and to establish the contribution of shared genetic factors to these associations. This requires a substantial family or twin study with measurements of exercise ability and the acute mood response to exercise. Various experimental design issues should be taken into account in these studies. First, the intensity at which an individual is exercising is an important determinant of the aversive responses to exercise: at intensities that exceed the individuals' ventilatory threshold (VT), when there is a transition from aerobic to anaerobic metabolism, negative changes in exercise induced mood response are observed (18). Measurements should therefore be standardized for the VT. Second, different types of exercise induced mood responses can be measured: during (immediate response on exercising) or (shortly) after the exercise bout (more complex, long lasting feelings). These responses may differ in origin, but are likely to contribute to the overall balance of appetitive and aversive effects of exercise, therefore, should both be included in measurements. For the assessment of exercise ability it is important to take into account a range of objective determinants like aerobic fitness, balance, flexibility and static, and dynamic muscle strength, but also record self-perceived exercise ability, particularly in relation to the relevant peer group.

Acknowledgment of the differential sensitivity to the psychological effects of exercise is of great importance. Some individuals may require a specific exercise program (with respect to intensity of exercise, absence or presence of competitive elements, and type of exercise) to create a situation in which the appetitive effects of exercise can predominate. This may ensure that these individuals continue to be engaged in regular exercise while maximizing their psychological benefits in terms of increased feelings of wellbeing and decreased levels of anxiety and depression.

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# Exercise and mental health: what did we learn in the last 20 years?

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Although an active lifestyle has always been recognized as the best way to achieve health in the entire history of civilization, over the last two decades, the concept of exercise as medicine (1), or as a preventive method, became increasingly accepted. Some authors consider physical exercise as a "polypill" that, besides many benefits in preventing and treating several diseases, has the advantage of not generating adverse responses and of being a low cost alternative compared to drugs, surgeries, and hospitalizations (2). Researches about the protective effects of physical training and of an active lifestyle in the prevention of metabolic and cardiovascular diseases are not altogether new. However, greater attention is being given to the effects of exercise upon the brain, cognitive function, and behavior (3–5). Since the classic study conducted by Van Praag (6), where the authors showed for the first time that animals submitted to voluntary exercise had an increased neurogenesis, exercise has been investigated as a potential enhancer of cognitive and behavioral functions. Fifteen years later, studies on animal models continue to unravel various neurobiological mechanisms associated with exercise. In another classic study on the neurobiology of exercise, Dishman et al. (3) showed us several ways to explain the prevention and treatment of diseases (including mental diseases) through physical exercise.

However, randomized control trials continue to progress slowly. Studies have shown behavioral, cognitive, and functional improvements in patients who are undergoing physical training, but few have focused on investigating possible neurobiological mechanisms in humans. A better functional capacity and an active lifestyle have been associated with a lower risk of developing neurodegenerative disorders (7), and mood and anxiety disorders (8–11), but the physiological mechanisms are unclear. Works investigating the acute and chronic effects of exercise on cognitive function show promising results in different age groups (children, youth, adults, and seniors) (12–15). However, many questions remain unanswered, such as the right amount of exercise to improve this protective response, the appropriate type, intensity and duration of the training session, and the minimum weekly frequency and duration of benefits after cessation of activity. It is time to think about what we have learned so far and what we still need to understand about exercise and mental health.

## WHAT DO WE KNOW SO FAR? HUMANS ARE MADE TO MOVE

In the evolutionary history of human species, several systems need to move to stay healthy and survive (16). Muscles, bones, and even the brain are made of billions of cells that need stimulation for biomolecular signals to occur. Our hearts need to keep beating in order to pump oxygen and energy substrate throughout the entire human body, as much as the skeletal muscles need to be constantly stimulated to synthesize specific myokines that are necessary to maintain health and metabolic activities (17, 18). The extracellular signaling, through neurotransmitters, hormones, growth factors, cytokines, or even mechanical forces, has to constantly occur in order to inhibit the cellular apoptosis and maintain mitochondrial activity and protein synthesis (2). Physical training can promote this stimulus from the brain to the muscle, or vice versa. Although there is a vast literature on the mechanisms of exercise on physical and mental health, one of the main hypotheses is associated with mitochondria, a critical organelle for the survival and the appropriate functioning of cells and, consequently, of every system.

Mitochondrion is a strong candidate to mediate the relationship between exercise and the reduced risk of frailty and mental illness. It is our powerhouse, generating the chemical energy (ATP) necessary for cell survival. On the other hand, it is also responsible for the production of reactive oxidative species (ROS) related to inflammatory processes, aging, and several metabolic and mental diseases (19, 20). According to Radak (21–23), although exercise is associated with acute increases of ROS, chronic alterations related to adaptation to this kind of stimulus contribute to an increased antioxidant enzymes activity. Moreover, exercise promotes mitochondrial biogenesis and makes enzymes more efficient (oxidant and antioxidant), contributing to improved metabolism, function, and cell survival throughout the entire body (24, 25).

Metabolism and protein synthesis maintenance is another important exercise mechanism for promoting health. Inducing the production of trophic factors (such as BDNF, IGF-I, VEGF, GNF) and neurotransmitters (such as dopamine, serotonin, and norepinephrine) contributes to various brain responses, for instance, increased neurogenesis, angiogenesis, synaptogenesis, and inhibition of caspases (3–6, 26–29). Moreover, the increase of neurotropic factors induces presynaptic signals associated with increased release of neurotransmitters in the synaptic cleft and the resulting growth in synaptic transmission and neuroplasticity (30–34). BDNF also contributes to increased long-term potential (LTP) (35–37). During exercise, besides

activating motor circuit areas, associative and limbic areas also benefit from the increased synthesis and release of dopamine. Moreover, the activation of opioid and cannabinoid systems contributes to acute anxiolytic response to exercise (30–34, 38).

## WHAT SHOULD WE DO? TYPE, FREQUENCY, DURATION, AND INTENSITY OF EXERCISE: IS MORE NECESSARILY BETTER?

Although many neurobiological mechanisms justify the use of exercise in treating mental illness, it is uncertain how we may prescribe this "polypill." For example, we know that both aerobic and strength training contribute to improve cognitive function, especially the executive function (13–15, 39), and to reduce depressive symptoms (4, 40, 41). It is also known that this improvement may occur through distinct or redundant neurobiological pathways, such as increased neurotrophins. However, there are currently no evidences indicating if certain exercises, e.g., stretching or swimming, would also be favorable. Moreover, it is known that aerobic exercise at moderate intensity (41, 42) contributes to reducing depression and increasing the rate of remission and response among elderly patients. However, it is unclear if these patients would benefit more from making high-intensity interval workouts. Studies indicate that patients with neurodegenerative diseases such as dementia benefit from aerobic exercises. Recently, our laboratory found that elderly people with Alzheimer's disease have better response to treatment when performing a 30-min walk on the treadmill at a moderate intensity (43). There is only one study submitting patients with AD to a strength training protocol, which found a favorable response in strength and functional capacity. However, the authors did not investigate clinical issues associated with the disease (44). Therefore, it is not possible to indicate this type of exercise for better response to AD treatment.

## CONCLUSION

Although there are many neurobiological evidences indicating exercise programs to reduce symptoms and increase treatment response of several mental disorders, there is still a long way to go in clinical randomized control trials. Authors in this area need to make an effort to find evidences that may help to determine a more adequate prescription of exercise (type, duration, frequency, and intensity) for each diagnosis of mental illness.

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# Trophic mechanisms for exercise-induced stress resilience: potential role of interactions between BDNF and galanin

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Current concepts of the neurobiology of stress-related disorders, such as anxiety and depression emphasize disruptions in neural plasticity and neurotrophins. The potent trophic actions of exercise, therefore, represent not only an effective means for prevention and treatment of these disorders, they also afford the opportunity to employ exercise paradigms as a basic research tool to uncover the neurobiological mechanisms underlying these disorders. Novel approaches to studying stress-related disorders focus increasingly on trophic factor signaling in corticolimbic circuits that both mediate and regulate cognitive, behavioral, and physiological responses to deleterious stress. Recent evidence demonstrates that the neural plasticity supported by these trophic mechanisms is vital for establishing and maintaining resilience to stress. Therapeutic interventions that promote these mechanisms, be they pharmacological, behavioral, or environmental, may therefore prevent or reverse stress-related mental illness by enhancing resilience. The present paper will provide an overview of trophic mechanisms responsible for the enhancement of resilience by voluntary exercise with an emphasis on brain-derived neurotrophic factor, galanin, and interactions between these two trophic factors.

**Keywords: galanin, running, BDNF, resilience, psychological, anxiety, depression**

## TROPHIC MECHANISMS FOR EXERCISE-INDUCED STRESS RESILIENCE: POTENTIAL ROLE OF INTERACTIONS BETWEEN BDNF AND GALANIN

Clinical studies convincingly establish the efficacy of exercise in the treatment of anxiety and affective disorders (1–3). However, understanding the neurobiological mechanisms responsible for these beneficial effects, a goal that necessitates the application of rodent models, remains a challenge. Since deleterious stress lies at the core of anxiety and depression, understanding the neurobiological impacts of stress, and the mechanisms for adapting to it will significantly enhance the development of more effective prevention and treatment. Recent advances in exercise neuroscience using rodent models have shed new light on the neural mechanisms by which physical activity produces long-term adaptations in brain circuits implicated in anxiety and depressive disorders. This literature reveals that the most significant impact of exercise on stress may not pertain to regulating transient states occurring in the presence of the stressor, but rather on moderating the long-term impact that acute stress may incur on subsequent stress events. The key benefit of exercise may thus involve the promotion of stress resilience.

The present paper will focus on stress resilience as a fundamental phenomenon underlying the beneficial effects of exercise, and it will briefly review the neurotrophic hypothesis of stress resilience. Two trophic mechanisms that may be involved in the stress resilience will be examined; one involving the widely studied brain-derived neurotrophic factor (BDNF) system and another based on the lesser-known trophic actions of the peptide galanin. The purpose of this comparison will be to point out a critical area for future investigation, which should aim to uncover how different trophic mechanisms may interact to promote optimal neural function.

## EFFECTS OF EXERCISE IN RODENT MODELS OF DEPRESSION AND ANXIETY AND THEIR IMPLICATIONS FOR STRESS RESILIENCE

Though exercise represents an effective intervention for stress-related disorders in humans, evidence for its antidepressant and anxiolytic efficacy in rodent behavioral models is surprisingly inconclusive. In recent, comprehensive reviews of the anxiolytic and antidepressant effects of exercise in rodent models a common theme emerges, in which that exercise produces mixed and conflicting effects in standard rodent tests of anxiety and depression (4–6). Much of the conflicting evidence derives from the species or strain used as subjects, duration, and mode of exercise employed as the independent variable, and the selection of model that serves as the dependent measure of depressive- or anxiety-like behavior. Experiments employing forced modes of exercise, such as treadmill or swimming, introduce the confounding factor of stressor exposure on subsequent measures of stress-related behavior and are thus difficult to interpret. Furthermore, rodent paradigms that putatively model depressive-like behavior are plagued by questions of validity, and the most widely employed "models," such as the forced swim or tail suspension tests, are better characterized as bioassays or screens for pharmacological manipulations with potential antidepressant activity (7). A particularly problematic aspect of these models is that they are too often assumed to represent the chronic, self-perpetuating nature of major depression by assessing a "snapshot" of spontaneous responsiveness to an acute stressor when no predisposing factors have been manipulated.

They also assume that antidepressant actions may be observed in a healthy subject. It is with these caveats in mind that one must cautiously interpret the reports that exercise may exert either antidepressant-like, "pro-depressive," or no effects in the forced swim or similar tests (5, 8, 9).

Similar problems of interpretation arise when critically examining exercise effects in anxiety models. When such models are applied as a single measure of spontaneous behavior in the presence of the mild stress associated with standard tests, it is difficult to ascertain whether increased responding reflects behavior reminiscent of anxiety or, rather, adaptive coping to the exigencies of the stressor. Both interpretations have been proposed in previous studies, and exercise has been variously characterized that has anxiogenic, anxiolytic, or without effect (4–6). This range of contradictory results is evident even when focusing on a single model, the elevated plus-maze. After systematically reviewing this literature, we have proposed that understanding the effects of exercise hinge upon examination of the longitudinal impact of stress exposure on subsequent responding (6). We have thus shown that the anxiolytic-like effects of exercise are only consistently observed in standard models of anxiety when rats have been previously exposed to a different type of stressor. Exercise, thus appears to promote resilience to stress.

## TROPHIC MECHANISMS IN STRESS RESILIENCE

Emerging concepts of the neurobiology of stress-related disorders, such as anxiety and depression emphasize disruptions in neural plasticity and trophic mechanisms (10, 11). Current research on the neurobiology of stress, thus, increasingly involves measures of neurogenesis, dendritic arborization, dendritic spine maintenance, synaptogenesis, and other forms of plasticity. This new perspective on the neurobiological basis of anxiety and depressive disorders is superseding traditional explanations that emphasize dysfunction in monoaminergic transmission as the primary etiological mechanism. The focus is thus shifting to the role of disruptions in trophic factor signaling, especially in corticolimbic circuits that mediate and/or regulate cognitive, behavioral, and physiological responses to stress. Recent evidence demonstrates that the neural plasticity supported by these trophic mechanisms is vital for establishing and maintaining stress resilience (12, 13). Stress-induced atrophy of the hippocampus has been linked to decreased resilience in clinical populations and rodent models (11, 14–16). Maintenance of plasticity in the medial prefrontal cortex (mPFC) also plays a crucial role in stress resilience, and disturbances in this plasticity are linked to the pathophysiology of depression and anxiety (17–21). The translational value of this new perspective on trophic mechanisms will be the identification and development of therapeutic interventions that enhance resilience-promoting plasticity, be they pharmacological, behavioral, or environmental.

## ROLE OF EXERCISE-INDUCED REGULATION OF HIPPOCAMPAL BDNF IN ANXIETY AND DEPRESSION

The prominence of trophic mechanisms in determining the pathophysiology of anxiety and depression compels further examination of the profound influence exercise exerts on trophic factor expression. Much work already has demonstrated the capacity for exercise to induce a variety of trophic factors in the brain and periphery, such as BDNF, insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), and the inflammatory protein VGF (11), but most of this previous research has focused on BDNF signaling in the hippocampus (11, 22–24).

Brain-derived neurotrophic factor is a member of the neurotrophin family, a group of structurally related peptide growth factors that signal through TrkB receptors (22). BDNF is directly implicated in various forms of hippocampal plasticity induced by exercise (25, 26), leading many researchers to hypothesize that this action may mediate antidepressant and anxiolytic effects of exercise (11, 15, 23). This hypothesis is supported by numerous findings of relationships between exercise, BDNF, hippocampal plasticity, and antidepressant actions. For example, exercise consistently elevates BDNF expression in the hippocampus (23, 27, 28) and potentiates the antidepressant activity of antidepressant drugs in the forced swim test [(9); though c.f. (8)]. Antidepressant effects of exercise in mice are eliminated by BDNF knockout and inhibition of MAPK signaling, an intracellular mediator of BDNF (29). Exercise also reliably enhances hippocampal neurogenesis (30). This evidence has provided the foundation for the hypothesis that the beneficial effects of exercise are mediated specifically by BDNF-induced neurogenesis in the hippocampus. This hypothesis is an extension, what is generally referred to as the "neurogenesis hypothesis of affective disorders." Some reports from the exercise literature support this hypothesis (11, 25), though systematic reviews of studies linking hippocampal BDNF to antidepressant actions in humans and rodent models found many disassociations between BDNF and depression (31, 32). With respect to neurogenesis specifically, exercise-induced hippocampal neurogenesis is associated with increased spontaneous anxiety-like behavior, an effect that is reversed after irradiation, which effectively eliminates neurogenesis (33, 34). As described above, the discrepancies in the literature may relate to whether the behavioral paradigm measures acute stress reactivity or the longitudinal impact of stress (i.e., resilience). They may also depend on the nature of trophic factor-mediated plasticity in the hippocampus. In addition to its neurogenic effects, exercise induces other forms of plasticity in hippocampal neurons, such as alterations in dendritic spine architecture (23), which must be considered in accounting for antidepressant or anxiolytic effects.

The studies presented above establish links between exercise, BDNF, and antidepressant actions. However, whether BDNF-dependent actions of exercise in the hippocampus reflect antidepressant effects *per se* or some underlying process such as stress resilience is not clear. Hippocampal administration of BDNF does not reverse the exaggerated stress response exhibited by rats previously exposed to uncontrollable stress, and a pharmacological manipulation that reduces hippocampal BDNF does not exacerbate the effects of stress on subsequent stress responses (35). These findings suggest that BDNF signaling in the hippocampus does not have a generalized influence on stress resilience.

## POTENTIAL ROLE OF EXERCISE-INDUCED REGULATION OF LOCUS COERULEUS GALANIN IN STRESS RESILIENCE

As discussed above, exercise increases the expression of a wide range of trophic factors throughout the brain. A fuller understanding of how trophic mechanisms are involved in the beneficial effects of exercise on stress-related behaviors, therefore, requires expanding the scope beyond BDNF in the hippocampus and examining other trophic systems. Galanin is a neuromodulatory peptide and trophic factor that exerts multiple effects through its interaction with specific G protein-coupled receptor subtypes designated GalR1, GalR2, and GalR3 (36, 37). Both galanin and its receptors are widely distributed in several brain systems, and galanin signaling thus impacts a variety of cognitive, behavioral, and endocrine functions. Some of the highest concentrations of galanin are found in the locus coeruleus (LC), where galanin is colocalized in over 80% of noradrenergic neurons (38). Galanin-containing LC neurons extensively innervate the mPFC, where galanin-immunoreactive terminals and GalR2 receptors are present in relatively high densities (39–41).

Research from my laboratory has repeatedly shown that 3 weeks of voluntary exercise elevates galanin gene expression in the LC in a running distance-dependent fashion (42–44). We have also shown that exercise exerts antidepressant effects in chronic models of depression (45), and chronic antidepressant treatment elevates galanin mRNA in the LC similarly to exercise (46). This evidence raises the obvious question of whether galanin exerts antidepressant and/or anxiolytic effects. Reviews of the extensive literature on the effects of galanin on anxiety- and depression-related behaviors show that galanin's effects on these behaviors, like those of exercise, are mixed and conflicting (47). Most of these previous experiments involved acute, central administration of galanin receptor ligands with subsequent tests of spontaneous behavior in standard models. With regard to galanin/GalR1/GalR2 transgenic mice, the findings are even more conflicting with predominantly negative findings in most standard anxiety and depression models (47).

Despite these confusing results, the behavioral evidence is clearer in experiments that examined galanin's influence on the longitudinal impact of stress. For example Lu et al. (48) reported no effect of GalR2 knockout on spontaneous behaviors such as elevated plus-maze, light/dark transition, forced swim, or tail suspension tests. However, GalR2 knock-out mice exhibited increased susceptibility to the repeated stress employed in a "learned helplessness"-like paradigm compared to wild type mice. Unlike the other tests, "learned helplessness" paradigms examine the impact of uncontrollable stress exposure on subsequent responding to repeated stressors. Loss of GalR2 led to a susceptible phenotype in this paradigm, suggesting that galanin signaling through GalR2 is necessary for resilience. Further supporting a specific role for GalR2 in resilience, transgenic overexpression of GalR2 in several frontocortical areas, including mPFC, was found to decrease immobility in a version of the forced swim test that involved pre-exposure to swim stress on the previous day (49). In contrast, GalR2 overexpression had no effect on elevated plus-maze or novel open field exploration in mice not previously exposed to stress. The behavioral literature thus points to functions for galanin beyond neuromodulatory effects. Galanin and GalR2 in particular, are evidently involved in protecting against the lasting consequences of an acute stress event by diminishing reactivity to subsequent stressors rather than by modulating reactivity to the acute stress event itself. This long-term protection suggests a role for galanin in the plasticity underlying resilience.

Galanin is well positioned as a trophic factor expressed in high concentrations in the LC to modify neural architecture in stress-responsive targets such as the mPFC. As described above, maintenance of dendritic spines in the mPFC may provide a cellular mechanism for resilience. Recent studies of galanin have revealed specific actions on neurite dynamics mediated by activation of GalR2 (50, 51). GalR2-mediated activation of Gq/11 influences multiple downstream targets, which includes inhibition of the RhoA GTPase. Galanin thus promotes neurite formation in neuronal cultures through a pathway involving GalR2-mediated inhibition of RhoA-ROCK signaling through LIMK, with subsequent activation of the actin-binding protein cofilin (51). Stress is associated with excess activation of RhoA, which leads to a reduction in spine densities (52). GalR2-mediated inhibition of RhoA-ROCK signaling thus provides a hypothetical mechanism for galanin-mediated protection against stress-induced spine atrophy. GalR2-signaling may also stabilize neurites via maintenance of microtubule integrity by promoting aggregation of microtubule-associated protein 2 (MAP2) and β-tubulin (53), a process that may also involve inhibition of RhoA (54). These actions of galanin represent candidate mechanisms for protection against dendritic spine atrophy induced by stress.

## POTENTIAL INTERACTIONS BETWEEN BDNF AND GALANIN IN OPTIMIZING NEURONAL FUNCTION

Though BDNF and galanin share common neurotrophic functions, focusing on how the systems interact provides a new approach to understanding neural plasticity. Intracellular signaling of BDNF and galanin converges in many pathways, but their mutual influence on MAP2 may reflect complementary mechanisms to promote spine maintenance during the physiological challenges imposed by stress at the cellular level. TrkB-mediated BDNF signaling promotes the expression of MAP2 and microtubule assembly (54), whereas GalR2-signaling may be more involved in maintaining microtubule assemblies by inhibiting MAP2 phosphorylation, as described above. The two trophic systems may thus mutually maintain microtubule integrity, but through distinct mechanisms. Conversely, BDNF and galanin signaling pathways diverge in the area of coflin activation. Binding of BDNF to TrkB activates a LIMK through a RAC1 pathway, which ultimately leads to the inactivation of cofilin (54). That GalR2-signaling leads to the activation of cofilin through inhibition of LIMK suggests that BDNF and galanin may exert counter-regulatory influences in their mutual function to promote spine maintenance.

Counter–regulatory interactions between galanin and BDNF are also evident at the systems level. Left unchecked, exercise-induced elevations in BDNF may lead to state of neuronal hyperexcitability (22). Exercise induces a long-term enhancement of glutamatergic activity through upregulation of NMDA receptors (30). Additionally, enhanced transmission through AMPA receptors promotes $Ca^{++}$-mediated BDNF release and signaling through TrkB (11, 54). The resulting BDNF-mediated effects on

synaptic plasticity may further enhance excitatory glutamatergic transmission. This positive feedback loop between BDNF and glutamatergic activities accounts for the increased seizure vulnerability and excitotoxicity seen following experimental manipulations that enhance BDNF function, particularly in the hippocampus (55–57). This potential state of hyperexcitability following BDNF upregulation may also account for the finding of increased vulnerability to kainic acid-induced excitotoxicity following direct injection into the hippocampus of anesthetized rats that had undergone several weeks of exercise (58). In contrast to this finding in anesthetized rats, we have shown decreased vulnerability to kainic acid-induced seizures in awake, freely behaving rats (59). The galanin receptor antagonist M40 blocked this exercise-induced protection against seizures. Taken together, the evidence suggests that under normal physiological conditions, the potential state of hippocampal hyperexcitability induced by elevated BDNF may be regulated by the galanin system. The anticonvulsant and neuroprotective properties of both endogenous and exogenous galanin are well established (50, 60, 61). The dense innervation of the hippocampus by galaninergic projections originating from the LC (62), the presence of galanin receptors in this structure (63), and the increase in galanin with exercise (42–44), all point to this system as a regulatory mechanism controlling the deleterious consequences of exercise-induced upregulation of BDNF.

## CONCLUSION

The trophic influences of exercise, which are mediated by a wide range of neural and humoral factors, are well known. This body of knowledge fits well with new concepts of anxiety and depression as they relate to disturbances in neuroplasticity, and it reveals a compelling neurobiological mechanism that explains the beneficial effects of exercise on stress-related disorders. The literature from rodent models suggests that the primary benefit of exercise may be the promotion of resilience to stress. The translational value of this hypothesis may be realized through the promotion of exercise as a means to mitigate the longitudinal and cumulative impact of the repeated stressors. Exercise may thus afford both preventative and therapeutic benefits. Given the array of neurotrophins influenced by exercise, the next challenge for future research will be to examine how these varied mechanisms coordinate to optimize neuronal health. The interactions between BDNF and galanin represent an informative example of how trophic mechanisms that mutually promote the maintenance and survival of neurons may require reciprocal regulatory influences to achieve their ultimate benefit.

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