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Biological mechanisms underlying the role of physical fitness in health and resilience

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Physical fitness, achieved through regular exercise and/or spontaneous physical activity, confers resilience by inducing positive psychological and physiological benefits, blunting stress reactivity, protecting against potentially adverse behavioural and metabolic consequences of stressful events and preventing many chronic diseases. In this review, we discuss the biological mechanisms underlying the beneficial effects of physical fitness on mental and physical health. Physical fitness appears to buffer against stress-related disease owing to its blunting/optimizing effects on hormonal stress responsive systems, such as the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system. This blunting appears to contribute to reduced emotional, physiological and metabolic reactivity as well as increased positive mood and well-being. Another mechanism whereby regular exercise and/or physical fitness may confer resilience is through minimizing excessive inflammation. Chronic psychological stress, physical inactivity and abdominal adiposity have been associated with persistent, systemic, low-grade inflammation and exert adverse effects on mental and physical health. The anti-inflammatory effects of regular exercise/activity can promote behavioural and metabolic resilience, and protect against various chronic diseases associated with systemic inflammation. Moreover, exercise may benefit the brain by enhancing growth factor expression and neural plasticity, thereby contributing to improved mood and cognition. In summary, the mechanisms whereby physical fitness promotes increased resilience and well-being and positive psychological and physical health are diverse and complex.

1. Introduction

The importance of physical fitness, regular exercise and physical activity has been acknowledged for over 7000 years, dating back to ancient Chinese and Greek civilizations [1,2]. Although its importance diminished during various periods of time throughout history, such as after the fall of the Roman Empire when the church dominated, during the period of industrialization, and in the Roaring Twenties when relaxation and enjoyment were most important, its significance remains widely recognized [2,3]. However, scientific data documenting the essentiality of physical activity for health did not emerge until the late 1800s and early 1900s when epidemiological studies clearly demonstrated that physically inactive persons were more likely to have coronary heart disease than those who led active lifestyles [3,4]. Since those first studies, the literature has become replete with evidence that physical inactivity serves a major role in the rising prevalence of obesity, cardiovascular disease (CVD), hypertension, type 2 diabetes, metabolic syndrome, insulin resistance, hyperlipidaemia, breast and colon cancers as well as depression and anxiety [5–10]. Moreover, physical inactivity is the fourth leading contributor to death worldwide [8].

The above-mentioned chronic, non-communicable diseases/disorders have also been associated with chronic stress and dysregulated neuroendocrine, inflammatory, metabolic and behavioural stress responses, which may contribute to their comorbid expression [11–14]. In contrast to a physically inactive lifestyle, an active

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lifestyle (i.e. high aerobic fitness) is inversely related to stress-related health problems and the development of chronic diseases/disorders [15–19]. Importantly, physical fitness, whether achieved through spontaneous physical activity or regular exercise, can confer resilience, defined as 'the ability to withstand, recover, and grow in the face of stressors and changing demands' [20], and serves as a stress resistance resource in a variety of ways [21–25]. The biological pathways whereby regular physical activity might confer resilience include (i) serving as a buffer against stress and stress-related disorders/chronic diseases, (ii) optimizing neuroendocrine and physiological responses to physical and psychosocial stressors, (iii) promoting an anti-inflammatory state, and (iv) enhancing neuroplasticity and growth factor expression [15–19,26–35].

In this review, we discuss these possible biological mechanisms underlying the beneficial effects of physical fitness on mental and physical health and resilience. First, the main physiological stress responsive systems—the hypothalamic–pituitary–adrenal (HPA) axis, the autonomic nervous system and the immune system—are introduced with a description of how these systems work together to orchestrate metabolic and behavioural adaptations to stress and how chronic activation of these stress systems can lead to dysregulation of multiple physiological and behavioural systems, maladaptive stress responses and increased vulnerability for the development of chronic disease. We then discuss how physical fitness can protect against the development of chronic, stress-related disease and promote health and resilience—by optimizing function and interaction of these physiological stress responsive systems and hence minimizing the prevalence of biological risk factors for disease. Finally, limitations regarding available studies are presented. It is important to note that the terms physical activity and exercise are used interchangeably (depending on the literature), recognizing that exercise represents a planned, structured and regular form of physical activity, whereas physical activity alone may be spontaneous and unplanned.

2. The stress responsive systems—hypothalamic–pituitary–adrenal axis, sympathetic nervous system and immune system: from adaptation to disease

The biological mechanisms underlying the relation between physical fitness and resilience are beginning to unfold and are both multifactorial and complex. The most important mechanisms relate to modulation of the body's main stress responsive systems—the HPA axis, the autonomic nervous system and immune system—and interactions among these systems [36–40]. The two main neuroendocrine/neural systems mediating the stress response are the HPA axis, with the resultant release of glucocorticoids (cortisol in humans and primates; corticosterone in rodents) and the sympathetic nervous system (SNS), which releases the catecholamines epinephrine (adrenaline) and norepinephrine. Activation of these stress responsive systems coordinates the response of other physiological and behavioural systems, including the cardiovascular, musculoskeletal and nervous systems, in preparation for the 'fight or flight' response, allowing an individual to successfully meet the demands of the challenge and then bring the body back to homeostasis [11,12]. The temporal effects of rising levels of catecholamines and glucocorticoids in the initial phase of the stress response are stimulatory, to include—mobilizing energy, increasing heart rate and blood pressure, and enhancing cognitive processes such as alertness, arousal, vigilance and attention [26,41,42], and also work together to coordinate a 'stress response' in the immune system. Just as an acute stress response prepares for 'fight or flight', the immune system adapts to changing needs by promoting immune readiness in the form of an initial inflammatory response. Continued exposure to glucocorticoids also serves an important adaptive role by exerting suppressive effects in an effort to restore initial brain and immune activity to baseline levels. Terminating the stress response in a timely manner is crucial for preventing the detrimental consequences of overactive neuroexcitatory, cardiovascular, metabolic and inflammatory responses [12,43].

More specifically, early in the stress response, low (permissive) levels of glucocorticoids and rising levels of catecholamines (epinephrine) promote leucocyte trafficking from storage sites (e.g. the spleen) to the circulation. With continuation of stress, glucocorticoid levels start to rise and immune cells are mobilized to the first lines of defence (e.g. skin, lungs, gastrointestinal and urogenital tracts, mucosal surfaces and lymph nodes) to prepare for subsequent immune challenges (e.g. wounds or infections). If glucocorticoid activation continues, then immunosuppressive effects are invoked to restore the immune activity to baseline levels and prevent an overshoot of inflammatory responses. During prolonged, chronic stress, high levels of glucocorticoids become maladaptive and inhibit certain aspects of immune function (cellular/inflammatory) below a healthy baseline. This leaves the immune system in an inefficient/vulnerable state to fight subsequent or concurrent infection and cancer [12,44,45]. On the other hand, chronic exposure to glucocorticoids can lead to a state of glucocorticoid resistance (reduced glucocorticoid sensitivity), which could lead to a state of unrestrained/enhanced inflammation and render one more susceptible to developing inflammatory disorders [46–50]. In addition, sympathetic activation can exert pro- and/or anti-inflammatory effects, depending on the type of adrenergic receptor to which catecholamines bind [36,51], whereas activation of the parasympathetic nervous system (both afferent and efferent vagal fibres) has been shown to exert an anti-inflammatory action [40,52]. Therefore, HPA axis dysregulation and autonomic nervous system imbalance can negatively impact immune function.

Acute exercise, as a physical challenge or stressor, activates these systems in a dose-dependent manner, such that the intensity of the exercise, as well as the duration, determines the magnitude of the stress response. For example, exercise at a low intensity (50% of maximal capacity or less) minimally activates and strenuous exercise (greater than 70% of maximal capacity) markedly activates the HPA axis as well as the sympathetic nervous and immune systems [53–56]. Upon termination of the exercise, the systems are supposed to regain homeostasis. However, when the temporal profile, duration and/or amplitude of classically observed, exercise-related stress responses are compromised, disturbances in stress responsive systems must be considered. In other words, when the responses suggest prolonged activation rather than returning to baseline, or are exaggerated beyond what is typically seen, these abnormal responses may be indicative of stress system dysregulation.

In summary, whereas stress responsive systems are adaptive when activated and terminated in a timely manner, prolonged (or insufficient) activation of these systems can

cause a variety of maladaptive responses. Specifically, psychological and physiological effects owing to sustained arousal (or depression/cognitive dysfunction), metabolic dysregulation and immune dysfunction/inflammation could lead to the development of various chronic diseases [14,43,44,57,58]. Indeed, dysregulation of the HPA axis, autonomic nervous system and neural–immune interactions are described in many stress- and inflammatory-related diseases/disorders (autoimmune, metabolic, cardiovascular, psychiatric and somatic) [13,39,57,59,60]. By contrast, individuals who rate high on well-being and stress resilience tend to show the opposite biological profile, to include lower cortisol levels, sympathetic activity, pro-inflammatory markers and metabolic and cardiovascular risk factors than those who rate low on these indices [61–64]. To this end, the science showing how regular exercise, physical activity and physical fitness promote a healthier and more resilient biological profile than an inactive lifestyle is presented.

3. Physical fitness serves as a buffer against stress and stress-related disorders/chronic diseases

The literature is replete with studies showing that regular physical activity and/or exercise may provide a protective effect against stress-related disorders and the development or severity of many chronic diseases [65–68]. Indeed, stress is highly associated with various illnesses [17,69–73], and physically fit persons appear to be less susceptible to life stressors, in particular with regard to illnesses [17,74,75]. A comprehensive review of the literature concluded that the majority of studies (both cross-sectional and prospective) found regular exercise to be an effective stress buffer: people with high exercise levels exhibit fewer health problems when they encounter stress [18]. However, the optimal amount and type of exercise necessary for maximal protection are not known. Several meta-analyses and reviews have shown that physical fitness and regular exercise buffer against behavioural stress disorders, such as depression and anxiety [76–82]. High physical (aerobic) fitness is also inversely related to metabolic stress-related disorders, such as obesity, CVD, type 2 diabetes and metabolic syndrome [16–19,33].

Interestingly, findings from a recent meta-analysis suggest that poor cardiorespiratory fitness is an independent and a better predictor of mortality than obesity, and that the risk for all-cause and cardiovascular mortality is higher in individuals with normal body mass index (BMI) and poor physical fitness, compared with individuals with high BMI and good physical fitness [83]. Additionally, people who exercise regularly report a higher quality of life and improved health status—both physically and mentally [18,84]. A recent meta-epidemiological study of randomized controlled trials found that exercise is equivalent to pharmacological interventions in terms of mortality benefits in the secondary prevention of coronary heart disease and the prevention of diabetes, and even more effective than drug treatment among patients recovering from stroke [85]. Exercise also compares favourably with antidepressant medications as a first-line treatment for mild-to-moderate depression and has also been shown to improve depressive symptoms when used as an adjunct to medications [76,81]. Moreover, exercise appears to be equal to or better than other interventions (e.g. cognitive behavioural therapy, but not pharmacotherapy) for the treatment of anxiety [77,81]. Thus, regular exercise and physical fitness are key to maintaining good health and may serve as viable therapeutic interventions for many chronic and stress-related diseases.

The beneficial effects of physical activity on positive mood are also well recognized [84,86,87]. Indeed, relative increases in cardiorespiratory fitness and habitual physical activity are dose-dependently associated with greater emotional well-being and lower depressive symptomatology in both men and women [6]. In addition to cross-sectional studies, longitudinal studies have demonstrated positive effects of exercise training and regular physical activity, and negative effects of exercise withdrawal, on mood and depressive symptoms [32,88–92]. Following eight weeks of physical training (jogging), adolescent females with depressive symptoms showed significant decreases in total depression scores, which were associated with reduced stress hormone levels—24 h urinary cortisol and epinephrine excretion—and increased cardiorespiratory fitness [88]. Interestingly, we demonstrated that when someone who exercises regularly is forced to abstain for two weeks, negative mood increases significantly and this increase is related to a decrease in fitness [89,92]. In addition, reduced baseline parasympathetic nervous system activity, as measured by heart rate variability (HRV), predicted the development of negative mood after deprivation of exercise [92]. These findings are relevant to understanding the effects of both exercise maintenance and short-term exercise withdrawal. Overall, the findings suggest that the relationship between physical fitness and mood may be mediated in part by the status of stress responsive systems.

Taken together, regular exercise and physical activity are key buffers against stress and many chronic and stress-related diseases/disorders. Possible biological mechanisms underlying the stress-buffering and health-promoting effects of physical fitness include: blunting/optimizing neuroendocrine stress (HPA and SNS) responses [26–29], reducing inflammation [30–32] and increasing growth factor expression and neural plasticity [33–35]. These pathways to better health and resilience are discussed in the following sections.

4. Physical fitness blunts/optimizes neuroendocrine and physiological responses to physical and psychosocial stressors

As noted earlier, an acute bout of exercise is a quantitative stressor such that the intensity of the exercise dictates the magnitude of the stress response [53,54,93,94]. Importantly, our group has shown marked variability in stress reactivity within a normal population at the same relative exercise intensity [55,56,89,92,94–105]. Specifically, some individuals show marked increases in adrenocorticotropin releasing hormone, cortisol and inflammatory responses, whereas others have blunted responses. These data support a plethora of human studies illustrating that some persons are inherently hypo- or hyper-reactive to stress [99,106,107]. Of note, persons highly reactive to physical stress (i.e. an acute exercise challenge) also appear to be highly reactive to mental stress [104]; whether this inherent stress reactivity dictates intrinsic inflammatory reactivity remains to be determined [55,108]. Overall,

improvements in physical fitness have been related to a reduction in stress reactivity—for both physical and mental/psychosocial stressors [99,109–118].

One important point with regard to HPA axis and SNS responses to exercise at the same absolute workload, as opposed to the same relative workload, is that physically fit persons have significantly lower responses than unfit persons [53,94,119,120]. However, if a physically inactive person participates in a well-designed exercise programme for six to 12 weeks, then their HPA and SNS responses after training will be significantly lower than prior to training. This demonstrates that those with a high aerobic fitness are better able to tolerate intense workloads and be minimally stressed by low ones compared with low physically fit individuals [53,54,93,94]. A high level of aerobic fitness also appears to confer protection against non-physical stressors—mental and/or psychological [109,119,121,122]. For example, Rimelle *et al*. [123] documented significantly lower cortisol and heart rate responses to psychosocial stress (Trier social stress test) in trained men compared with untrained men. Moreover, significantly greater calmness and better mood, and a trend towards lower state anxiety, were noted in these trained men during the stress protocol. In addition, higher aerobic fitness among older women has been shown to attenuate age-related increases in HPA axis reactivity, as indicated by a blunted cortisol response to psychological stress [124]. High-fit individuals also exhibit reduced cortisol responses to a combined challenge of physical (cycling) and mental stress [119].

Whereas reduced HPA axis reactivity to a given stressor has repeatedly been reported in physically fit individuals, the finding of reduced sympathetic reactivity is less consistent. Both blunted and augmented catecholamine stress responses have been demonstrated in high- versus low-fit persons during exposure to psychological stressors [120,125]. Along these same lines, de Geus *et al*. [111] showed that aerobic fitness was associated with higher cardiovascular reactivity to mental stress, but lower heart rate and blood pressure at rest and during recovery. Although highly fit and untrained individuals have also been shown to exhibit similar cardiovascular and SNS responses to a novel task, fit individuals exhibit attenuated responses upon repeated exposure to the task [109]. This suggests highly fit persons are able to adapt more rapidly to novel stressors than those who are unfit. Meta-analytic reviews have also shown both positive and negative associations between fitness and cardiovascular reactivity [28,29,110]: those with higher fitness levels may exhibit slightly greater cardiovascular reactivity to some acute laboratory stressors, but overall they demonstrate better (more rapid) recovery, which indicates a more optimized stress response compared with low-fit individuals [28].

With regard to immune reactivity to an acute stressor, higher physical fitness is associated with lower inflammatory cytokine responses to a mental stressor, as well as a less pronounced reduction in HRV, indicating greater parasympathetic control [126]. Regular exercisers also show attenuated leucocyte trafficking and adhesion molecule expression in response to a mental stressor compared with less physically active individuals [127]. Overall, these data suggest that fitness may be an important confounder in studies of stress reactivity, and that low fitness could increase stress responsivity by altering HPA axis, autonomic nervous system and immune functioning.

In summary, these findings are consistent with the concept of physiological toughening as a mechanism by which regular exercise can improve stress tolerance [113,128]. Whereas acute exposure to a psychological or physical (e.g. exercise) stressor might induce a transient stress response (increased HPA, SNS and inflammatory responses), repeated, intermittent exposure to that stressor, with enough time to recover in between, can lead to physiological 'stress training' or 'toughening'. The biological profile associated with physiological toughening is characterized by an increased initial catecholamine response, followed by a rapid recovery, along with reduced HPA axis responses. This protective physiological profile appears to be associated with improved performance during challenging/stressful situations, increased tolerance to stressors (i.e. reduced behavioural suppression/depression), increased emotional stability (i.e. reduced anxiety/freezing), and improved immune function. Importantly, Sothmann *et al*. [122] hypothesized the concept of cross-stressor adaptation: exercise training serves as an intermittent stressor on the body that can alter/optimize responsiveness to other types of stressors (e.g. psychological, cognitive, startle). Thus, improvements in physical fitness may optimize neuroendocrine and physiological responses and adaptations to physical and psychosocial stressors.

5. Physical fitness promotes an anti-inflammatory state

Another mechanism whereby regular exercise and/or physical fitness may confer resilience is through minimizing inflammation. For example, psychological stress, physical inactivity/low aerobic fitness and abdominal adiposity/obesity have all been associated with persistent, systemic, low-grade inflammation, and adverse effects on mental and physical health [129–131]. Systemic markers of inflammation include tumour necrosis factor alpha (TNFα), interleukin (IL)-1, IL-6, IL-8 and C-reactive protein (CRP), with elevated basal IL-6 and CRP levels being closely associated with metabolic syndrome, obesity, type 2 diabetes, CVD, persistent depressive symptomatology and cognitive dysfunction. Likewise, these conditions, along with physical inactivity, have been shown to predict all-cause mortality [132–136]. Pro-inflammatory cytokines can influence virtually every pathophysiological domain relevant to depressive symptomatology, including neuroendocrine function, neurotransmitter metabolism and neuroplasticity, and ultimately affect behavioural resilience and well-being [61,137,138]. Indeed, many features of depression overlap with those of 'sickness behaviour', including fatigue, psychomotor retardation, anorexia, anhedonia, somnolence, lethargy, muscle aches, hyperalgesia, cognitive dysfunction and depressed mood [139–141]. Pro-inflammatory cytokines also facilitate the mobilization of energy sources to meet the metabolic demands of various internal and external environmental challenges. Therefore, sustained catabolic effects of an enhanced inflammatory state may also contribute to an 'inflammatory' metabolic syndrome [58].

Interestingly, inflammatory biomarker concentrations, particularly of CRP, are lower across a wide range of individuals who engage in regular physical activity as compared with those who are inactive [31,142]. Many studies have shown that high aerobic capacity is inversely related to CRP levels [143–146] and that exercise interventions, both aerobic and

resistance in nature, reduce levels of CRP [144,147–152]. However, not all exercise studies have shown a significant effect on CRP [153–156]. A meta-analytic study by Kelley & Kelley [155] with five randomized controlled trials reported an approximately 3% reduction in CRP levels across the exercise groups, but this was not statistically significant. Negative results may be related to the lack of isolating subjects with elevated/high-risk CRP levels (greater than 3.0 mg l^{-1}) to begin with. Moreover, the negative studies found other positive benefits of exercise, such as improved body composition and physical fitness, regardless of its effect on CRP levels.

In addition to tracking a change in biomarker expression over the course of an exercise programme, recent clinical studies have characterized baseline inflammatory marker expression to help elucidate which biological mechanisms are most important in clinical recovery from a disease/disorder. For example, in a randomized control trial designed to assess the relative efficacy of aerobic exercise to augment selective serotonin reuptake inhibitor (SSRI) treatment of major depressive disorder (MDD) in treatment-resistant patients, those who had high basal levels of serum TNFα were found to have a greater decrease in depressive symptoms over the 12 week aerobic exercise intervention [157]. Moreover, a positive correlation between change in serum IL-1β levels and depressive symptom scores was observed [157]. These results suggest that high serum TNFα levels may differentially predict better outcomes with exercise treatment as opposed to antidepressant medications, wherein high serum TNFα levels are linked to a poor treatment response [157].

Another mechanism whereby physical fitness and regular exercise may promote health and resilience is through changes in body composition, in particular changes in adipose tissue content. Physical inactivity is typically associated with an accumulation of visceral fat mass, and increased abdominal fat is associated with impaired glucose and lipid metabolism. These compromised biomarkers include high serum levels of insulin, glucose, and total and low-density lipoprotein cholesterol [158], as well as enhanced production of pro-inflammatory cytokines (adipokines), e.g. IL-6 and TNFα [159], which may all contribute to the development of insulin resistance and hyperlipidaemia [160,161]. Interestingly, adipose tissue may account for approximately 30% of circulating IL-6 levels under basal conditions [162]. Although fitter and physically active individuals generally demonstrate lower levels of inflammatory markers at rest, it is unclear whether these effects are mediated by adiposity [31]. Overall, the benefits of regular exercise may, in part, be attributed to its anti-inflammatory effects via reduction in visceral fat mass. Proposed mechanisms by which exercise reduces visceral adipose tissue inflammation include: reduced adipocyte size, reduced macrophage infiltration, increased blood flow, increased mitochondrial function, facilitated fatty acid oxidation, decreased oxidative stress and improved resistance to cell stress [30,32]. Interestingly, higher levels of physical activity are associated with lower basal levels of inflammation (i.e. IL-6, CRP) even after adjustment for adiposity (i.e. BMI and waist-to-hip ratio) [132,163]. In other words, the effect of physical inactivity on these inflammatory markers is not dependent on obesity, but rather additive to the presence of obesity.

Another important tissue contributing to the anti-inflammatory milieu in a physically fit person is skeletal muscle. The amount of IL-6 released from contracting skeletal muscle (myokine) during exercise is dependent on the intensity and duration of the acute bout of exercise (overall amount of contracting muscle involved) [164]. This IL-6 promotes an anti-inflammatory environment by increasing the synthesis of anti-inflammatory cytokines (i.e. interleukin 1 receptor antagonist and IL-10) and inhibiting pro-inflammatory cytokines (i.e. TNFα) [159]. Although the IL-6 released from monocytes/macrophages (including those in adipose tissue) typically has pro-inflammatory effects [159,165], intramuscular IL-6 release is associated with activation of distinct signalling pathways, which may mediate its anti-inflammatory effects [159]. Monocytes/macrophages are not major contributors to the IL-6 response to exercise [159]. Contracting muscle-derived IL-6 during exercise also acts as a hormone-like energy sensor to stimulate hepatic glucose synthesis and release under conditions of low muscle glycogen concentration [164]. Skeletal muscle of trained, physically fit individuals is less dependent on plasma glucose and muscle glycogen for energy substrate during exercise than muscle from untrained persons [166]. Thus, the need for IL-6-induced stimulation of hepatic glucose release in the trained individual is less than for untrained, inactive persons. In fact, the more physically active a person is, the lower their basal, as well as exercise-induced, plasma IL-6 levels appear to be [132,167–169]. Moreover, exercise training is associated with increased insulin sensitivity in both skeletal muscle and adipose tissue [170].

Evidence from animal studies also shows that acute strenuous exercise increases and exercise training decreases central nervous system pro-inflammatory cytokine expression [171]. Regular exercise has also been shown to reduce brain inflammation in response to immune challenges, such as stroke [172] or peripheral infection [173]. And, as in the periphery, exercise-induced IL-6 production in the brain can exert an anti-inflammatory and protective role by inhibiting inflammatory TNFα signalling and attenuating neural cell death [174].

Given that regular exercise typically reduces inflammation, normalizes insulin resistance and improves several characteristics of metabolic syndrome and depressive symptomatology, it is plausible that exercise may be especially effective in decreasing the risk for the development of various comorbidly expressed conditions with low-grade systemic inflammation at their root. Thus, regular exercise may promote behavioural and metabolic resilience [30,32–34,129,159,175–179]. Adipose tissue and contracting skeletal muscle have been reported to serve as endocrine organs to release molecules (such as cytokines) that orchestrate the metabolism and function of other organs, including the brain. The balance between the amounts of visceral adipose tissue and duration and intensity of 'contracting' skeletal muscle likely serves an important role in the balance of pro- versus anti-inflammatory cytokines, which in turn contributes to improved mood, cognition, metabolic function and overall well-being.

6. Physical fitness enhances neuroplasticity and growth factor expression

The beneficial effects of physical activity and increased cardiorespiratory fitness on brain health are well recognized. Chronic stress, exemplified by high level glucocorticoid exposure, decreases neurotrophic factor expression/signalling, neurogenesis and gliogenesis in the brain [180]; this appears to be associated with reduced volumes of stress-sensitive brain

regions (e.g. hippocampal and prefrontal cortex) as well as depression and cognitive dysfunction [181,182]. By contrast, regular exercise has been shown to enhance positive mood, decrease depression and anxiety (as discussed earlier), and increase cognitive function, such as learning and memory in both animal and human studies [32–34,171,183–185]. Possible biological mechanisms mediating these effects include structural (e.g. increased neurogenesis, synaptogenesis, gliogenesis and angiogenesis) [186–189] and cellular/molecular (e.g. altered central monoamine neurotransmission and increased growth factor expression) [33,186,190–197] changes in the brain. Together, they can promote enhanced neuroplasticity and may be capable of blocking and/or reversing the detrimental effects of chronic stress on the brain.

One important growth factor that has received much attention is brain-derived neurotrophic factor (BDNF) [198–200]. BDNF plays a critical role in integrating behavioural and metabolic responses to various challenging environments, including exercise [198–200]. In the hypothalamus, BDNF inhibits food intake and increases energy expenditure; in the hippocampus, BDNF promotes synaptic plasticity and neurogenesis, thereby improving cognitive function, mood and neuroprotection [198]. Whereas hippocampal and/or serum/plasma BDNF levels are downregulated by chronic psychosocial stress and inflammation [138,180,201], central and peripheral BDNF levels can be upregulated by acute exercise [33,198,202,203]. Interestingly, brain BDNF has been shown to be a major source of circulating BDNF [204]. Importantly, a recent systematic review of how acute exercise and/or training affect peripheral BDNF levels reported that the majority of human studies showed a transient (exercise intensity-dependent) increase in serum/plasma BDNF, but only about 30% showed training-induced increases in basal and/or acute exercise-induced BDNF concentration [35]. Evidence showing a long-lasting BDNF response to acute exercise or training is lacking. Thus, studies with prolonged periods of the training period and in different populations (i.e. trained versus untrained, healthy versus diseased) are necessary to elucidate whether basal serum/plasma BDNF concentrations are influenced by physical fitness and/or regular activity levels.

In terms of structural changes that may occur with regular exercise, imaging studies in humans have shown that increased aerobic/cardiorespiratory fitness is associated with increased brain grey matter volume and white matter integrity, especially in the prefrontal cortex and hippocampus [205,206]. Interestingly, stress- and age-sensitive regions of the brain also seem to be most responsive to the beneficial effects of a physically active lifestyle. Moreover, aerobic exercise training-induced increases in hippocampal volume have been associated with increased serum BDNF levels, and higher pre-intervention fitness has been shown to be protective against age-related hippocampal volume loss and cognitive decline [207]. Exercise-induced increases in BDNF and hippocampal volume have also been associated with reduced depressive symptoms [182,208].

Interestingly, higher basal levels of serum BDNF predict improved efficacy of a 12 week aerobic exercise programme in reducing depressive symptoms in treatment-resistant MDD patients currently on SSRIs [209]. In addition, the therapeutic effects of basal BDNF levels appeared to become greater as BMI increased, suggesting that the effect of the BDNF 'boost' from pre-treatment may be even more important in those with high BMI—a condition usually associated with low peripheral BDNF levels [209]. Animal studies support the findings of a synergistic, therapeutic effect of exercise and medication, and that enhancement of BDNF expression may be an important element in the clinical response to antidepressant treatment [210]. Enhanced BDNF is also associated with optimized regulation of energy metabolism and cardiovascular function, where mice with impaired BDNF expression exhibit elevated plasma glucose and insulin levels, elevated basal heart rates, an impaired heart rate response to stress, and are obese [198].

Indeed, low levels of serum/plasma BDNF have been found in various chronic disease states and metabolic conditions associated with insulin resistance—neurodegenerative disorders, major depression, impaired cognitive function, CVD, type 2 diabetes and obesity—and this could be owing to enhanced inflammation and/or reduced growth factor expression [198,202,203]. However, not all studies have shown reduced levels of peripheral BDNF in obese persons, which may be dependent on the age and gender of the population studied, as well as the source of BDNF measured (i.e. serum, plasma, platelets) [211,212]. For example, obese women have been shown to exhibit elevated levels of serum BDNF and these BDNF levels were positively correlated with body weight and BMI [211]. It may be that the increased BDNF levels observed in obesity are secondary to the positive energy imbalance associated with this chronic disease state and that they may represent an adaptive mechanism to counteract the condition of positive energy imbalance by stimulating energy expenditure and decreasing food intake. Interestingly, a recent study by Huang *et al*. [212] showed no difference in plasma BDNF levels between obese and non-obese people. However, when peripheral blood mononuclear cells where stimulated with lipopolysaccharide (endotoxin), those extracted from obese people showed an exaggerated BDNF release from their immune cells, which again may be a protective compensatory mechanism. Further studies are needed to clarify the exact role of BDNF in the pathophysiology of obesity and energy homeostasis. In support of the beneficial role of exercise-enhanced peripheral BDNF expression, Araya *et al*. [213] showed that after aerobic exercise training (over 10 weeks), overweight and obese people exhibited increased levels of serum and platelet BDNF levels, but no significant change in plasma BDNF. Moreover, these changes were associated with post-training improvements in anthropometric and metabolic parameters.

Importantly, physical exercise can improve growth factor signalling directly or indirectly by reducing pro-inflammatory signalling [33]. Exercise-induced increases in brain monoamines (norepinephrine and serotonin) may also contribute to increased expression of hippocampal BDNF [194]. In addition, other growth factors—insulin-like growth factor-1 (IGF-1) and vascular endothelial growth factor—have been shown to play an important role in BDNF-induced effects on neuroplasticity [33,172,190,192], as well as exerting neuroprotective effects of their own [33,214,215], thereby contributing to the beneficial effects of exercise on brain health. Like BDNF, increases in circulating IGF-1 levels in response to acute exercise are only transient and possibly time-dependent as it relates to chronic training (i.e. increases seen after 12 weeks of training) [216]. Clearly, growth factor expression and neuroplasticity are fertile areas of research with the potential to further elucidate mechanisms of how physical activity and exercise can be powerful preventive and therapeutic tools for optimal brain health.

7. Limitations

Studies examining how physical fitness contributes to health and resilience have limitations that must be acknowledged. First, some studies have not objectively quantified aerobic fitness (via measuring VO_2 max) or physical activity (using an accelerometer/pedometer), which is essential for being able to accurately interpret the results. Second, further research is needed to determine the type, frequency, duration and intensity of physical activity or a prescribed exercise programme that optimally confers health benefits. This will depend on many factors, including population characteristics—age, gender, life events, genetic predisposition, current level of physical fitness, body composition/degree of adiposity, nutritional status and any existing psychological or physiological pathological conditions. Discrepant results among studies may also reflect the outcome and assessment methods used. Likewise, better characterization of biological markers at baseline is important, to include genetic predispositions to stress-related disorders, adherence to exercise programmes, motivation and stress reactivity. Do these biological markers change over the course of an exercise treatment/programme? If so, are they stable over a given period of time after the exercise programme has been completed? In addition, examining how participants respond to psychological or physical challenges before and after long-term exercise interventions may help elucidate which mechanisms are most important in preventing the onset of disease and/or for clinical recovery from a pre-existing disorder. These are some of the issues that remain to be uncovered.

8. Conclusion

Overall, the clinical implications of a physically inactive lifestyle are profound, and the literature clearly demonstrates that having a valid measure of physical fitness, in particular aerobic fitness, may be one of the best indicators of resilience, as well as long-term health and risk of chronic diseases. Promoting physical fitness as a pathway to resilience is based on solid, scientific evidence, as noted in many ancient and current sources. Physical fitness blunts/optimizes stress reactivity, confers physiological and psychological benefits, and serves as a buffer against stress; all possible mechanisms that can protect against the development of stress-related disorders and chronic illness.

The biological mechanisms whereby regular exercise and physical fitness promote psychological and physical health are diverse and complex. Physical fitness, achieved through regular exercise and/or spontaneous physical activity, can protect against the development of chronic stress- and inflammatory-related disease by optimizing physiological and neuroendocrine stress responsivity, promoting an anti-inflammatory state, and enhancing neuroplasticity and growth factor expression. Together, these biological mechanisms facilitate efficient activation, recovery and communication among the stress responsive systems. Indeed, the biological profile exhibited by physically fit individuals is comprised of lower HPA axis, SNS and inflammatory activity, in addition to greater insulin sensitivity and neuroplasticity, and higher levels of neurotrophic factors, which may all contribute to the beneficial effects of regular exercise/physical activity with regard to metabolic, cardiovascular and behavioural resilience. Therefore, regular exercise may be an especially effective intervention in treating and/or preventing a variety of comorbidly expressed conditions characterized by dysregulated neuroendocrine, inflammatory, metabolic and behavioural stress responsive pathways.

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