Maturitas 106 (2017) 48–56

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Review article

Exercise and mental health

Kathleen Mikkelsen[a], Lily Stojanovska[a], Momir Polenakovic[b], Marijan Bosevski[c], Vasso Apostolopoulos[a,*]

[a] Centre for Chronic Disease, College of Health and Biomedicine, Victoria University, Melbourne, Australia
[b] Macedonian Academy of Science and Arts, Skopje, Macedonia
[c] University Cardiology Clinic, Medical School, Skopje, Macedonia

ARTICLE INFO

Keywords:
Inflammation
Immune system
Exercise
Mental health
Mood stress

ABSTRACT

There is a growing body of literature that recognizes the positive effects of exercise on mood states such as anxiety, stress and depression, through physiological and biochemical mechanisms, including endorphins, mitochondria, mammalian target of rapamycin, neurotransmitters and the hypothalamic-pituitary-adrenal axis, and via the thermogenic hypothesis. In addition, psychological mechanisms influence the effects of exercise on mood states, as suggested by both the distraction hypothesis and the self-efficacy hypothesis. Exercise has also been shown to reduce inflammation via several different processes (inflammation, cytokines, toll-like receptors, adipose tissue and via the vagal tone), which can contribute to better health outcomes in people suffering from mood disorders.

1. Introduction

There are many studies advocating the positive effects of exercise on mental health [1–8]. The general outcome from research indicates that exercise can bring about many physiological changes which result in an improvement in mood state, self-esteem and lower stress and anxiety levels. The physical effects of exercise include reduction of blood pressure, enhanced cardiovascular fitness, weight loss, and prevention of chronic diseases such as cancer, diabetes, hypertension, obesity, osteoporosis and cognitive conditions like Alzheimer's [9–13]. As yet, there is no conclusive proof that implicates a single mechanism or group of mechanisms that reliably affect the exercise-mood relationship, nor does it seem that the nature of exercise being either aerobic or anaerobic is a significant factor as both forms of exercise can bring about an improvement in mental health [14–16].

It appears that the benefits of exercise come about by numerous physiological or psychological changes. Physiological effects of exercise can include an increase in endorphin levels [17–20], body temperature [21–24], mitochondrial function and mitochondriogenesis [25–27], an increase in the mammalian target of rapamycin (mTor) signalling [28–30], neurotransmitter production [31–34] and attenuation of the hypothalamic pituitary-adrenal (HPA) axis response to stress [15,27,31]. Whilst psychological effects may include a distraction from feelings of depression and anxiety [35–37] and positive feelings associated with mastery and selfefficacy [8,38–40]. There is much evidence that inflammation and inflammatory diseases contribute to mood disorders and poor mental health, and it seems that exercise may help to lower inflammation and be beneficial in contributing to better mental health outcomes in patients who suffer from inflammatory disorders [1,41–44]. The purpose of this article is to highlight current and developing knowledge of the positive effects of exercise on mental health.

2. Methodology

This review article presents current knowledge of the benefits associated with exercise on mental health and the physiological and psychological mechanisms contributing to these benefits. PubMed, Google Scholar and Medline were searched for relevant articles using the following key terms: Exercise OR physical activity AND mental health, exercise OR physical activity AND depression, exercise OR physical activity AND stress, exercise OR physical activity AND anxiety, exercise AND inflammation, exercise AND inflammatory disease. Publications in the last 10 years are mostly cited.

3. Exercise and mental health

There has been much research into the effects of exercise on mental health [45,46]. This research repeatedly suggests that regular physical activity can significantly improve mental health and lessen symptoms of depression anxiety and stress [14,47–50]. It is even suggested that physical activity can enhance mental wellbeing as equally as

* Corresponding author.
E-mail address: vasso.apostolopoulos@vu.edu.au (V. Apostolopoulos).

http://dx.doi.org/10.1016/j.maturitas.2017.09.003
Received 28 August 2017; Received in revised form 4 September 2017; Accepted 6 September 2017

psychotherapy [49]. In fact, just 20–40 min of aerobic exercise can improve anxiety and mood for several hours, although people suffering from acute anxiety have been shown to respond better than those suffering from chronic anxiety [48,49]. In addition, physical activity tends to occur less in people who suffer from depression and the mental health benefits of exercise are more pronounced in people suffering from anxiety and depression compared to those that do not [51]. Panic disorder is also improved with physical activity. Furthermore, depressed mood, which is associated with increased anger, confusion, fatigue, tension, and reduced vigour, could be alleviated by exercise (as measured by the profile of mood states psychological rating scale); although this was more pronounced in patients who suffered depressed mood prior to exercise compared to those who did not [11]. Likewise, the beneficial effects of exercise are also seen in the elderly and adolescents with depression or anxiety, although such reports are limited [48]. On the contrary, exercise can have a detrimental effect on the mental health of people who become overly addicted. Exercising to an excessive degree can result in mood and behavioural disorders and a decline in physical health [49].

3.1. Aerobic versus non-aerobic exercise regimes

It is important when considering the effect of exercise on mental health that the definition of "exercise" is understood. Often the term exercise is used as an umbrella term to encompass both physical activity and exercise, yet exercise is essentially a subcategory of physical activity. Physical activity involves bodily movement produced by skeletal muscles which expends energy, whereas exercise is described as "planned, structured, repetitive and purposive in the sense of improvement or maintenance of one or more components of physical fitness" [52]. Physical fitness, by contrast, is a set of attributes that people set out to achieve or innately possess. Physical fitness can be divided into health-related fitness (cardiorespiratory and muscular endurance, muscular strength, body composition, flexibility) and skill related fitness (agility, balance, co-ordination, speed, power, reaction time). It is necessary to make the distinction between health and skill related fitness, when defining the nature of the physical activity in order to improve mental health.

Most studies which ascertain the effects of exercise on mental health, use an exercise program focussing largely on cardiorespiratory conditioning, utilizing aerobic exercise forms which use prolonged activity of large muscle groups, eg. treadmills [1,5]. There are fewer studies on alternate forms of physical training which work on muscular strength, flexibility, agility, balance and co-ordination. This type of training can come in the form of yoga, tai chi, dance, martial arts etc. However, such non- aerobic exercise forms also show increased benefits to mood outcomes. Indeed, yoga and swimming activity was shown to greatly improve anger, confusion, tension, and depression in people when compared to those that did not partake in any physical activity [47]. Hence, aerobic exercise may not be the only form of exercise which can positively affect mood enhancement. In a randomized controlled study of 79 participants with anxiety disorders, the effects of aerobic (brisk walks or jogging) versus non-aerobic (muscular strength, flexibility and relaxation) exercise regimes showed that anxiety scores were improved similarly in both groups [16]. Likewise, 91 inpatients with major depression, dysthymic disorder or depressive disorder were randomly assigned to aerobic versus non aerobic exercise regimes for 8 weeks and depression scores were reduced in both groups. There were no differences between the groups, hence, the anti-depressive effects noted are not restricted to the aerobic physical activity regime [53]. Furthermore, aerobic exercise and meditation-relaxation therapies could be as effectual in decreasing symptoms of depression as psychotherapy. A study involving 74 participants with clinical depression were randomly allocated to either running therapy, psycho-therapy or meditation-relaxation therapy for 12 weeks. Symptoms of depression were reduced significantly in all 3 groups but statistical comparisons between the 3 groups were non-significant [54]. Oh et al. conducted a study which set out to understand the relationship between different types of exercise and quality of life of 7550 patients in Korea suffering from metabolic syndrome. The study compared resistance training, flexibility and walking on 5 subsets of quality of life (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). It was noted that all exercise regimes showed improved quality of life than those who did not exercise, and walking exercise was found to further increase quality of life in those patients who suffered from metabolic syndrome than those who did not [55].

The consistency of exercise may also play a part in positive health outcomes. Data from several waves of the Taiwanese longitudinal study on ageing, dating from 1996 to 2007, was retrospectively analysed. It was concluded that consistent exercise, even if the duration was as short as 15 min, 3 times a week was significantly associated with lower risk of depressive symptoms [7]. It is apparent that exercise improves mental disorder symptomatology and both aerobic and non-aerobic exercise regimes appear to be similarly effective.

3.2. Beneficial effects of exercise on mental health

One of the most common mental health disorders is anxiety, which affects a person's ability to concentrate, sleep and carry out daily tasks. Studies indicate that exercise can reduce anxiety levels, whereas those who are not physically active are associated with higher levels of anxiety. Indeed, a meta-analysis study of 42,264 persons showed that exercise improved anxiety levels, with exercise being more beneficial to those with anxiety compared to those with non-clinical, normal range psychological disorder [51]. Furthermore, depression which is categorized into a range of different types can be prevented if exercise is included on a regular basis. Exercise can also be used to treat symptoms of mild depression. In fact, regular exercise is significantly associated with lower depression and anxiety frequency in a cross sectional study of 269 adults [56]. Likewise, in healthy adults, qigong exercise was shown to relieve anxiety and reduce stress levels in a systematic review of 7 randomized controlled studies [57]. In 18 male runners with exercise addiction, during exercise withdrawal for 2 weeks there was an increase in depression, fatigue, anger and confusion and decreased vigour mood compared to control non-withdrawal group [58]; such symptoms improved once exercise resumed. In addition, in a meta-analysis study of 48,207 participants, it was shown that exercise improved depression [51]. In a systematic review of 8 randomized clinical trials, reduction of anxiety symptoms were noted but was less effective to anti-depressant medication, although exercise combined with medication significantly improved clinical global impression outcomes [59]; in these studies there were no differences in aerobic versus non-aerobic exercise regimes. In cancer patients, a home-based exercise regime 3 days/week for 40 min over 12 weeks significantly improved anxiety and depression levels compared to the usual care group of patients [60]. In addition, patients with end stage renal disease randomized to either endurance or resistance training 3 times/week for 6 months significantly improved mood and reduced anxiety [61]. Furthermore, individuals with posttraumatic stress disorder who completed 2 weeks of stationary bike aerobic exercise reported significant clinical reductions in posttraumatic stress disorder severity [62]. Even after a single bout of exercise (either yoga or aerobic exercise) in patients with schizophrenia, showed significant decreased anxiety and psychological stress and increased subjective wellbeing compared to patients with schizophrenia with no exercise [63]. Similarly, 41 participants who completed a single session of 30 min aerobic exercise showed significant reductions in all dimensions of anxiety sensitivity but not intolerance of uncertainty or distress compared to control subjects [64]. Thus, exercise seems effective to improve certain mental health vulnerabilities, and may be a viable adjunctive treatment for psychotherapy.

As depression and anxiety are commonly seen in the ageing

population (in addition to insomnia), especially postmenopausal women, a randomized controlled pedometer based walking trial was conducted in 106 postmenopausal women for 12 weeks. It was clear that the levels of insomnia, anxiety and depression were significantly decreased [65]. In addition, the ageing population will develop some degree of decline in cognitive capacity. In a meta-analysis study, the effects of exercise training in elderly individuals with cognitive impairment and dementia showed that exercise training increases fitness, physical function, cognitive function, and positive behaviour [10]. Another study highlighted the improvement of quality of life in elderly Icelanders after completing 12 weeks of resistance training [9]. Similarly, young adults and children can benefit from mental health effects gained by participating in regular physical activity. In a systematic review of 16 randomized controlled trials, a trend was noted in favor of exercise in reducing anxiety and depression scores in children and young individuals up to the age of 20 [66]. More recently, Iceland has implemented an afterschool exercise program for all children which has successfully decreased crime rate and depression amongst the their youth [67].

3.3. The negative effects of exercise on mental health

Very high training loads can lead to detrimental effects, such as, induction of an anti-inflammatory state which may increase the risk of developing minor infections such as upper respiratory tract infections. This is a phenomenon often seen in elite athletes who spend many hours training hard [43]. The anti-inflammatory effects of exercise may contribute to a reduction in the efficacy of the immune system. In fact a study of endurance athletes prone to upper respiratory infection, found that IL-10 production was 4 times higher than in athletes that were illness free [68]. Negative self-image and perceptions of body weight are more likely to lead people towards physical activity, particularly adolescents [69] however, exercise as a weight management strategy can be compulsive and lead to distressing health outcomes, especially when coupled with eating disorders such as bulimia, purging and restrictive types such as anorexia nervosa [70,71]. People who become exercise dependent and exercise obsessive are at risk of suffering exercise induced injury. Often it is difficult however for these people to abstain from their exercise regime as they can experience withdrawal symptoms similar to those of substance addicts. Drawing on the data from a study conducted in 1601 college students, it was shown that exercise dependence adversely affected psychological health, with exercise dependent students scoring higher on anxiety and depression scales and suffering negative affect's on mood, self-satisfaction, social behaviour and energy levels [72].

4. The physiological mechanisms of exercise on mood states

There are several physiological and biochemical hypotheses put forward as to why exercise improves mood and mental health. These include the endorphin hypothesis, the thermogenic hypothesis, mitochondrial dysfunction, mammalian target of rapamycin (mTOR), neurotransmitter dysfunction and the hypothalamic pituitary-adrenal (HPA) axis, all of which have been proposed to play a mechanistic role in altered mental states (Fig. 1).

4.1. Endorphin hypothesis

The principal function of endorphins is to aid the body to endure pain in periods of prolonged pain and stress. Numerous athletes report feelings of euphoria, sedation and analgesia following intense training sessions and these feelings of well-beingoften referred to as the "runners high" is a well-known phenomenon amongst athletes. These effects have primarily been attributed to the action of endorphins and indeed several studies have verified elevated plasma levels of endorphins after exercise [18,20]. In 30 mildly depressed males randomly assigned to 1 of 3 groups of varying exercise intensity for 6 weeks, it was noted that those undergoing high and moderate intensity exercise showed improvement in depression levels whilst the low intensity group did not; the endorphin levels in this study was inconclusive [73]. However, in exercise addicted runners who withdrew from running for 2 weeks – upon exercise resuming, there was an increased correlation in endorphin levels [58]. Additionally, other studies have shown that the administration of naloxone (an endorphin antagonist), in high doses can prevent opiate receptor activity associated with mood changes [19,74]. It is difficult however, to verify the significance of the results supporting the endorphin hypothesis as serum levels may not reflect endorphin levels in the central nervous system and assessment of this is a highly invasive procedure which in itself, would affect mood. Of interest, the endocannabinoid system has positive effects on depression. Indeed, high intensity exercise in 11 healthy individuals markedly increased levels of endocannabinoids which may influence the effects of depression [75]. More recently, subjective feelings of well-being were assessed after prolonged exercise in mice (via a running wheel) and noted that endocannabinoid levels were significantly increased and anxiety and sensation of pain were decreased [17]. This is one of the first demonstrations that the "runners high" may correlate with the expression of cannabinoid receptors and subsequently have an effect on depression outcomes.

4.2. Thermogenic hypothesis

The thermogenic hypothesis states that an increase in body temperature is responsible for increase in mood elevation after exercise which can lead to a reduction in symptoms of anxiety [49,76]. An increase in temperature in certain brain regions, such as the brain stem may be the main contributing factor to a decrease in muscular tension and feelings of overall relaxation [77]. This thermogenic hypothesis however remains largely unsupported and in a few studies refuted. For example, the relationship between body temperature and anxiety in respect to exercise was studied. Three temperatures; normal, cooler than normal and warmer than normal were compared. It was noted that although all 3 temperatures resulted in reduced anxiety of the participants there was not enough variance between the 3 temperatures to account for this reduction [22]. Furthermore, the thermogenic hypothesis was studied in acute exercise declaring increased body temperature may lead to decreased self-reported anxiety, however, no correlation to support this hypothesis was noted [24]. Conversely, in a different study, an increase in body temperature caused an increase in anxiety when body temperature was manipulated experimentally [21,23].

4.3. Mitochondrial function

Energy production, modulation of calcium signalling and cellular redox balance are important contributions made by mitochondria to the maintenance of everyday cell and tissue functions. The numbers and location of mitochondria in the body have great impact on their functional role, and maintenance of a healthy mitochondrial population involves an intricate system of quality control. Skeletal muscle, which comprises 40% of total body mass, undergoes a natural process with ageing called sarcopenia. Sarcopenia is a gradual loss of muscle mass which is thought to be attributed to several factors such as, malnutrition, inflammation, oxidative stress, physical inactivity, imbalance of protein homeostasis and dysregulation of apoptotic and necrotic pathways. It is believed that the progressive accumulation of somatic dysfunction can result in a decline in mitochondrial biogenesis and function, which in turn is central to the pathophysiology of a wide range of human diseases including, depression [26,78].

Mitochondria plays a regulatory role in synaptic strength and cellular resilience of neuronal circuits within the brain. Current theories of depression and mood disorders, centre around brain neuroplasticity and

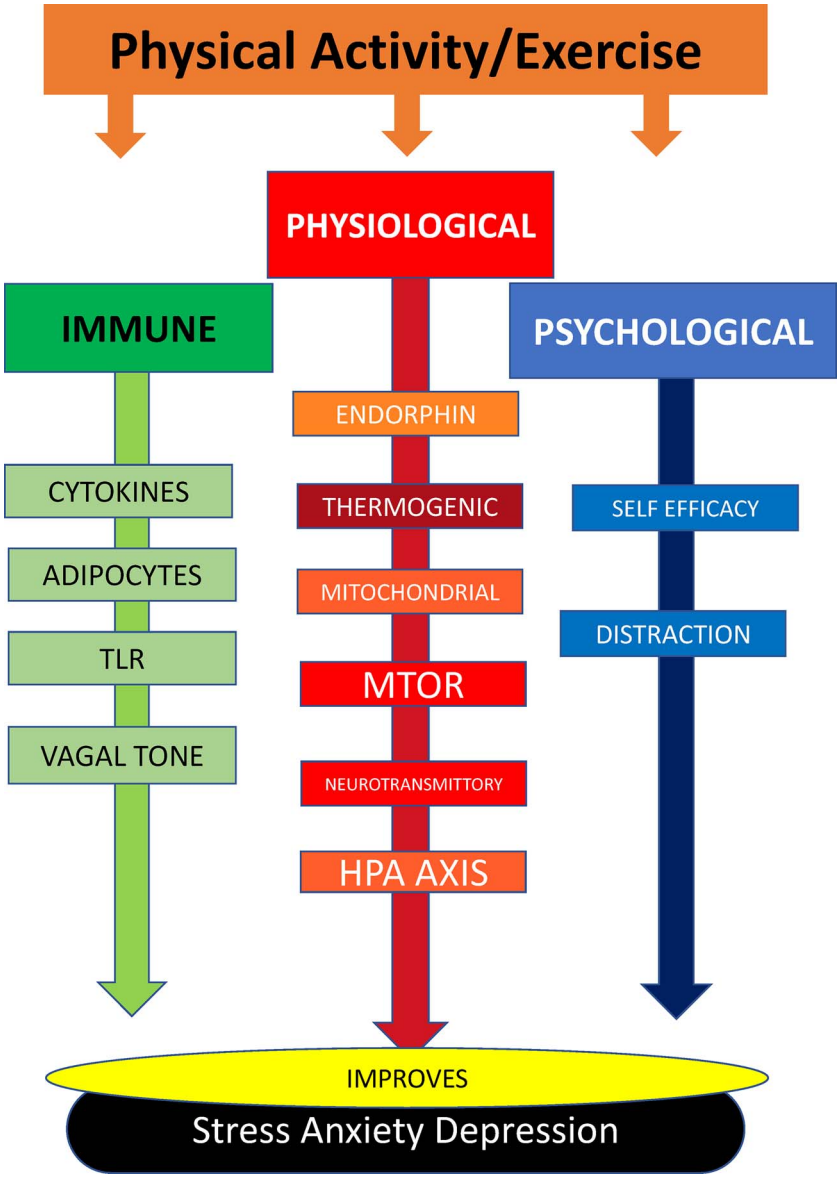

Fig. 1. The complex effects of exercise to improve stress, anxiety and depression. TLR, toll-like receptors; MTOR, mammalian target of rapamycin signaling; HPA axis, hypothalamic pituitary-adrenal axis.

neurogenesis. It is thought that poor mental health may stem from poor neuroplasticity which may result in an inability to respond and adapt to stress or aversive stimuli. Mitochondria plays an integral role in neuroplasticity as grey matter has a high number of mitochondria and undergoes intense neuronal activity. In fact, a resting cortical neuron is said to consume 4.7 billion ATP molecules per second [79]. Chronic stress can lead to structural and functional impairment in certain regions of the brain but neural plasticity, by function, may block or reverse this process. Mitochondrial biogenesis transpires at a greater rate during neuronal development and repair; failure for this to occur due to declining mitochondrial health or function can contribute to an inability for the nervous system to take part in neuroplasticity, neurogenesis and neuronal development [26,78–81]. It is well documented that exercise/physical activity is directly related to increased mitochondriogenesis, and that individuals who primarily undertake aerobic training, show an increase in mitochondrial numbers and oxygen utilization capabilities [25,82,83]. In the elderly (60–80year-old adults), a 4-month aerobic exercise program ameliorates loss of skeletal muscle mitochondrial content [84]. Targeting mitochondrial dysfunction or enhancing mitochondrial function via exercise may provide a novel treatment for depression and mood related disorders.

4.4. Mammalian target of rapamycin (mTOR)

mTOR is a serine/threonine protein kinase which controls cell growth and metabolism [85]. mTOR plays an important role in development and ageing and is associated with learning, memory and antidepressant effects. Disorders associated with mTOR signalling have been incriminated in many neurological disorders [86]. In particular, the drug ketamine, a glutamate/NMDA antagonist, which is used in the treatment of depression, acts by enhancing mTOR signalling and thus, harnessing its antidepressant effect [87]. In much the same way exercise activates mTOR in brain regions which deals with cognition and emotional behaviours and can help improve mental health states by reducing the effects of stress, anxiety and depression [88]. In rats, mTOR mediates signalling in skeletal muscle cells immediately after exercise [28] and both voluntary and forced exercise increases mTOR positive neurons in the brain in the medial prefrontal cortex, striatum, hippocampus, hypothalamus and amygdala. Thus, a relationship exists between mTOR signalling and improved cognitive function and mental health [88].

4.5. Neurotransmitters

Serotonin, dopamine, noradrenaline and glutamate imbalances are often noted in the central nervous systems of people suffering from depression [89]. In addition, monoamine abnormalities have been implicated in people expressing anxiety spectrum disorders [3]. Serotonin is the most commonly treated neurotransmitter imbalance and provides the strongest evidence for the involvement of monoamine disparity in the pathogenesis of depression. Furthermore, ageing is linked to noticeable impairments in brain serotonin transmission, linking to depression in later life. Depression is successfully managed in some patients with selective serotonin reuptake inhibitors (SSRI) which work to prevent the reuptake of monoamines such as serotonin and noradrenaline, thereby, increasing the availability of these in the brain [90]. It is thought that exercise can also increase serotonergic and adrenergic levels in the brain, effectively acting in the same way as the SSRI antidepressants. Indeed, in untrained participants assigned to either an aerobic exercise group or a stretching control group, the levels of blood serotonin were increased (similar to the effect of SSRI's) after exercise in the aerobic group which also correlated to decreased levels of depression. Hence, exercise appears to work in much the same way as anti-depressants [50]. Moreover, 16 senior males (64 years old) partaking in a 16-week aerobic training exercise study showed increased levels of plasma tryptophan [91]; blood tryptophan levels are known to be in parallel elevated to brain serotonin levels which may be involved in antidepressant effects of exercise in older adults.

4.6. The hypothalamic pituitary-adrenal (HPA) axis

The HPA axis is responsible for adaptive responses to physical and psychological stressors. There is much evidence from studies of people suffering from depression and anxiety to implicate HPA dysfunction especially via hyperactivity of HPA response [92–94]. HPA dysfunction seen in anxiety or depression can be characterized by heightened or reduced cortisol production, hypersecretion of corticotrophin releasing hormone [95] and compromised sensitivity to glucocorticoids [96]. In fact, voluntary exercise adjusts the release of corticotrophin-releasing factor from the hypothalamus and adrenocorticotropic hormone from the anterior pituitary [15,97] and such changes in the HPA axis modulates stress reactivity and anxiety in humans [3]. The adrenal glands produce cortisol in response to stress and chemical signalling. The main role of cortisol production in exercise is to raise blood sugar levels to ensure the delivery of glucose to the appropriate organs to fuel the body. For this to occur, cortisol inhibits the secretion of insulin and promotes proteolysis and lipolysis for glucose production. Cortisol is also responsible for dampening inflammation by inhibiting pro-inflammatory cytokines (TNF-alpha and IL-6) which are stimulated by the contraction of skeletal muscle. When IL-6 levels are elevated this can stimulate the release of the IL-1 receptor antagonist, increasing the secretion of anti-inflammatory cytokines. When depression is marked by hyperactivity of the HPA axis, exercise has the ability to attenuate the HPA response to stress. Human research in this area has mostly centred around the model of "toughness", stating that exercise trained individuals have a hyposensitive HPA response to exercise challenge and mental stress [98].

5. The psychological mechanisms of exercise on mood states

When discussing the effects of exercise on mental health it is pertinent to consider the psychosocial aspects at play. Exercise routines and physical activity through sport have been shown to provide a distraction from negative thoughts and ruminations, and a boost in self-esteem through self-efficacy or mastery. The often social aspect of physical activity can also provide an outlet for people suffering from depression, anxiety and/or stress [99].

5.1. Distraction hypothesis

The distraction hypothesis suggests that rather than physiological change produced by exercise that the mental 'time out' could be responsible for the mood elevating effects of exercise. It seems that distracting oneself from negative and worrying thoughts is a technique used by some to help cope with depression. The distraction hypothesis was first conceptualized almost 40 years ago, based on a study whereby 3 groups were given mental time out, one group via exercise another via an equivalent period of meditation and the third resting quietly in a reclining chair. It was clear that all 3 groups showed similar reductions in anxiety and stress and it was concluded that the distraction hypothesis may contribute to improved mental health [100].

In 1987 Nolen Hoeksema hypothesized a responses style theory of depression whereby it was predicted that a depressed mood would be more likely to be alleviated by distracting active responses than by ruminating passive responses. In a study of 35 males and 34 females randomly assigned to engage in either, (i) active distracting task, (ii) a passive distracting task, (iii) an active ruminating task or (iv) a passive ruminating task, it was shown that the active distracting task had a greater capacity to alleviate a depressed mood followed by passive distracting, active ruminating and passive ruminating [101]. It is interesting to note that in many gyms and fitness centres around the world, large television screens or personal monitors are provided for patrons, along with loud music in an attempt to distract people from the effort and physicality of the exercise they are undertaking. In a study investigating attentional distraction during exercise, it was found that listening to music had a positive effect on running distance, on a field endurance test and on exercise intensity during an exercise session with 53 school boys [37]. Another study recruited recreational gym users and found that utilizing a motivational music video had improved high intensity exercise performance [35], whilst a third study found that the attentional distraction of music had positive effects on the perseverance of obese children during treadmill exercise sessions [36].

5.2. Mastery/self efficacy

The self-efficacy/mastery hypothesis theory states that the physiological effects of completing an important and effortful task such as, an exercise session brings about a feeling of mastery which, in itself, elevates mood. Self-efficacy or one's belief in one's ability to succeed has been positively associated with exercise participation and negatively related to depressive symptoms. The theory of self-efficacy highlights the importance of self-regulation. The higher the level of perceived self-efficacy the more likely an individual will maintain adherence to self-set goals [40]. Physical fitness and heathy lifestyle have long been linked to positive self-esteem, and those with strong self-esteem are less likely to succumb to depressive behaviour [60]. In fact, the effect of self-efficacy for exercise adherence was determined in older women who had suffered heart failure in a 12 week home based walking program [39]. Improved quality of life, and depressive symptoms in the women who participated in the exercise self-efficacy program were noted, compared to the control group who participated in education alone [39]. Overall there seems to be some evidence to indicate that distraction and mastery/self-efficacy can contribute to the mood elevating effects of exercise.

6. The inflammatory mechanisms of exercise on mood states

Chronic inflammation is a prime contributor to chronic diseases, leading cause of death in the world [102]. Chronic inflammation has also been attributed to the pathogenesis of depression and poor mental health [41]. There is a growing body of evidence linking the immune and nervous systems. It is becoming increasingly clearer, that the immune system plays a vital part in the pathogenesis of mental health disorders. These can include anxiety, mood changes and depression.

Often it is the under consumption of nutrients which leads to dysregulation of the immune system. Poor nutrition can cause modifications in the function and production of certain neurotransmitters which in turn can increase sensitivity to mental health disorders. Furthermore, an inflammatory response within the gut is thought to invoke an influx of inflammatory mediators via the vagal/brain reflex. This in turn leads to increased activation of neurotoxic metabolites, affecting neurotransmitter production which can result in an inhibition of neurogenesis and neuroplasticity [103]. Regular exercise has also shown to alleviate depressive symptoms in patients with inflammatory related diseases such as chronic obstructive pulmonary disease [1] and Alzheimer's [2].

The positive effects of exercise on mental health may well be due to the ability of exercise to reduce inflammation. Previous studies established that the anti-inflammatory effects of exercise may be attributed to 4 main mechanisms, (i) change in cytokine release [44,104], (ii) reduction of visceral fat mass [43], (iii) down regulation of toll-like receptors [105] and (iv) increase in vagal tone [106]. As inflammation plays a key role in the pathogenesis of depression and anxiety for a subset of individuals, it is clear there is a pertinent purpose for studying the link between inflammation and mental health.

6.1. Exercise and cytokines

In the last 5 years, there has been an upsurge of interest in understanding the effects of exercise on the stimulation of anti- and pro-inflammatory cytokines. Exercise is known to induce a stress response which can increase the number of inflammatory cells in circulation. Monocytes in circulation during exercise can increase by 4.8-fold, whilst dendritic cells (DC), neutrophils and natural killer cells are also increased although after prolonged exercise natural killer (NK) cells are reduced [107]. As such, exercise stimulates a marked systemic increase in many different cytokines and cell surface markers. In particular systemic IL-6 levels increase with exercise as it is produced by contracting muscle [12]. In fact larger amounts of IL-6 are produced in response to exercise than any other cytokine [108]. This increase is related to exercise intensity, duration, the mass of the muscle recruited and the individual's capacity for endurance. IL-6 participates in the inflammatory process and as such is considered a pro-inflammatory cytokine but it also indirectly acts as an anti-inflammatory cytokine by stimulating the production of other anti-inflammatory cytokines [109]. IL-6 stimulates an anti-inflammatory environment by inhibiting the production of pro-inflammatory cytokines, TNF-alpha and IL-1, IL-8 and IL-15 [45,110], and stimulating the secretion of anti-inflammatory cytokines, IL-1 receptor antagonist and IL-10 [111]. IL-6 pro inflammatory cytokines IL-1 and TNF-alpha have been linked to depression, depressive type behaviours and psychosis [103]. Exercise has also been shown to directly increase a T helper 2 anti-inflammatory cytokine profile [104]. Physical activity can change the neuro-immune status in depression by altering macrophage migration inhibitory factor, central nervous system specific CD4+ T cells, M2 microglia, astrocytes, CX3CL1 and insulin-like growth factor-1. All of these factors relate to improvements in neuro-immunological function in relation to depression [45].

6.2. Exercise and adipose tissue

In 2013 the American medical association formally classified obesity as a disease [112]. In fact, obesity is linked with the pathology of many diseases including diabetes, heart disease, metabolic syndrome, liver disease, cancer, and inflammatory disorders. Obesity is now the single biggest threat to public health and has taken over from smoking as the number one cause of premature death [35]. Obesity causes a consistent state of low grade chronic inflammation caused by the activation and dysregulated production of pro-inflammatory cytokines. Adipose tissue is composed of adipocytes (or fat cells), connective tissue, nerve tissue and immune cells, and is viewed as the primary metabolic and endocrine organ. Adipose tissue can be differentiated into white adipose (white fat cells) which store lipids that release fatty acids during periods of fasting, or brown adipose (brown fat cells) which contain an abundance of mitochondria and is primarily used to generate heat, burning lipids and glucose to maintain homeostasis [107]. In obesity, the nature of adipose tissue changes. In lean individuals, small adipocytes promote metabolic homeostasis but in obesity large adipocytes enlist macrophages and other immune cells which produce inflammatory cytokines, changing the adipose tissue milieu and contributing to a complex inflammatory network.

Adipose tissue is responsible for the production of pro-inflammatory cytokines IL-1, IL-6, IL-17 and TNF-αlpha, INF-γamma as well as monocyte chemoattractant protein [107,113]. Exercise however, can instigate the loss of adipose tissue which in turn reduces serum pro-inflammatory cytokine levels. Studies show that higher levels of IL-6 [114] and TNF-alpha [115] are secreted by adipose tissue of obese compared to lean subjects. IL-6 is one of the most frequently studied cytokines in relation to depression [103]. A meta-analysis comprising 583 patients amongst 18 different studies of depression and suicidality noted that high levels of IL- 6 (along with IL-1 beta) was highly associated with suicidality compared to non-suicidality and control subjects [116]. Similarly, studies have shown that administration of TNF-alpha is linked to depressive behaviour in mice, whilst anti-TNF-alpha treatment reverses depressive behaviour in mice and increases depressive scores in humans, whereas depressive behaviours are not evident in TNF-knockout mice [103,117]. Adipocytes also function as endocrine organs which have numerous metabolic roles and secrete adipokines and hormones such as leptin and adiponectin which play a role in insulin sensitivity and regulation of body weight. As a person becomes larger and adipocytes increase in size, dysregulation occurs which can predispose the person to insulin resistance and metabolic disorders [118]. The interplay between obesity, inflammation and depression may be mediated through diet and exercise via the loss of adipose tissue, and the restoration of immune function [46,107].

6.3. Exercise and toll-like receptors (TLR)

TLR play an important role in immunity by detecting and recognizing microbial pathogens. The TLR pathway mediates whole body inflammation and has been implicated in the pathogenesis of inflammatory disease. In fact there is a growing body of evidence implicating TLR signalling in rheumatoid arthritis, atherosclerosis, asthma, type 1 diabetes, systemic lupus erythematosus, multiple sclerosis and bowel inflammation [119]. TLR signalling in antigen presenting cells, produces inflammatory cytokines and proteins which contribute to inflammation, and there is even evidence to suggest there may be a link between sedentary lifestyle, disease and TLR pathways. Several studies however, have found that a prolonged bout of exercise can reduce the effect on toll-like receptor expression (TLR 1,2,4) on monocytes for several hours after exercise [42]. A recent study by Durer et al. found that acute high intensity exercise reduced human monocyte TLR expression in humans with type 2 diabetes [120], whilst, another study showed a temporary reduction in TLR4 expression after prolonged cycling at 75% VO_2 max in 9 healthy endurance trained males [121]. In addition, the expression of TLR4 was consistently lower in subjects that were physically active compared to inactive subjects and in addition, reduced after training in previously inactive subjects.

In a murine study, exercise preconditioning, regulated the TLR4/nuclear factor-κB signalling pathway, and improved cerebral ischemia/reperfusion induced neurological deficits in rats [122]. These findings suggest that exercise may be an important activity for reducing the expression of TLR by contributing to lower levels of inflammation, yet another significant aspect of TLR signalling reduction has been correlated directly to mental health. In fact, mRNA expression of TLR3 and TLR4 were significantly increased in the dorsolateral prefrontal cortex

of depressed suicide victims and in depressed non-suicide victims compared to control, yet protein expression of TLR3 and TLR4 was increased significantly in depressed suicide victims but not in non-depressed suicide victims. These results suggest that protein expression of TLR3 and TLR4 is dysregulated in suicide independent of diagnosis, but possibly not in depression [123]. These findings collectively suggest that further studies into the role of TLR's in mental function and the use of exercise as an adjunct therapy could be of great benefit in the bid to improve mental health and healing.

6.4. Exercise and vagal tone

The vagus nerve connects the brain to the abdomen and is responsible for regulation of metabolic homoeostasis, and through cholinergic signalling, can regulate pro-inflammatory responses via the inflammatory reflex. Acetylcholine from the vagus nerve interacts with the innate immune system and serves to restrain the inflammatory cascade. Weakened vagal tone, can contribute to a pro inflammatory environment and production of pro-inflammatory elements released by macrophages. In a complicated response to this inflammatory environment, which involves the tryptophan and kynurenine pathways, neurotoxic metabolites are formed [124]. Physical activity and exercise have been show to increase vagal tone, in fact, high intensity interval exercise training was shown to increase vagal modulation and decrease heart rate in chronic heart failure patients [125,126]. This increase in vagal tone changes the cholinergic, anti-inflammatory reflex leading to a reduction in systemic inflammation [106]. There is a susceptibility for individuals who suffer from inflammation to be more prone to stress, anxiety and depression [127] thus targeting the gut brain axis through the means of exercise may lead to decreased inflammation and improve symptoms of poor mental health.

6.5. The negative impact of exercise to immune cells

So far, we have focused on the positive effects exercise play on the immune system, however, there is evidence that prolonged bouts of strenuous exercise can temporarily supress or dysregulate immune function for a period of 3–24 h after exercise. This timing however, depends on the intensity and duration of the exercise undertaken. Previous studies have suggested that an exercise bout of 2 h of moderate exercise per day correlates with a 29% reduction of developing an upper respiratory tract infection in comparison to a sedentary person [128], however, a competitive ultra-endurance running event leaves the athlete with a 100–500% chance of developing an infection [42,68,129]. Immune changes which occur after intense, strenuous exercise can include increase in oxidative stress, decrease in TLR's, increase in apoptosis in lymphocytes, decrease in neutrophil chemotaxis, a decrease in lymphocyte proliferation, macrophage inactivation and an increase in IL-4, IL-10 and transforming growth factor beta [42,109]. These changes can all contribute to immune function depression which creates a short period of time for opportunistic intracellular pathogens to take advantage of a host with a weakened immune system. Although this may present a problem for elite athletes who need to maintain peak health for optimal athletic performance, it is less of a concern for most of the population who do not maintain such vigorous training schedules. Predominantly, exercise of moderate intensity serves as a protective measure against the susceptibility to infections.

7. Conclusion

Mental health disorders including those of anxiety, depression and stress are usually treated with medication and psychotherapy. Some individuals however, prefer alternative approaches such as exercise. We present here evidence that exercise can alleviate symptoms of anxiety, depression, and stress states. It is clear that exercise improves mental well-being and is a viable preventative or adjunct treatment option for improved mental health outcomes.

Contributors

K.M. and V.A. wrote the article.
L.S., M.P. and M.B. edited and discussed the article.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received specifically for this review.

Provenance and peer review

This article has undergone peer review.

Acknowledgements

VA was supported by the Centre for Chronic Disease and all authors acknowledge the support of the College of Health and Biomedicine, Victoria University, Australia. VA was supported by the Victoria University start-up funds.

References

[1] S.M. Abd El-Kader, O.H. Al-Jiffri, Exercise alleviates depression related systemic inflammation in chronic obstructive pulmonary disease patients, Afr. Health Sci. 16 (4) (2016) 1078–1088.
[2] S.M. Abd El-Kader, O.H. Al-Jiffri, Aerobic exercise improves quality of life, psychological well-being and systemic inflammation in subjects with Alzheimer's disease, Afr. Health Sci. 16 (4) (2016) 1045–1055.
[3] E. Anderson, G. Shivakumar, Effects of exercise and physical activity on anxiety, Front. Psychiatry 4 (2013) 27.
[4] J.B. Bartholomew, D. Morrison, J.T. Ciccolo, Effects of acute exercise on mood and well-being in patients with major depressive disorder, Med. Sci. Sports Exerc. 37 (12) (2005) 2032–2037.
[5] J.J. Broman-Fulks, et al., Effects of aerobic exercise on anxiety sensitivity, Behav. Res. Ther. 42 (2) (2004) 125–136.
[6] A. Byrne, D.G. Byrne, The effect of exercise on depression, anxiety and other mood states: a review, J. Psychosom. Res. 37 (6) (1993) 565–574.
[7] Y.C. Chang, et al., Effects of different amounts of exercise on preventing depressive symptoms in community-dwelling older adults: a prospective cohort study in Taiwan, BMJ Open 7 (4) (2017) e014256.
[8] L.B. DeBoer, et al., Exploring exercise as an avenue for the treatment of anxiety disorders, Expert Rev. Neurother. 12 (8) (2012) 1011–1022.
[9] O.G. Geirsdottir, et al., Physical function predicts improvement in quality of life in elderly Icelanders after 12 weeks of resistance exercise, J. Nutr. Health Aging 16 (1) (2012) 62–66.
[10] P. Heyn, B.C. Abreu, K.J. Ottenbacher, The effects of exercise training on elderly persons with cognitive impairment and dementia: a meta-analysis, Arch. Phys. Med. Rehabil. 85 (10) (2004) 1694–1704.
[11] A.M. Lane, D.J. Lovejoy, The effects of exercise on mood changes: the moderating effect of depressed mood, J. Sports Med. Phys. Fitness 41 (4) (2001) 539–545.
[12] B.K. Pedersen, C.P. Fischer, Beneficial health effects of exercise–the role of IL-6 as a myokine, Trends Pharmacol. Sci. 28 (4) (2007) 152–156.
[13] D.E. Warburton, C.W. Nicol, S.S. Bredin, Health benefits of physical activity: the evidence, CMAJ 174 (6) (2006) 801–809.
[14] T.M. DiLorenzo, et al., Long-term effects of aerobic exercise on psychological outcomes, Prev. Med. 28 (1) (1999) 75–85.
[15] S.K. Droste, et al., Effects of long-term voluntary exercise on the mouse hypothalamic-pituitary-adrenocortical axis, Endocrinology 144 (7) (2003) 3012–3023.
[16] E.W. Martinsen, A. Hoffart, O. Solberg, Aerobic and non- aerobic forms of exercise in the treatment of anxiety and disorders, Stress Med. 5 (1989) 115–120.
[17] J. Fuss, et al., A runner's high depends on cannabinoid receptors in mice, Proc. Natl. Acad. Sci. U. S. A. 112 (42) (2015) 13105–13108.
[18] V.J. Harber, J.R. Sutton, Endorphins and exercise, Sports Med. 1 (2) (1984) 154–171.
[19] M.N. Janal, et al., Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone, Pain 19 (1) (1984) 13–25.
[20] Z. Tendzegolskis, A. Viru, E. Orlova, Exercise-induced changes of endorphin contents in hypothalamus: hypophysis, adrenals and blood plasma, Int. J. Sports Med. 12 (5) (1991) 495–497.

[21] K.F. Koltyn, W.P. Morgan, Influence of wet suit wear on anxiety responses to underwater exercise, Undersea Hyperb. Med. 24 (1) (1997) 23–28.
[22] S.J. Petruzzello, D.M. Landers, W. Salazar, Exercise and anxiety reduction: examination of temperature as an explanation for affective change, J. Sport Exerc. Psychol. 15 (1) (1993).
[23] D.L. Reeves, et al., Endogenous hyperthermia in normal human subjects: experimental study of emotional states (II), Int. J. Psychosom. 32 (4) (1985) 18–23.
[24] S.D. Youngstedt, et al., Does body temperature mediate anxiolytic effects of acute exercise? J. Appl. Physiol. (1985) 74 (2) (1993) 825–831.
[25] A.S. Aguiar Jr.et al., Effects of exercise on mitochondrial function, neuroplasticity and anxio-depressive behavior of mice, Neuroscience 271 (2014) 56–63.
[26] Y. Bansal, A. Kuhad, Mitochondrial dysfunction in depression, Curr. Neuropharmacol. 14 (6) (2016) 610–618.
[27] A.L. Lopresti, S.D. Hood, P.D. Drummond, A review of lifestyle factors that contribute to important pathways associated with major depression: diet, sleep and exercise, J. Affect. Disord. 148 (1) (2013) 12–27.
[28] D.R. Bolster, et al., Immediate response of mammalian target of rapamycin (mTOR)-mediated signalling following acute resistance exercise in rat skeletal muscle, J. Physiol. 553 (Pt 1) (2003) 213–220.
[29] K. Watson, K. Baar, mTOR and the health benefits of exercise, Semin. Cell Dev. Biol. 36 (2014) 130–139.
[30] J.H. Woo, et al., Effects of treadmill exercise on skeletal muscle mTOR signaling pathway in high-fat diet-induced obese mice, J. Phys. Ther. Sci. 28 (4) (2016) 1260–1265.
[31] A. Clark, N. Mach, Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes, J. Int. Soc. Sports Nutr. 13 (2016) 43.
[32] D.M. de Coverley Veale, Exercise and mental health, Acta Psychiatr. Scand. 76 (2) (1987) 113–120.
[33] L. Sun, Q. Sun, J. Qi, Adult hippocampal neurogenesis: an important target associated with antidepressant effects of exercise, Rev. Neurosci. (2017).
[34] H.M. van Praag, Depression, Lancet 2 (8310) (1982) 1259–1264.
[35] M.J. Barwood, et al., A motivational music and video intervention improves high-intensity exercise performance, J. Sports Sci. Med. 8 (3) (2009) 435–442.
[36] I. De Bourdeaudhuij, et al., Effects of distraction on treadmill running time in severely obese children and adolescents, Int. J. Obes. Relat. Metab. Disord. 26 (8) (2002) 1023–1029.
[37] B. Deforche, I. De Bourdeaudhuij, Attentional distraction during exercise in overweight and normal-weight boys, Int. J. Environ. Res. Public Health 12 (3) (2015) 3077–3090.
[38] L.M. Delahanty, et al., Psychological predictors of physical activity in the diabetes prevention program, J. Am. Diet. Assoc. 106 (5) (2006) 698–705.
[39] R. Gary, Exercise self-efficacy in older women with diastolic heart failure: results of a walking program and education intervention, J. Gerontol. Nurs. 32 (7) (2006) 31–39 quiz 40-1.
[40] J. Middelkamp, et al., The effects of a self-Efficacy intervention on exercise behavior of fitness club members in 52 weeks and long-term relationships of transtheoretical model constructs, J. Sports Sci. Med. 16 (2) (2017) 163–171.
[41] R. Dantzer, et al., From inflammation to sickness and depression: when the immune system subjugates the brain, Nat. Rev. Neurosci. 9 (1) (2008) 46–56.
[42] M. Gleeson, Immune function in sport and exercise, J. Appl. Physiol. (1985) 103 (2) (2007) 693–699.
[43] M. Gleeson, et al., The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease, Nat. Rev. Immunol. 11 (9) (2011) 607–615.
[44] A.M. Petersen, B.K. Pedersen, The anti-inflammatory effect of exercise, J. Appl. Physiol. (1985) 98 (4) (2005) 1154–1162.
[45] V. Apostolopoulos, et al., Physical and immunological aspects of exercise in chronic diseases, Immunotherapy 6 (10) (2014) 1145–1157.
[46] L. Stojanovska, et al., To exercise: or, not to exercise, during menopause and beyond, Maturitas 77 (4) (2014) 318–323.
[47] B.G. Berger, D.R. Owen, Mood alteration with yoga and swimming: aerobic exercise may not be necessary, Percept. Mot. Skills 75 (3 Pt 2) (1992) 1331–1343.
[48] S.A. Paluska, T.L. Schwenk, Physical activity and mental health: current concepts, Sports Med. 29 (3) (2000) 167–180.
[49] J.S. Raglin, Exercise and mental health: beneficial and detrimental effects, Sports Med. 9 (6) (1990) 323–329.
[50] B. Wipfli, et al., An examination of serotonin and psychological variables in the relationship between exercise and mental health, Scand. J. Med. Sci. Sports 21 (3) (2011) 474–481.
[51] M. Wegner, et al., Effects of exercise on anxiety and depression disorders: review of meta- analyses and neurobiological mechanisms, CNS Neurol. Disord. Drug Targets 13 (6) (2014) 1002–1014.
[52] C.J. Caspersen, K.E. Powell, G.M. Christenson, Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research, Public Health Rep. 100 (2) (1985) 126–131.
[53] E.W. Martinsen, A. Hoffart, O. Solberg, Comparing aerobic with nonaerobic forms of exercise in the treatment of clinical depression: a randomized trial, Compr. Psychiatry 30 (4) (1989) 324–331.
[54] M.H. klein, A.S. Gurman, A comparative out- come study of group psychotherapy vs exercise treatments for depression, Mental Health 13 (3–4) (1985).
[55] S.H. Oh, et al., Relationship between types of exercise and quality of life in a Korean metabolic syndrome population: a cross-sectional study, Metab. Syndr. Relat. Disord. 15 (4) (2017) 199–205.
[56] F.J. Khanzada, N. Soomro, S.Z. Khan, Association of physical exercise on anxiety and depression amongst adults, J. Coll. Phys. Surg. Pak. 25 (7) (2015) 546–548.
[57] C.W. Wang, et al., Managing stress and anxiety through qigong exercise in healthy adults: a systematic review and meta-analysis of randomized controlled trials, BMC Complement. Altern. Med. 14 (2014) 8.
[58] H.K. Antunes, et al., Exercise deprivation increases negative mood in exercise-addicted subjects and modifies their biochemical markers, Physiol. Behav. 156 (2016) 182–190.
[59] K. Jayakody, S. Gunadasa, C. Hosker, Exercise for anxiety disorders: systematic review, Br. J. Sports Med. 48 (3) (2014) 187–196.
[60] H.M. Chen, et al., Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer, Br. J. Cancer 112 (3) (2015) 438–445.
[61] W. Dziubek, et al., The level of anxiety and depression in dialysis patients undertaking regular physical exercise training–a preliminary study, Kidney Blood Press. Res. 41 (1) (2016) 86–98.
[62] M.G. Fetzner, G.J. Asmundson, Aerobic exercise reduces symptoms of posttraumatic stress disorder: a randomized controlled trial, Cogn. Behav. Ther. 44 (4) (2015) 301–313.
[63] D. Vancampfort, et al., State anxiety, psychological stress and positive well-being responses to yoga and aerobic exercise in people with schizophrenia: a pilot study, Disabil. Rehabil. 33 (8) (2011) 684–689.
[64] D.M. LeBouthillier, G.J. Asmundson, A single bout of aerobic exercise reduces anxiety sensitivity but not intolerance of uncertainty or distress tolerance: a randomized controlled trial, Cogn. Behav. Ther. 44 (4) (2015) 252–263.
[65] P. Abedi, P. Nikkhah, S. Najar, Effect of pedometer-based walking on depression: anxiety and insomnia among postmenopausal women, Climacteric 18 (6) (2015) 841–845.
[66] L. Larun, et al., Exercise in prevention and treatment of anxiety and depression among children and young people, Cochr. Database Syst. Rev. 3 (2006) CD004691.
[67] E. Young, How Iceland Got Teens to Say No to Drugs, The Atlantic, 2017 (cited 2017) Available from: https://http://www.theatlantic.com/health/archive/2017/01/teens-drugs-iceland/513668/%22.
[68] M. Gleeson, et al., Respiratory infection risk in athletes: association with antigen-stimulated IL-10 production and salivary IgA secretion, Scand. J. Med. Sci. Sports 22 (3) (2012) 410–417.
[69] H. Sampasa-Kanyinga, et al., Perceptions and attitudes about body weight and adherence to the physical activity recommendation among adolescents: the moderating role of body mass index, Public Health 146 (2017) 75–83.
[70] R. Dalle Grave, S. Calugi, G. Marchesini, Compulsive exercise to control shape or weight in eating disorders: prevalence, associated features, and treatment outcome, Compr. Psychiatry 49 (4) (2008) 346–352.
[71] D.K. Voelker, J.J. Reel, C. Greenleaf, Weight status and body image perceptions in adolescents: current perspectives, Adolesc. Health Med. Ther. 6 (2015) 149–158.
[72] M. Li, J. Nie, Y. Ren, Effects of exercise dependence on psychological health of Chinese college students, Psychiatr. Danub. 27 (4) (2015) 413–419.
[73] R. Balchin, et al., Sweating away depression? The impact of intensive exercise on depression, J. Affect. Disord. 200 (2016) 218–221.
[74] M.E.A.D. Coen, Naloxone blocking of running-induced mood changes, Ann. Sport Med. (1987) 3.
[75] E. Heyman, et al., Intense exercise increases circulating endocannabinoid and BDNF levels in humans–possible implications for reward and depression, Psychoneuroendocrinology 37 (6) (2012) 844–851.
[76] J.S. Raglin, W.P. Morgan, Influence of exercise and quiet rest on state anxiety and blood pressure, Med. Sci. Sports Exerc. 19 (5) (1987) 456–463.
[77] H.A. deVries, Tranquilizer effect of exercise: a critical review, Phys. Sportsmed. 9 (11) (1981) 46–55.
[78] M.R. Duchen, G. Szabadkai, Roles of mitochondria in human disease, Essays Biochem. 47 (2010) 115–137.
[79] X.H. Zhu, et al., Quantitative imaging of energy expenditure in human brain, Neuroimage 60 (4) (2012) 2107–2117.
[80] B. Czeh, M. Simon, Neuroplasticity and depression, Psychiatr. Hung. 20 (1) (2005) 4–17.
[81] Y.H. Wei, et al., Mitochondrial theory of aging matures–roles of mtDNA mutation and oxidative stress in human aging, Zhonghua Yi Xue Za Zhi (Taipei) 64 (5) (2001) 259–270.
[82] Y. Kim, M. Triolo, D.A. Hood, Impact of aging and exercise on mitochondrial quality control in skeletal muscle, Oxid. Med. Cell Longev. 2017 (2017) 3165396.
[83] J. Vina, et al., Mitochondrial biogenesis in exercise and in ageing, Adv. Drug Deliv. Rev. 61 (14) (2009) 1369–1374.
[84] N.T. Broskey, et al., Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training, J. Clin. Endocrinol. Metab. 99 (5) (2014) 1852–1861.
[85] M.N. Hall, mTOR-what does it do? Transplant. Proc. 40 (10 Suppl) (2008) S5–S8.
[86] C.A. Hoeffer, E. Klann, mTOR signaling: at the crossroads of plasticity, memory and disease, Trends Neurosci. 33 (2) (2010) 67–75.
[87] M.M. Harraz, et al., Antidepressant action of ketamine via mTOR is mediated by inhibition of nitrergic Rheb degradation, Mol. Psychiatry 21 (3) (2016) 313–319.
[88] B.A. Lloyd, et al., Exercise increases mTOR signaling in brain regions involved in cognition and emotional behavior, Behav. Brain Res. 323 (2017) 56–67.
[89] V. Maletic, et al., Neurobiology of depression: an integrated view of key findings, Int. J. Clin. Pract. 61 (12) (2007) 2030–2040.
[90] S.D. Hood, C.J. Bell, D.J. Nutt, Acute tryptophan depletion. Part I: rationale and methodology, Aust. N. Z. J. Psychiatry 39 (7) (2005) 558–564.
[91] M.O. Melancon, D. Lorrain, I.J. Dionne, Changes in markers of brain serotonin activity in response to chronic exercise in senior men, Appl. Physiol. Nutr. Metab. 39 (11) (2014) 1250–1256.
[92] R.K. Dishman, et al., Physical self-concept and self-esteem mediate cross-sectional relations of physical activity and sport participation with depression symptoms

among adolescent girls, Health Psychol. 25 (3) (2006) 396–407.
[93] R. Landgraf, et al., Hyper-reactive hypothalamo-pituitary-adrenocortical axis in rats bred for high anxiety-related behaviour, J. Neuroendocrinol. 11 (6) (1999) 405–407.
[94] T. Steckler, F. Holsboer, J.M. Reul, Glucocorticoids and depression, Baillieres Best Pract. Res. Clin. Endocrinol. Metab. 13 (4) (1999) 597–614.
[95] C.M. Pariante, S.L. Lightman, The HPA axis in major depression: classical theories and new developments, Trends Neurosci. 31 (9) (2008) 464–468.
[96] P.W. Gold, G.P. Chrousos, Organization of the stress system and its dysregulation in melancholic and atypical depression: high vs low CRH/NE states, Mol. Psychiatry 7 (3) (2002) 254–275.
[97] P. Salmon, Effects of physical exercise on anxiety, depression, and sensitivity to stress: a unifying theory, Clin. Psychol. Rev. 21 (1) (2001) 33–61.
[98] A.L. Brosse, et al., Exercise and the treatment of clinical depression in adults: recent findings and future directions, Sports Med. 32 (12) (2002) 741–760.
[99] H.A. Eyre, E. Papps, B.T. Baune, Treating depression and depression-like behavior with physical activity: an immune perspective, Front. Psychiatry 4 (2013) 3.
[100] M.M. Bharke, Anxiety reduction following exercise and meditation cognitive therapy and research, Cognit. Ther. Res. 2 (4) (1978).
[101] S. Nolen-Hoeksema, J. Morrow, B.L. Fredrickson, Response styles and the duration of episodes of depressed mood, J. Abnorm. Psychol. 102 (1) (1993) 20–28.
[102] CDC, Chronic Diseases. The Leading Cause of Death and Disability in the United States. Chronic Diseaseoverview, (2017) Available from https://http://www.cdc.gov/chronicdisease/overview/index.htm.
[103] K. Mikkelsen, et al., The effects of vitamin B on the immune/cytokine network and their involvement in depression, Maturitas 96 (2017) 58–71.
[104] F. Euteneuer, et al., Immunological effects of behavioral activation with exercise in major depression: an exploratory randomized controlled trial, Transl. Psychiatry 7 (5) (2017) e1132.
[105] M. Gleeson, B. McFarlin, M. Flynn, Exercise and toll-like receptors, Exerc. Immunol. Rev. 12 (2006) 34–53.
[106] F.S. Routledge, et al., Improvements in heart rate variability with exercise therapy, Can. J. Cardiol. 26 (6) (2010) 303–312.
[107] V. Apostolopoulos, et al., The complex immunological and inflammatory network of adipose tissue in obesity, Mol. Nutr. Food Res. 60 (1) (2016) 43–57.
[108] B.K. Pedersen, A. Steensberg, P. Schjerling, Exercise and interleukin-6, Curr. Opin. Hematol. 8 (3) (2001) 137–141.
[109] R. Terra, et al., Effect of exercise on the immune system: response, adaptation and cell signaling, Rev. Brass Med. Esporte 18 (3) (2012).
[110] R. Schindler, et al., Correlations and interactions in the production of interleukin-6 (IL-6), IL-1, and tumor necrosis factor (TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF, Blood 75 (1) (1990) 40–47.
[111] A. Steensberg, et al., IL-6 enhances plasma IL-1ra: IL-10, and cortisol in humans, Am. J. Physiol. Endocrinol. Metab. 285 (2) (2003) E433–7.
[112] M. frellick, AMA Declares Obesity a Disease AMA 2013 Annual Meeting 201, (2013) (cited 2017) Available from: http://www.medscape.com/viewarticle/806566.Ref.
[113] S. Pudkasam, et al., Breast cancer and exercise: the role of adiposity and immune markers, Maturitas (2017), http://dx.doi.org/10.1016/j.maturitas.2017.04.022 pii: S0378-5122(17)30545-5, [Epub ahead of print].
[114] S.K. Fried, D.A. Bunkin, A.S. Greenberg, Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid, J. Clin. Endocrinol. Metab. 83 (3) (1998) 847–850.
[115] P.A. Kern, et al., The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity: weight loss, and relationship to lipoprotein lipase, J. Clin. Invest. 95 (5) (1995) 2111–2119.
[116] C. Black, B.J. Miller, Meta-analysis of cytokines and chemokines in suicidality: distinguishing suicidal versus nonsuicidal patients, Biol. Psychiatry 78 (1) (2015) 28–37.
[117] M.P. Kaster, et al., Depressive-like behavior induced by tumor necrosis factor-alpha in mice, Neuropharmacology 62 (1) (2012) 419–426.
[118] A.S. Greenberg, M.S. Obin, Obesity and the role of adipose tissue in inflammation and metabolism, Am. J. Clin. Nutr. 83 (2) (2006) 461S–465S.
[119] S.K. Drexler, B.M. Foxwell, The role of toll-like receptors in chronic inflammation, Int. J. Biochem. Cell Biol. 42 (4) (2010) 506–518.
[120] C. Durrer, et al., Acute high-intensity interval exercise reduces human monocyte Toll-like receptor 2 expression in type 2 diabetes, Am. J. Physiol. Regul. Integr. Comp. Physiol. 312 (4) (2017) R529–R538.
[121] M. Oliveira, M. Gleeson, The influence of prolonged cycling on monocyte Toll-like receptor 2 and 4 expression in healthy men, Eur. J. Appl. Physiol. 109 (2) (2010) 251–257.
[122] L. Zhu, et al., Exercise preconditioning regulates the toll-Like receptor 4/nuclear factor-kappaB signaling pathway and reduces cerebral Ischemia/reperfusion inflammatory injury: a study in rats, J. Stroke Cerebrovasc. Dis. 25 (11) (2016) 2770–2779.
[123] G.N. Pandey, et al., Toll-like receptors in the depressed and suicide brain, J. Psychiatr. Res. 53 (2014) 62–68.
[124] A. Halaris, Inflammation-associated co-morbidity between depression and cardiovascular disease, Curr. Top. Behav. Neurosci. 31 (2017) 45–70.
[125] T. Guiraud, et al., High-intensity interval exercise improves vagal tone and decreases arrhythmias in chronic heart failure, Med. Sci. Sports Exerc. 45 (10) (2013) 1861–1867.
[126] H. Hepburn, et al., Cardiac vagal tone, exercise performance and the effect of respiratory training, Eur. J. Appl. Physiol. 94 (5–6) (2005) 681–689.
[127] C.L. Raison, L. Capuron, A.H. Miller, Cytokines sing the blues: inflammation and the pathogenesis of depression, Trends Immunol. 27 (1) (2006) 24–31.
[128] C.E. Matthews, et al., Moderate to vigorous physical activity and risk of upper-respiratory tract infection, Med. Sci. Sports Exerc. 34 (8) (2002) 1242–1248.
[129] D.C. Nieman, et al., Infectious episodes in runners before and after the Los Angeles Marathon, J. Sports Med. Phys. Fitness 30 (3) (1990) 316–328.