Neuroscience and Biobehavioral Reviews 107 (2019) 525–539

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity

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ARTICLE INFO

Keywords:
Exercise
Depression
Mental health
Neuroplasticity
Inflammation
Hippocampus
Oxidative stress
Self-esteem
Self-efficacy
Social support
HPA
Stress
BDNF
Non-pharmacological

ABSTRACT

Physical activity can treat and prevent depressive symptoms, but its antidepressant mechanisms are yet to be established. In this review, we comprehensively assess key biological and psychosocial mechanisms through which physical activity exerts antidepressant effects, with a particular focus on exercise.

Exercise, a subset of physical activity, influences a range of biological and psychosocial processes also implicated in the pathophysiology of depression. We focus on the capacity for exercise to elicit changes in neuroplasticity, inflammation, oxidative stress, the endocrine system, self-esteem, social support and self-efficacy. We also discuss how a better understanding of these mechanisms can inform the way we design and implement exercise-based interventions to maximise their antidepressant effects on an individual basis. We conclude by presenting a conceptual framework of the key biological and psychosocial mechanisms underlying the relationship between physical activity and depressive symptoms, and the moderators and confounders that may influence it.

1. Introduction

Depression is a common mental health disorder that can have a major impact on individual wellbeing and daily functioning (Kessler, 2012). According to the World Health Organization, depression affects around 300 million people and is now the leading cause of disability worldwide (WHO, 2017). Depression is characterised by persistent low mood, dysphoria, impaired motivation and several other symptoms, ranging from psychomotor to cognitive impairments (American Psychiatric Association, 2013). Depression is also associated with serious physical health comorbidities including cardiovascular disease (Correll et al., 2017; Hare et al., 2014), metabolic risk factors such as adiposity (Capuron et al., 2017), premature mortality (Correll et al., 2017; Walker et al., 2015) and a large financial cost to society (Chisholm et al., 2016). The treatment and prevention of depression remains a public health priority (Cuijpers et al., 2012; Jorm et al., 2017).

Depression is a complex condition, its heterogeneity exemplified by the fact that two people can be diagnosed with depression and not share a single symptom (Fried and Nesse, 2015). This poses considerable challenges for traditional treatments, which include pharmacotherapy, psychotherapy, or a combination of both. These forms of therapy have provided invaluable benefits for the treatment of depression. For example, the widespread use of antidepressant medications demonstrates their scalability and accessibility (Kantor et al., 2015). Treatment effects tend to be small-to-modest for pharmacotherapy (Cipriani et al., 2018) and psychotherapy (Cuijpers et al., 2019), with a third of people with depression remaining non-responsive to treatment (Rush et al., 2006). Pharmacotherapy can also cause several adverse side-effects, such as headaches and nausea (Anderson et al., 2012). A substantial

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https://doi.org/10.1016/j.neubiorev.2019.09.040
Received 28 June 2019; Received in revised form 27 August 2019; Accepted 29 September 2019
Available online 02 October 2019

minority of people with depression do not seek treatment at all (Hasin et al., 2018). Pharmacotherapy and psychotherapy are also unable to address the physical comorbidities associated with depression (Correll et al., 2017). Both pharmacotherapy and psychotherapy will continue to play an important role in the treatment of depression in the future. But evidence suggests that the increased provision of these treatments for common mental health disorders has had little impact on prevalence and novel methods of treating and preventing these conditions are still needed (Jorm et al., 2017).

Physical activity is consistently reported as having antidepressant effects (Schuch et al., 2018). Physical activity refers to any bodily movement by the skeletal muscles that requires energy expenditure (Caspersen et al., 1985). A recent meta-analysis of 49 prospective cohort studies including 1,837,794 person-years found that people with high levels of physical activity had 17% lower odds of depression (OR = 0.83, CI = 0.79, 0.88) than people with low physical activity (Schuch et al., 2018). Other meta-analyses have also found that low physical activity is associated with a greater risk of depression (Mammen and Faulkner, 2013; Teychenne et al., 2010). Other meta-analyses found that low cardiorespiratory fitness (CRF), an indicator of physical inactivity, was associated with a 64% higher risk of depression (HR = 1.64, CI = 1.29, 2.08) than high CRF across at least 3,540,450 person-years of data (Kandola et al., 2019; Schuch et al., 2016a).

The benefits of physical activity for depression extend beyond risk reduction. Exercise refers to a subset of physical activity that is planned and structured towards improving physical fitness (Caspersen et al., 1985), such as running or weight training. Several systematic reviews have found that exercise can reduce the symptoms of depression with a moderate-to-large effect size and can be a useful addition to pharmacotherapy and psychotherapy (Bridle et al., 2012; Cooney et al., 2013; Josefsson et al., 2014; Kvam et al., 2016; Schuch et al., 2016b). In people with depression, CRF is inversely correlated with symptom severity (Papasavvas et al., 2016). Including exercise in the treatment of depression also has several additional benefits. For example, exercise can reduce the risk of cardiovascular disease (Cornelissen and Smart, 2013), which is elevated in people with depression (Correll et al., 2017).

Despite extensive research on the efficacy of exercise and physical activity, the mechanisms through which they produce antidepressant effects remain unclear. An attempt has been made to understand the psychosocial and biological mechanisms of physical activity in the mental health of young people (Lubans et al., 2016). But little has been done to summarise these mechanisms in adults and focussing on depression.

This review will provide a comprehensive summary of the key biological and psychosocial mechanisms through which physical activity produces an antidepressant effect. We conducted non-systematic literature searches to identify possible mechanisms that are influenced by physical activity and may also play a role in the pathophysiology of depression. We primarily included mechanisms based on the strength of the underlying evidence. But there is a paucity of direct, high-quality evidence in this area, particularly within the psychosocial domain. To avoid omitting potentially important but understudied mechanisms, we also considered other factors such as their conceptual plausibility or their role in other forms of depression treatment.

Much of this review will focus on exercise specifically, as clinical research typically utilises this form of activity. Structured exercise plans are an efficient method to operationalise and standardise physical activity within a clinical trial. It is also possible that other characteristics of exercise are conducive to depression treatment. For example, exercise is typically performed during leisure time, which is associated with mental health benefits, unlike other domains such as activity during work (White et al., 2017).

We will also detail how furthering our understanding of these mechanisms can help to identify other factors that moderate or confound the relationship between physical activity and depression. For simplicity, we will assume a fundamental overlap in the mechanisms through which physical activity and exercise influence mental health.

2. Biological mechanisms

Physical activity elicits a wide range of biological changes in the brain, with the majority of studies focusing on exercise specifically (Voss et al., 2013). The remarkable breadth and diversity of these changes suggests that exercise may produce its effects through multiple pathways. This section will outline several pathways relevant to depression, with a particular focus on long-term, rather than acute, effects of exercise in adults.

The exercise protocols vary across studies in this review and it is possible that this can lead to different results in some areas. Most use moderate-to-vigorous intensity aerobic exercise, such as running or cycling, at around 50–80% heart rate reserve or participants' maximal heartrate. Sessions are typically between 30 and 60 min, between one and three times per week over the course of 1–12 months. The type of activity also varies, such as individual or group-based exercise and supervised or unsupervised exercise. Other forms of exercise, such as resistance training, elicit a divergent physiological response to aerobic exercise and may have a differential impact on the brain (Cassilhas et al., 2012) and psychosocial factors, such as self-esteem (Moore et al., 2011). But it is beyond the scope of this review to comprehensively document the differential impact of these other forms of exercise.

It is also important to note that due to technological and ethical issues, studies on molecular or cellular mechanisms tend to use animal models. But research has increasingly been able to directly or indirectly replicate these findings in humans (Voss et al., 2013). We prioritise findings from human interventional or observational studies where possible, but use animal models to fill in knowledge gaps and provide supplementary detail.

2.1. Neuroplasticity and depression

Disruptions in neuroplasticity pathways may contribute to the pathophysiology of depression (Pittenger and Duman, 2008), and targeting these mechanisms of neuroplasticity could be a promising, novel treatment approach (Kays et al., 2012; Krystal, 2007). Several meta-analyses have found depression to be associated with structural abnormalities in the brain, including reductions in hippocampal, prefrontal, orbitofrontal and anterior cingulate cortex volumes (Bora et al., 2012; Du et al., 2012; Kempton et al., 2011; Koolschijn et al., 2009; Lai, 2013; Sacher et al., 2012; Schmaal et al., 2015; Zhao et al., 2014) and white-matter integrity (Wang et al., 2014). These findings appear be independent of confounders such as medication use, age, and comorbid psychiatric conditions (Du et al., 2012; Van Tol et al., 2010; Zhao et al., 2014). Depression is also associated with differences in cerebral blood flow across multiple brain regions (Cooper et al., 2019).

The most consistently affected area in people with depression is the hippocampus (Schmaal et al., 2015), an area implicated in processes relevant to depression, such as emotional processing (Zheng et al., 2019), and stress regulation (Dranovsky and Hen, 2006). Several key cellular and molecular mechanisms of neuroplasticity are also disrupted in depression (Pittenger and Duman, 2008). For example, meta-analyses indicate that peripheral brain derived neurotrophic factor (BDNF) levels are lower in people with depression (Brunoni et al., 2008; Molendijk et al., 2014; Sen et al., 2008) and this may contribute to the pathophysiology of depression and antidepressant treatment (Castrén and Rantamäki, 2010; Duman and Monteggia, 2006; Krishnan and Nestler, 2008; Pittenger and Duman, 2008). Animal models suggest that depression can impair several cellular processes, including hippocampal neurogenesis, which has a direct influence on stress regulation, depression and anxiety symptoms (Anacker et al., 2013; Eisch and Petrik, 2012; Hill et al., 2015; Sahay and Hen, 2007).

Stimulating molecular and cellular mechanisms of neuroplasticity

may counteract some of these structural abnormalities and promote brain function in areas relevant to depressive symptoms.

2.1.1. Exercise and neuroplasticity

Several recent systematic reviews have found that exercise can increase the volume of both the left and right portions of the hippocampus and several cortical regions in healthy participants (Firth et al., 2018; Li et al., 2017; Zheng et al., 2019). Several randomised controlled trials (RCTs) have also found that exercise interventions can produce increases in prefrontal and anterior cingulate cortex volumes (Colcombe et al., 2006; Ruscheweyh et al., 2011). Several cross-sectional and longitudinal studies in healthy participants have also found that exercise and higher levels of CRF are associated with larger volumes in the hippocampus (Bugg and Head, 2011; Chaddock et al., 2010; Cole et al., 2019; Erickson et al., 2009; Frodl et al., 2019; Szabo et al., 2011; Zotcheva et al., 2019) and cortical regions (Bento-Torres et al., 2019; Bugg and Head, 2011; Erickson et al., 2007; Flöel et al., 2010; Gordon et al., 2008; Gujral et al., 2019; Rovio et al., 2010; Tamura et al., 2015; Weinstein et al., 2012; Williams et al., 2017; Zotcheva et al., 2019). There is also some evidence that exercise and CRF improvements can promote white matter integrity from systematic review (Sexton et al., 2015) and longitudinal (Zhu et al., 2015) data. However, not all studies have found an influence of exercise on brain morphology (e.g. Krogh et al., 2014).

Exercise stimulates several cellular and molecular processes in the brain that support its functioning. Exercise and CRF improvements are associated with adaptive improvements in cerebral blood flow (Bailey et al., 2013; Maass et al., 2015; Pereira et al., 2007) and animal models suggest this is driven by angiogenesis (Ding et al., 2006; Morland et al., 2017). By creating a more efficient vascular delivery system for neurotrophic factors and oxygen, these vascular changes could be crucial to exercise-induced neuroplasticity (Stimpson et al., 2018). It also supports other cellular mechanisms, such as neurogenesis (Boldrini et al., 2012). While direct study *in vivo* is not currently possible, there is indirect evidence that exercise increases the rate of neurogenesis in humans (Pereira et al., 2007; Erickson et al., 2011). This is supported by consistent evidence in animals that exercise independently stimulates hippocampal neurogenesis (Cotman et al., 2007; Vivar et al., 2013; Voss et al., 2013), including in models of stress and depression (Nakajima et al., 2010).

Exercise increases the circulation of several neurotrophic factors. Most notably, it increases concentrations of BDNF in serum or plasma samples from humans (Coelho et al., 2013; Huang et al., 2014). Animal models suggest that the exercise-induced increase in BDNF occurs in the brain (Cotman et al., 2007; Voss et al., 2013). Exercise has also been found to increase BDNF in animal models of stress and depression (Adlard & Cotman, 2004; Sartori et al., 2011; Zheng et al., 2006). Animal studies also show that exercise increases the circulation of vascular endothelial growth factor (VEGF) (Morland et al., 2017), an essential growth factor for angiogenesis (Ferrara, 2000) that also mediates neurogenesis and synaptic plasticity (De Rossi et al., 2016).

Exercise also induces several other cellular and molecular changes that contribute towards neuroplasticity, such as synaptic plasticity (Vivar et al., 2013), or the release of insulin growth factor 1 (IGF-1) and fibroblast growth factors (FGF) (Bolijn and Lucassen, 2015). Through the release of neurotrophic factors, exercise stimulates a cascade of cellular mechanisms that produce changes in the structure and function of several brain regions, including the hippocampus (El-Sayes et al., 2019; Hendrikse et al., 2017; Kandola et al., 2016). However, it is beyond the scope of this review to cover all of these changes in detail, or the complex interactions between them (for detailed reviews see Cotman et al., 2007; El-Sayes et al., 2019; Van Praag, 2009; Voss et al., 2013).

2.1.2. Exercise and neuroplasticity in depression

Evidence from human and animal studies suggest that depression is associated with structural abnormalities and dysregulation of some neuroplastic mechanisms. Exercise stimulates many of the same neuroplastic mechanisms and is associated with growth in several brain regions that are adversely affected in people with depression, such as the hippocampus, prefrontal and anterior cingulate cortices (Gujral et al., 2017). It also stimulates cerebral blood flow (Maass et al., 2015; Pereira et al., 2007), which appears to be affected in people with depression (Cooper et al., 2019). It stands to reason that exercise could counteract some of the impairments seen in people with depression, but there is a lack of research investigating this.

Schuch et al. (2016b) conducted a systematic review of the biological effects of exercise in people with depression, which found exercise produces changes in cortical activity, endocrine response, and oxidative stress. But the authors note the lack of research in this area and methodological limitations make it difficult to draw any definitive conclusions. The difficulty of accurately measuring cellular and molecular changes in human brains has made it difficult to replicate animal findings in humans. For example, the results of meta-analyses have been mixed as to whether exercise increases serum or plasma BDNF levels in people with depression (Dinoff et al., 2017, 2018; Kerling et al., 2017; Kurebayashi and Otaki, 2018). But animal models consistently show exercise can produce elevations of BDNF in the brain (Voss et al., 2013).

Longitudinal data suggest that improvements in CRF correlate with improvements in depressive symptoms and brain morphological changes (Zotcheva et al., 2019), but interventional work is necessary to infer causation. Only one RCT by Krogh et al. (2014) has investigated the impact of exercise on brain structure in people with depression. In this study, 79 people with depression were randomised to an exercise group with three 45-minute supervised cycling sessions per week at 80% of their maximal heart rate, or to a control condition. They found no change in hippocampal volume or serum samples of BDNF, VEGF, or IGF-1 in either group after the trial. However, this trial also found no significant changes in depressive symptoms (Krogh et al., 2012), making it difficult to infer anything about the antidepressant mechanisms of exercise. Poor adherence to the exercise intervention may have contributed to these findings, with participants in this study attending an average of just one session per week. A recent pilot of a 12-week exercise programme in 11 younger and older people with depression had a mean adherence of 91% to exercise sessions (Gujral et al., 2019). This study found improvements in cardiorespiratory fitness, which correlated with increases in anterior cingulate cortical volume.

More research is needed in people with depression to determine whether exercise can stimulate neuroplasticity in a similar way to that in people without depression and animal models. Neuroplasticity could be an important pathway through which exercise exerts its antidepressant effects.

2.2. Inflammation and depression

There are several lines of evidence to suggest that chronic, low-grade inflammation may play a role in the pathophysiology of depression (for detailed reviews, see Dantzer et al., 2008; Miller et al., 2009; Raison et al., 2006).

Several meta-analyses have found that people with depression have elevated levels of a range of pro-inflammatory markers, including interleukin (IL)-6, IL-1, tumour necrosis factor alpha (TNF-α), C-reactive proteins (CRP) and several other IL receptors and receptor antagonists (Dowlati et al., 2010; Howren et al., 2009; Köhler et al., 2017; Valkanova et al., 2013). Prospective cohort studies have also found people with depression have elevated IL-6 and CRP levels (Khandaker et al., 2014) with a mendelian randomisation study suggesting these factors could be causal (Khandaker et al., 2019). People with depression are also more likely to have a greater proportion of adipose tissue and metabolic dysregulations that can promote the circulation of pro-inflammatory adipokines (Capuron et al., 2017). Inflammatory

medication can also produce depressive symptoms (Friebe et al., 2010). Finally, people with depression are also at a greater risk of conditions that indicate a dysfunctional or weakened immune system (Benros et al., 2013).

Inflammation can disrupt multiple pathways involved in depression (Kiecolt-Glaser et al., 2015), such as dysregulating BDNF (Calabrese et al., 2014) or neurotransmitter systems through kynurenine pathways (Cervenka et al., 2017; Schwarcz et al., 2012). A systematic review of 14 trials found that anti-inflammatory medications can significantly decrease depressive symptoms (Köhler et al., 2014).

2.2.1. Exercise and inflammation

Several meta-analyses have found exercise interventions can reduce a number of circulating inflammatory factors, including IL-6, IL-18, CRP, leptin, fibrinogen, and angiotensin II (Fedewa et al., 2017, 2018; Lin et al., 2015). Prospective cohort studies have also found that low levels of physical activity are associated with elevated CRP, IL-6 and fibrinogen (Hamer et al., 2012; Rana et al., 2009). Physical activity and exercise act through several pathways to create an anti-inflammatory environment (Gleeson et al., 2011; Pedersen, 2017). While we are focussing on long-term effects, it is useful to first understand the acute effects of exercise on inflammation.

Muscles are secretory organs (Febbraio and Pedersen, 2002) that release myokines when contracting during exercise, the most responsive of which is IL-6 (Ostrowski et al., 1999). According to one meta-analysis, 30–60 minutes of moderate-to-high intensity exercise elicits around a 145% increase in IL-6 (Brown et al., 2015). IL-6 is typically preceded by the release of TNF-α, triggering inflammation (Febbraio and Pedersen, 2002). But with acute exercise, IL-6 does not cause inflammation as it is associated with the release of anti-inflammatory IL-10 and IL-1 receptor antagonists (IL-1ra) (Cabral-Santos et al., 2019; Pedersen and Fischer, 2007; Steensberg et al., 2003) that inhibit the production of inflammatory markers by monocytes and macrophages, such as IL-1β, IL-1α and TNF-α (Lancaster and Febbraio, 2014). IL-1ra continues to increase for several hours post-exercise (Steensberg et al., 2003), extending the post-exercise period of anti-inflammation. During this process, the adrenal gland and medulla also secrete adrenaline and cortisol, which help to promote IL-10 and reduce TNF-α even further (Steensberg et al., 2003; van der Poll et al., 1996v).

Repeating these acute bouts of exercise causes a homeostatic adjustment to lower basal levels of inflammation. In addition to the actions of myokines, exercise also reduces inflammation by modulating the circulation of adipokines. The accumulation of adipose tissue increases the circulation of adipokines that can include elevations in IL-6, TNF-α and leptin (Ouchi et al., 2011). Exercise can reduce this inflammation through counteracting the accumulation of adipose tissue (Thompson et al., 2012). Animal models suggest exercise can also modulate the immune cell profile of adipose tissue to contain a greater proportion of anti-inflammatory M2 to pro-inflammatory M1 macrophage cells (Kawanishi et al., 2010, 2013). There is also some evidence to suggest that exercise can influence the morphology of monocyte cells to have a reduced expression of toll-like receptor (TLR) subtypes that modulate inflammatory responses, such as TLR4 (Flynn et al., 2003; McFarlin et al., 2004; Timmerman et al., 2008), which regulates TNF-α (Akira et al., 2006).

Through these pathways, exercise can stimulate physiological changes that help to create a lasting anti-inflammatory environment. Other mechanisms may also contribute to this process, but it is beyond the scope of this review to cover all of them (see Gleeson et al., 2011).

2.2.2. Exercise, inflammation and depression

There is converging evidence that exercise has anti-inflammatory effects, and that inflammation plays a role in the pathophysiology and treatment of depression (Eyre and Baune, 2014; Eyre et al., 2013). However, there is a noticeable lack of direct research into the anti-inflammatory properties of exercise in people with depression.

Of the limited data available, findings are mixed. In their meta-analyses, Schuch et al. (2016b) identified three studies (Hennings et al., 2013; Krogh et al., 2012; Rethorst et al., 2013) measuring long-term changes in inflammatory markers and found exercise did not produce any significant changes in people with depression. However, in a more recent RCT by Euteneuer et al. (2017) 98 participants with major depression were assigned to cognitive behavioural therapy (CBT) treatment with or without an exercise component, or a waiting list for 16 weeks. The exercise protocols included four individualised 40-minute, unsupervised exercise sessions per week of at least moderate intensity. They found an increase in the anti-inflammatory marker IL-10 in the plasma of those in the exercise group, relative to the other two groups. They also found no significant difference in symptom reduction between the CBT groups, so it is unclear whether the inflammatory changes relate to symptom improvements. Another recent 12-week trial found that exercise was associated with reductions in serum samples of pro-inflammatory IL-6 and symptoms in people with depression (Lavebratt et al., 2017).

In a 10-week exercise trial in elderly participants without a diagnosis of depression, serum CRP, IL-6, and IL-8 decreased compared to a control (Kohut et al., 2006). There was also a decline in depressive symptoms. However, a decline in depressive symptoms was also found in the control group, suggesting it may not be related to the anti-inflammatory effects of exercise. Another study in people without depression found that a six-week moderate intensity exercise programme led to reductions in depressive symptoms and TNF-α (Paolucci et al., 2018). However, the study also found that high intensity interval training increased TNF-α and IL-6 levels, despite a decrease in depressive symptoms. This would suggest that the decreases in depressive symptoms were not driven by inflammation. One population-based study found that CRP levels explained less than 5% of the association between physical activity and depression risk (Hamer et al., 2009).

Findings in animal models have been more consistent (Eyre et al., 2013). Several animal studies have found that exercise can reduce depression-like behaviours and this correlates with inflammatory changes, such as increases in IL-10 and decreases in pro-inflammatory myokines in the hippocampus (Moon et al., 2012; Sigwalt et al., 2011).

While there is a lack of research in people with depression, some preliminary findings from recent trials do show an association between exercise, inflammation, and depressive symptoms (e.g. Euteneuer et al., 2017; Lavebratt et al., 2017). It is possible that exercise may reduce depressive symptoms through modulating inflammation, predominantly in people with elevated levels of inflammatory markers, such as TNF-α. For example, one study found that higher baseline TNF-α levels were associated with larger reductions in depressive symptoms following an exercise intervention (Rethorst et al., 2013). More work needs to be done to determine whether exercise can reduce inflammation in people with depression, whether these inflammatory changes influence depressive symptoms and if this is influenced by baseline inflammation.

2.3. Oxidative stress and depression

Oxidative and nitrosative stress occurs when excess reactive oxygen species (ROS) and reactive nitrogen species (RNS) are produced as a by-product of metabolic processing, and have harmful effects on the body. When ROS and RNS begin to outweigh antioxidants, they can cause damage to lipids, proteins, DNA, and even cell death (Maes, 2011). For simplicity, this will be referred to as oxidative stress.

Organs such as the brain are particularly vulnerable to this damage because it has a high metabolic rate and lower antioxidant levels (Maes, 2011). As a result, oxidative stress pathways may contribute towards the pathophysiology of psychiatric disorders, such as depression.

A recent systematic review collected data from 18 studies on two markers of oxidative stress, 8-hydroxy-2′-deoxyguanosine (8-OHdG) and F2-isoprostanes (Black et al., 2015). They found evidence of DNA

and lipid damage in people with depression. An earlier review of 23 observational studies found that depression was associated with greater oxidative stress, and lower antioxidant levels (Palta et al., 2014).

Oxidative stress may affect depression through multiple pathways. For example, it can degrade antioxidant defences, and stimulate the production of pro-inflammatory cytokines (for detailed reviews see Maes, 2011; Moylan et al., 2013). Over time, the resulting damage may counteract neuroplasticity and contribute towards some of the structural abnormalities in people with depression. Methods for promoting antioxidant defences to counteract oxidative stress could be a novel treatment strategy for psychiatric conditions such as depression (Pandya et al., 2013).

2.3.1. Exercise and oxidative stress

Exercise causes acute spikes in oxidative stress, but long-term exercise is protective against oxidative stress (Bloomer, 2008). A recent meta-analysis of 19 trials found that exercise was associated with a reduction in indicators of oxidative stress, and an increase in antioxidants (de Sousa et al., 2017d). These effects were found regardless of intensity, volume, type of exercise or population group.

Regular exercise produces an adaptive response to ROS through increasing the production of antioxidant enzymes and enzymes that repair ROS damage (Radak et al., 2008). This may be partially achieved through the upregulation of antioxidant genes (Gomez-Cabrera et al., 2008). This leads to a reduction in ROS damage, and greater resilience to ROS damage in the future. Animal models suggest that exercise may reduce oxidative stress in specific brain regions, such as the hippocampus (Marosi et al., 2012).

2.3.2. Exercise, oxidative stress and depression

Oxidative stress may contribute towards the pathophysiology of depression, and exercise could be a useful tool for counterbalancing this. But again, research in people with depression is lacking.

To date, just one RCT has directly investigated this relationship. Schuch et al. (2014) conducted a 12-week exercise intervention in 26 people with severe depression. The exercise sessions consisted of three supervised sessions per week using either a treadmill, stationary bike or a stepper at an intensity chosen by the participant. They found that exercise was associated with a reduced level of serum thiobarbituric acid-reactive substances (TBARS), a marker of oxidative stress.

More research is necessary to understand how exercise influences oxidative stress in people with depression.

2.4. The neuroendocrine system and depression

The neuroendocrine system maintains homeostasis by regulating the body's internal environment and influencing mood and behaviour. In healthy people, the hypothalamic-pituitary-adrenal (HPA) axis effectively mediates physiological responses to stress. But several psychiatric conditions are associated with dysregulation of the HPA axis, including depression (for a review, see Chrousos, 2009).

In humans, prolonged cortisol exposure may cause similar neurotoxicity, and contribute towards structural brain changes (Cole et al., 2010; van Tol et al., 2010v) and cognitive deficits (Ballmaier et al., 2008) associated with depression. Animal models of HPA dysfunction have shown that persistent increases in glucocorticoid circulation (cortisol in humans) exert a range of neurotoxic effects across prefrontal and hippocampal regions, including desensitisation of associated cell receptors, microglial activation, cell death, and reduction of neurogenesis and BDNF circulation (Willner et al., 2013).

Interventions that normalise HPA axis tone may minimise the corresponding neural harms and support the treatment of depression.

2.4.1. Exercise and the neuroendocrine system

Exercise causes initial elevations in the circulation of cortisol to elevate blood glucose for energy production, but regular engagement produces an adaptive, protective response (Fuqua and Rogol, 2013; Hötting et al., 2016).

Habitual exercise leads to a blunting of the cortisol response that may reflect increased HPA resilience (Heijnen et al., 2016). Endurance runners show a normalising of awakening cortisol levels following a rest day (Gouarné et al., 2005), compared to chronic psychological stress where cortisol levels remain elevated (Wüst et al., 2000). In one study, a 10-week exercise intervention combined with meta-chlorophenylpiperazine to exert neuroendocrine stress, resulted in a blunted cortisol response following the training period, compared to placebo (Broocks et al., 2001).

While limited, available evidence suggests that exercise may act as a positive stressor for select neuroendocrine pathways, with regular engagement dampening HPA activity and cortisol sensitivity.

2.4.2. Exercise, the neuroendocrine system and depression

Several lines of evidence point to the direct influence of exercise on the neuroendocrine system and HPA activity (Heijnen et al., 2016). HPA hyperactivity and prolonged elevation of cortisol levels may contribute to the pathophysiology of depression, and exercise may help to negate these effects. However, there is a lack of research into the effects of exercise on the neuroendocrine system in people with depression, and results are mixed.

A pilot study conducted by Foley et al. (2008) in 23 people with depression found that a 3-month exercise intervention reduced depressive symptoms and decreased cortisol awakening response. However, a subsequent larger-scale 16-week trial failed to replicate these effects (Krogh et al., 2010). A more recent 12-week exercise intervention in individuals with depression who maintained high participation rates led to reductions in copeptin levels, a surrogate measure of vasopressin and corticotrophin secretion (Krogh et al., 2013).

There is some preliminary evidence that exercise may exert some of its antidepressant effects through influencing cortisol reactivity and HPA response. But more research is needed to support these claims.

3. Psychosocial mechanisms

Physical activity has several psychosocial benefits that may influence depressive symptoms. Studies in this area are more balanced as to their investigation of physical activity or exercise, but aerobic exercise is still most common. Some studies also focus on engagement in sport. For simplicity, we will consider sport as a proxy measure of exercise engagement. It is important to note that psychosocial research in this section is generally less developed than the biological section and many studies are reliant on self-report questionnaires and use observational study designs. In this section, we will explore the associations between exercise and self-esteem, social support and self-efficacy in relation to depression.

3.1. Self-esteem and depression

Self-esteem is a global evaluation of self-worth and self-image, encompassing cognitive, behavioural and affective processes (Agarwala and Sharma, 2016). People with depression have lower levels of self-esteem, which may contribute to symptoms such as a sense of worthlessness (Keane and Loades, 2017; Orth et al., 2008; Van de Vliet et al., 2002). The relationship between self-esteem and depression may be cyclical; poor self-esteem can increase depressive symptoms, thereby further exacerbating self-esteem deficits.

Physical self-perception is a sub-domain of self-esteem that refers to how a person perceives their physical self-concept and body image (Inchley et al., 2011). Physical self-perception may be an important component of the relationship between self-esteem and depression (Knapen et al., 2005).

There is a negative association between perceived weight status and mental health (Ali et al., 2010; Tang et al., 2010). Those with body

image dissatisfaction or who perceive themselves as being unattractive have an elevated risk of depression (Jackson et al., 2014). People with depression also have significantly lower scores on physical self-perceptions than controls and this relationship explains some of the variance in affect between people with and without depression (Van de Vliet et al., 2002).

While it is not possible to rule out reverse causality here, preliminary evidence suggests poor physical self-perceptions may influence depressive symptoms, and this could underlie the relationship between self-esteem and depression. It is possible that exercise can remediate this by promoting self-esteem, potentially through improving physical self-perception, such as and body image. But research in people with depression is lacking.

3.1.1. Exercise and self-esteem

Aerobic and resistance exercise interventions, of intensities ranging from light to vigorous, can promote physical self-perception (Anderson et al., 2006; Feuerhahn et al., 2014; Moore et al., 2011; Özdemir et al., 2010) and improve body image (Alleva et al., 2015; Campbell and Hausenblas, 2009). The improvements in physical self-perception may underlie improvements in self-esteem. Cross-sectional studies have found that physical activity is associated with higher self-esteem scores, quality of life and positive affect, and this relationship is mediated by physical self-perception (Feuerhahn et al., 2014; Sani et al., 2016).

It is possible that improvements in body composition underlie the improvements in physical self-perception, such as reductions in body fat and increases in muscle mass (Slentz et al., 2005; Annesi & Porter, 2015). However, Anderson et al. (2006) found improvements in self-perceptions regardless of actual changes to body composition. A systematic review also found exercise improved body image, independent of fitness level, or actual changes in body composition (Campbell and Hausenblas, 2009). Overall, this suggests that exercise has a positive impact on self-esteem and the effects can occur even in the absence of body compositional improvements.

3.1.2. Exercise, self-esteem and depression

Theoretical models such as the Exercise and Self-Esteem Model (Sonstroem and Morgan, 1989), suggest that increases in self-esteem are important for the mood enhancing effects of exercise. Studies using structural equation modelling have found that self-esteem, or physical self-concept mediate the relationship between physical activity and depression (Dishman et al., 2006; Ryan, 2008).

A 16-week psychomotor therapy intervention with an exercise component in psychiatric inpatients (32% with depression), found decreases in anxiety and depression levels post-intervention, which were correlated with improvements in physical self-concept (Knapen et al., 2005). Another study in women with elevated depressive symptoms found that a seven-week exercise intervention led to increases in self-esteem, physical self-perception, and decreases in depressive symptoms compared to a wait-list control group (Legrand, 2014).

These initial findings suggest that through improving self-esteem and physical self-perception, exercise can influence depressive symptoms. But further RCTs in people with depression are necessary to confirm this.

3.2. Social support and depression

Social support refers to the assistance that social relationships and transactions provide. It encompasses both supportive actions and perceptions of those actions (Heaney and Israel, 2008). People with depression often report a lack of social support (Bettge et al., 2008; Väänänen et al., 2014), while feelings of sufficient social support have a protective effect against depression (Piko et al., 2009).

It is possible that social support plays a role in the pathophysiology of depression by restricting the number of opportunities for interaction and emotional disclosure. Improving social support could act as a buffer against stressful events and prevent the worsening of depressive symptoms (Ozbay et al., 2007).

3.2.1. Exercise and social support

Physical activity can help to improve social support networks, providing opportunities for interaction and socialisation. These benefits may be particularly pronounced in interactive forms of exercise, such as team sports.

A systematic review of 20 prospective studies found support from friends and family was associated with physical activity engagement in the future (Scarapicchia et al., 2017). In a prospective cohort study of 5395 adults, those meeting recommended physical activity guidelines with high levels of emotional support at baseline, were more likely to maintain this level of activity at follow-up (Kouvonen et al., 2011). There is also longitudinal evidence to suggest sport participation in adolescence can decrease the risk of depression in adulthood, and social support may mediate this relationship (Babiss and Gangwisch, 2009; Jewett et al., 2014; Sabiston et al., 2016).

3.2.2. Exercise, social support and depression

It is possible that by providing opportunities for socialisation, physical activity can enhance social support to create a buffer against depressive symptoms.

In an RCT of 946 people with depression, a 12-week exercise intervention led to greater reductions in symptom severity in those with greater access to supportive social relationships, compared to those with lower access (Hallgren et al., 2017). There was also a better treatment response in those with high compared to low availability of social relationships (OR = 2.17, CI = 1.40, 3.36). In a cross-sectional study of more than 40,000 adults, the inverse relationship between physical activity and symptoms of depression were partially mediated by social support and social engagement (Harvey et al., 2010).

Preliminary evidence suggests that social support could be another mechanism through which exercise produces antidepressant effects.

3.3. Self-efficacy and depression

Self-efficacy refers to situation-specific self-confidence (Bandura, 1977). That is, the belief that one can achieve a specific task.

Models of self-efficacy could account for some of the symptom progression in depression (Maddux and Meier, 1995). Poor self-efficacy can create an aversive cycle whereby a person does not pursue achievable goals or tasks, leading to feelings of frustration at their self-inefficacy (Bandura et al., 1999). This could worsen depressive symptoms, particularly when these goals or tasks are important to self-esteem. Poor self-efficacy may affect the ability to deal with emotional challenges, such as the onset and development of depressive symptoms (Taneichi et al., 2013).

Cross-sectional and longitudinal evidence suggests that low levels of self-efficacy are associated with a greater risk of depressive symptoms (Tahmassian and Moghadam, 2011; Tak et al., 2016; Taneichi et al., 2013). People with depression have lower levels of self-efficacy, which may contribute towards their symptoms.

3.3.1. Exercise and self-efficacy

Engaging in health behaviours, such as exercise, increases feelings of self-efficacy, and increases the likelihood of further engagement (Rodgers et al., 2014). A meta-analysis of 20 intervention studies found that physical activity improved several measures of self-efficacy within the domain of exercise (Higgins et al., 2013). Interventions had a significant effect on exercise self-efficacy (G = 0.208, 95% CI = 0.027, 0.388) and on barrier self-efficacy (G = 0.128, 95% CI = 0.05, 0.20). Barrier self-efficacy is the confidence to overcome barriers and engage in exercise. Exercise creates a perception of improved physical abilities and mastery of a skill, which results in increased self-efficacy (White et al., 2009). This demonstrates the importance of ensuring that

exercise is enjoyable and manageable. For example, by starting at lower intensities and with smaller bouts, and helping to self-monitor to realise success.

3.3.2. Exercise, self-efficacy and depression

Exercise could help to improve self-efficacy, which may generalise to other domains, and counteract depressive symptoms. However, few studies are available to investigate this in people with depression.

An RCT in people with moderate or severe depression found an 8-week internet-based exercise intervention reduced depressive symptoms, and increased self-efficacy, compared to an inactive control group (Haller et al., 2018). Another study in people with depression or low mood found self-efficacy mediates the relationship between physical activity and depression scores (Pickett et al., 2012). In people without depression, a 7-week exercise intervention led to reductions of depressive symptoms compared to a stretching control group, and these symptom improvements were positively associated with self-efficacy (Wipfli et al., 2011). One cross-sectional study found that physical activity increased self-efficacy, which correlated with a reduction in depressive symptoms in people without depression (Trumpeter, 2015). However, with cross-sectional study designs there is a possibility of reverse causation, which is common in physical activity research (Ekelund et al., 2016).

These initial findings suggest that physical activity may promote self-efficacy and this can influence depressive symptoms.

4. Moderators and confounders

The heterogeneity of depression poses significant challenges for prescribing treatments that are uniformly effective. One method of addressing this is to identify factors that influence treatment response and develop more personalised approaches in psychiatry (Ozomaro et al., 2013). These factors could be moderators (e.g. intervention length) or confounders (e.g. physical health complications).

So far, just one review has attempted to systematically identify moderators of exercise on depression (Schuch et al., 2016d). They found significant moderators include symptom type (somatic, state anxiety, and global functioning), life satisfaction, self-esteem, social support, marital status, and BDNF and TNF-α levels. However, the review contained only 11 studies, with a high heterogeneity, and did not include a meta-analysis. Furthermore, just four trials aimed to assess moderators prospectively, with the majority of findings being post-hoc. Previous conceptual models have suggested that factors such as frequency, intensity, type and context of physical activity can influence the mechanisms it stimulates and subsequent mental health outcomes (Lubans et al., 2016).

Understanding the biological and psychosocial mechanisms through which exercise produces an antidepressant effect can provide a scientific basis for identifying and prospectively studying moderators in future trials. For example, if neuroplasticity is established as a key pathway then exercise trials should consider factors that mediate the effect of exercise on neuroplasticity in the brain, such as gender, ovarian hormones, endocrine function, hormone circulation, genetic variations (e.g. BDNF polymorphisms), and CRF (El-Sayes et al., 2019). This section will briefly give examples of how further research in this area can benefit the design and implementation of exercise as a treatment for depression.

4.1. Identifying the best responders

Establishing the relative importance of different aspects of neuroplasticity could help to identify subgroups of people with depression who may benefit more from exercise than others. A meta-analysis of data from 8927 participants found people with depression had significantly smaller hippocampal volumes, but this was moderated by age of onset (Schmaal et al., 2015). People diagnosed with depression after the age of 21 did not show any structural abnormalities compared to controls. It is possible that people with an earlier onset of depression will respond better to exercise due to a larger capacity for neuroplasticity-driven change in the hippocampal region.

People with different perceptions of body image may also moderate their response to exercise. One study found that those who perceived themselves as being overweight only responded to exercise if they had severe depression scores (El Ansari et al., 2011). Whereas those who perceived their body as being 'just right' responded to exercise with moderate and severe depression scores.

Narrowing down on the specific contributions of different mechanisms could also help to identify biomarkers for treatment success. In a recent review, Medina et al. (2015) propose that biomarkers of inflammation, or BDNF production could serve as indicators for treatment response to exercise in people with depression. Indeed, several studies have found that people with elevated markers of inflammation, such as TNF-α and IL-6, show greater reductions in depressive symptoms in response to exercise than those without (Lavebratt et al., 2017; Rethorst et al., 2013; Schuch et al., 2016c). Other studies suggest that BDNF levels could also moderate the effect of exercise on depression (Rethorst et al., 2017; Schuch et al., 2016d; Toups et al., 2011), although this is not always the case (Gujral et al., 2014).

Exercise may also interact differentially with certain subsets of depressive symptoms. For example, some people with depression experience cognitive impairments, such as memory deficits (Rock et al., 2014). As the hippocampus plays an important role in memory formation (Burgess et al., 2002), exercise could be useful for promoting hippocampal functioning and alleviating cognitive deficits in people with depression (Kandola et al., 2016). However, the majority of exercise studies use clinical interviews, or depression scales that do not distinguish between subsets of symptoms. Schuch et al. (2017a,b) also point out that commonly used scales such as the Hamilton Rating Scale for depression are not appropriate for assessing mild to moderate depressive symptoms, which is the severity that exercise appears to be most effective at targeting. Clinical interviews may be more appropriate for detecting more mild and moderate cases of depression.

4.2. Determining the optimal exercise protocols

Understanding the mechanisms underlying the antidepressant effect of exercise can help to develop optimal exercise protocols for maximising effect. For example, different 'doses' of exercise are likely to elicit different biological responses. Longer exercise durations cause larger acute changes in IL-6 and IL-10 exercise (Cabral-Santos et al., 2019; Fischer, 2006), and exercise interventions with longer session durations and more frequent sessions have a larger impact on basal IL-6 (Hayashino et al., 2014). But extreme forms of exercise, such as marathon running, can increase acute inflammation (Gleeson et al., 2011) and have adverse immunosuppressant effects over time (Gleeson and Bishop, 2013). It is possible that different exercise session durations would be appropriate for different people. For example, extreme forms of exercise, such as marathon running, could exacerbate the inflammatory response and worsen depressive symptoms in people with elevated baseline inflammation.

The intensity of exercise during a session can elicit different neural responses (Cabral et al., 2019), which may influence how it affects depressive symptoms. For example, higher intensity exercise may produce greater changes in neuroplasticity than moderate intensity exercise (Andrews et al., 2019) and moderate-to-vigorous intensity exercise is most effective for reducing depressive symptoms (Schuch et al., 2016b). But if inflammation is established as a key underlying mechanism, it is possible that higher intensity exercises elicit greater pro-inflammatory responses (Paolucci et al., 2018) and negate the antidepressant effect. Determining the appropriate intensity may vary case to case, depending on factors such as the extent to which exercise will elicit significant changes in neuroplasticity or reductions in

inflammation in an individual.

In their model, Stimpson et al. (2018) suggest that while exercise produces several functional, but transient changes in neuroplasticity, such as elevations in BDNF circulation, improvements in cardiorespiratory fitness (CRF) are necessary for more lasting structural changes and cognitive benefits. Increases in CRF could be a useful benchmark to determine whether an exercise intervention was of sufficient intensity. Unfortunately few exercise trials measure CRF (Cooney et al., 2013), but CRF is associated with a lower risk of depression in population-based studies (Schuch et al., 2016a), and is modestly correlated with symptom severity in people with depression (Papasavvas et al., 2016). A recent exercise trial found that CRF was significantly associated with symptom reduction and predicted treatment success, independent of exercise frequency or intensity (Rahman et al., 2018). Several systematic reviews have found small or non-significant effects of an exercise at post-intervention follow ups (Cooney et al., 2013; Krogh et al., 2011; Kvam et al., 2016). It is possible that symptom improvements result from the transient effects of exercise in the brain during interventions, but insufficient CRF change may limit these effects post-intervention if activity levels decline.

It is also possible that exercise trials are of insufficient length. Most exercise interventions for depression are around 16 weeks (Cooney et al., 2013; Kvam et al., 2016). A 16-week period may only be sufficient to induce functional connectivity changes (Cabral et al., 2019). There is some evidence that exercise must last for at least six months to induce structural changes, for example, in hippocampal volume (Kleemeyer et al., 2015). Longer exercise interventions may induce structural changes that have a more pronounced impact on depressive symptoms.

The optimal exercise protocols may vary between people. For example, Higgins et al. (2013) notes that greater increases in exercise self-efficacy occur when sessions were shorter, and less structured. But longer, more structured sessions produce greater increases in barrier self-efficacy. Such findings suggest longer, more structured exercise interventions may be more appropriate for people with more significant barriers that prevent them from exercising.

4.3. Confounding factors

Many studies adjust their analysis to account for factors that confound the relationship between exercise and depression, such as alcohol use, age, gender, or physical health status. But population-level factors are difficult to measure and could be significant confounders, such as social deprivation. People in lower socioeconomic groups, experiencing greater social isolation, or in areas of greater deprivation, are more likely to be physically inactive (Beenackers et al., 2012; Gidlow et al., 2006). Social deprivation is also a significant predictor of the prevalence and persistence of depressive symptoms (Ostler et al., 2001; Wickham et al., 2014). The extent to which social deprivation confounds the relationship between exercise and depression is unclear as few exercise studies appropriately measure or adjust for social deprivation. One recent study found no difference in depressive symptoms between physically active and sedentary women living in deprived neighbourhoods (Teychenne et al., 2017). Such findings highlight a clear need for greater understanding in this area. While we use social deprivation as an example here, there are a range of population-level factors that could act as confounders and warrant further empirical attention, such as access to green spaces.

5. Conclusion

5.1. Summary

Physical activity, predominantly through exercise, produces its antidepressant effect through multiple biological and psychosocial pathways. As can be seen in Fig. 1, a variety of interdependent changes take place in the brain to produce an environment that is protective against depression. For example, neurotrophins (e.g. VEGF) stimulate downstream cellular processes (e.g. angiogenesis) that cause lasting changes in brain structure (e.g. improved vasculature) that improve brain functioning in areas implicated in depression (e.g. hippocampus) and related processes (e.g. stress regulation). While our understanding of how exercise affects the brain is growing, little is known about the complex interplay between these pathways and how they may relate to depression. For example, there is evidence that the IL-6 gene directly influences hippocampal morphology (Baune et al., 2012) and may represent a shared mechanism through which exercise influence depressive symptoms.

It is also worth noting that there may be some overlap in the mechanisms that underlie how exercise and antidepressant medications operate. For example, animal models suggest that antidepressants and exercise both impact neurogenesis through similar pathways and their combination could have a complementary effect on reducing depression-like symptoms (Micheli et al., 2018). A better understanding of these mechanistic overlaps between exercise and other forms of depression treatment will be beneficial for maximising their treatment potential.

Several psychosocial factors accompany, and potentially interact with, these biological changes to influence depression, such as self-esteem. While there is less research into the psychosocial benefits of exercise on depression, they are likely to be of parallel importance. Of the studies that do focus on psychosocial mechanisms, many use an observational study design. People with depression have lower physical activity levels (Schuch et al., 2017a). This heightens the risk of reverse causation confounding results from observational studies and more interventional studies are needed to account for this.

Even less attention has been attributed to identifying factors that moderate or confound the relationship between exercise and depression. Research continues to quantify a growing number of social, psychological and environmental factors that influence mental health and may confound the effects of exercise. There is a particular paucity of research into population-level factors that must be addressed, such as social deprivation. It will be essential to incorporate this into any attempts to understand exercise as an antidepressant.

Factors that moderate the effects of exercise are equally important in determining how best to design and implement exercise-based interventions for depression. A better understanding of the mechanisms that underlie the relationship between exercise and depressive symptoms will be essential for informing this process. It is likely that an individualised approach would be most appropriate given that the influence of each underlying mechanism is likely to differ across individuals.

While the remarkable range and diversity of adaptive neural mechanisms that exercise stimulates does complicate our understanding of how it works in the brain, it is a nice problem to have. We chose to focus on the mechanisms with the strongest evidence base in human research. Determining which mechanisms have the strongest evidence base will inherently involve a degree of subjectivity given the lack of research in this area prohibiting a truly systematic approach. There are other biological mechanisms not covered here that may also play an important role in the antidepressant effects of physical activity and exercise, such as endocannabinoid signalling (e.g. Fuss et al., 2015) or mitochondrial functioning (e.g. Aguiar et al., 2014). Several psychosocial mechanisms may also prove influential. For example, poor self-regulation following negative life events can contribute towards depression (Joorman and Stanton, 2016), and may be improved through exercise (Ahn et al., 2016). Exercise can also have a positive effect on health behaviours associated with depression, such as sleep (Kredlow et al., 2015).

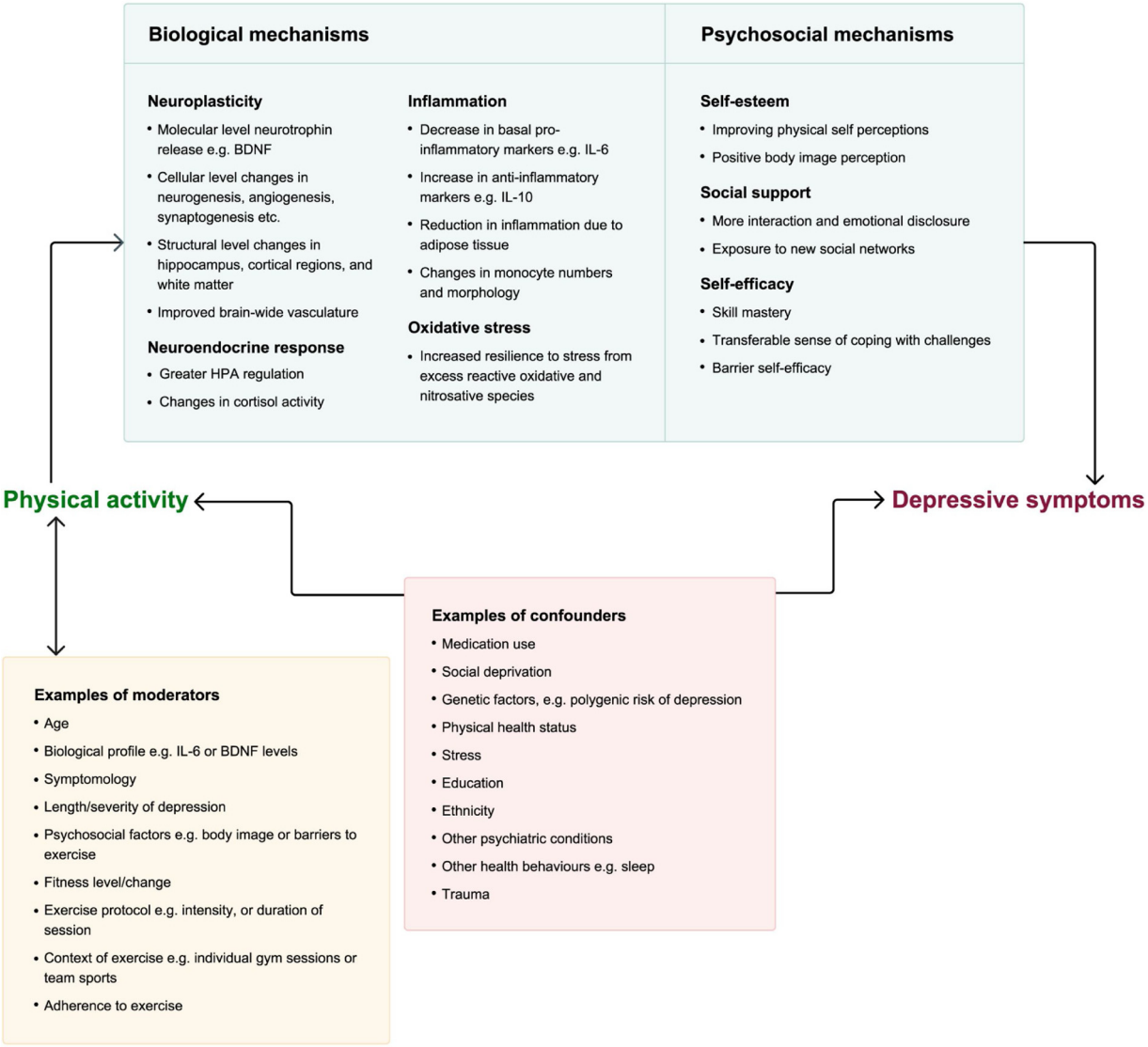

Fig. 1. Mechanisms, moderators, and confounders of the relationship between physical activity and depressive symptoms.

5.2. Future directions

Our understanding of exercise as an antidepressant has grown substantially in the past couple of decades. But much of this understanding is built on research in people without depression, with few studies investigating the biological and psychosocial impact of exercise in people with depression. Of the limited research that is available, sample sizes, and adherence to exercise interventions is low, and factors such as antidepressant use may be influencing biomarker response (Schuch et al., 2016c). Systematic reviews of exercise trials more broadly, have found a high degree of heterogeneity that makes comparison across trials a challenge, and inhibits understanding in this area (Cooney et al., 2013; Schuch et al., 2017b).

A greater amount of sufficiently powered studies is needed to investigate the biological and psychosocial effects of exercise in people with depression, using consistent methodologies and samples. It would also be beneficial for future research to directly investigate the relationship between different exercise protocols, such as whether different intensities act through different mechanisms to produce different effects on depressive symptoms. Understanding these mechanisms will also allow for exercise-based interventions to be combined with other forms of therapy that work on overlapping mechanisms to enhance their effect (Hendrikse et al., 2017). Such research will not only provide some clarity on the biological and psychosocial basis of exercise, but on the factors underpinning mental illness. While there are technological limitations on measuring certain microscale biological changes, we should continue to explore the use of more novel methods of approximating these changes, such as multi-model MRI methods (e.g. Thomas et al., 2015).

Amongst the most practical directions for future research would be to focus on understanding factors that confound or moderate the effect of exercise on depression. This could involve the inclusion of additional measures to exercise trials, such as CRF tests, MRI scans, or blood sampling. This can help to identify factors that predict greater treatment response to exercise. More detailed information about divergent symptomologies, or related factors such as body image, and self-efficacy would help to determine the individual profiles that are best suited to exercise. Wherever possible, studies should consider population-level factors that may be confounding, such as social deprivation.

Funding declaration

AK is supported by an ESRC scholarship (ES/P000592/1); GAF is supported by the Mitacs Globalink Award; CMS is funded by the Canada Research Chairs Program; JH is funded by an RTS scholarship; BS is supported by Health Education England and the National Institute for

Health Research HEE NIHR ICA Program Clinical Lectureship (ICA-CL-2017-03-001) and the Maudsley Charity and the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care South London at King's College Hospital NHS Foundation Trust.

Declaration of Competing Interest

None.

Acknowledgements

Thank you to Prof. David Osborn and Dr Joseph Hayes for their guidance throughout the process of this research and to Poppy Dorans for developing the figure. We would also like to thank Daisy McInnerney for her help in preparing the final manuscript.

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