Effects of exercise on mood disorders

Exercise as a potential treatment for depression

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Summary

Globally, mood disorders have an increasingly high occurrence. There are several treatments offered, including antidepressant drugs and behavioural therapy. However, in recent years there has been a growing interest in exercise as a potential treatment. This paper discusses the causes of depression based on monoaminergic and stress systems in order to subsequently evaluate the effects of exercise on mood by means of a literature review. There is much evidence supporting the idea that aerobic and anaerobic exercise have a stimulating effect on monoaminergic systems as well as BDNF and IGF-1 levels, dependent on the intensity and duration of the intervention which suggests that a personalized training program would be recommended. Exercise also influences the levels of circulating cortisol. Individual differences may also affect the effectiveness of exercise as a treatment and more factors are involved in depression. In short, current results are promising, however, more research is required to provide more details on how to use exercise in a treatment plan.

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Foreword

Dear reader,

At this moment, you are about to join my literature journey. I spent the last four weeks reading, analysing and meditating on mood disorders, with a focus on depression. Though this might sound depressing, it was increasingly intriguing to study and think about the causes of depression and the potential treatments.

After finishing my bachelor's research project on Whole Body Vibration as a potential treatment for pathological ageing, I chose to continue my study in exercise. However, I am quite interested in mental disorders which is why I wanted to focus on a different expertise of behavioural neurosciences, namely mood disorders. Unfortunately, mood disorders are progressively more common. Personally, I have many acquaintances suffering from such mental illnesses. I had heard of exercise being used as a treatment for depression and this made sense to me for I, myself, experience an elevation of mood when I exercise. I am aware of many of its physical effects, but I have, moreover, experienced exercise as stress-reducing. This came to mind when I considered to look into exercise and depression for my bachelor's thesis. Luckily, it was possible to choose this topic and now, you commenced reading the product. I hope you enjoy reading this paper.

Benthe de Rue

Introduction

Occasional brief feelings of a low mood in response to events in life are common. This includes, for example, moments of disappointment. However, mood disorders, also known as affective disorders, refer to a prolonged, more severe emotional state that can no longer be controlled by the patient. The most common mood disorder is called a depression and is also the disorder of interest in the current paper. With an increasingly high occurrence worldwide, major depression globally accounts for more infirmity than any other disorder (Saveanu & Nemeroff, 2012).

There are many individual differences in vulnerability for developing depression. This depends on genes, childhood experiences, stress exposure. A number of causes will be discussed in the first chapter of this thesis, among which the monoamine hypothesis of mood disorders and diathesis-stress hypothesis are included (Bear et al., 2015; Delgado, 2000). The latter is based on the idea that vulnerability for developing mental illnesses is predisposed due to genetic and/or environmental factors. This may entail a disturbance of the hypothalamic-pituitary-adrenal (HPA) system (Abela & Sullivan, 2003; Beck & Bredemeier, 2016). Interesting findings involving factors like brain-derived neurotrophic factor (BDNF) and insulin-like factor (IGF-1) propose a valuable basis for treatment of depression (Dwivedi, 2009; Levada & Troyan, 2017; Naert et al., 2011). Current treatments of mood disorders include mostly antidepressant drug administration as well as psychotherapy (Bear et al., 2015). However, recently there has been a growing interest in the effects of exercise on depression.

Exercise has been known to stimulate physical fitness and general health. Moreover, for many people exercise positively affects wellness. Much research is done using experiments aiming at a reduction of depressive symptoms with aerobic as well as anaerobic exercise interventions driven by an increasing interest in exercise as a potential treatment for depression (Stanton & Reaburn, 2014). Studies have provided evidence for effects of exercise on monoamines, BDNF and IGF-1 (Bang et al., 1990; Bjørnebekk et al., 2005; Carro et al., 2000; Eliakim et al., 1998). They also found interesting evidence for exercise to affect HPA axis activity (Hill et al., 2008; Zheng et al., 2006). Because of such findings, links are suggested between depression and exercise. Exercise may have an inhibitory effect on symptoms of depression. Several hypotheses have been suggested to explain this link, among which the thermogenic, endorphin and monoamine hypothesis are included (Craft & Perna, 2004).

The current paper will first focus on the definition of a mood disorder and the theories for its cause and involved factors. After that, exercise will be discussed for its effects and benefits. Then, it will be attempted to classify a link between depression and exercise in order to discuss its potential to serve as a treatment for depression. Therefore, the central research question for this thesis is:

What are the effects of exercise on mood disorders and should exercise be used as a treatment for depression?

This question will be answered using a number of sub-questions. Namely:

1. *What causes and defines mood disorders?*
2. *What are the effects and benefits of exercise?*
3. *How are mood disorders and exercise linked?*
4. *What individual differences should be taken into consideration?*
5. *How can exercise serve as a treatment for mood disorders?*

This will be established using literature consisting of previously performed research.

Chapter 1 Mood disorders

Depression is a mood disorder that primarily affects the patient's wellbeing, but also his behaviour and (quality of) life. It is a mental health problem and it predominantly involves disturbance of an individual's emotional state. In contrast to the common brief feelings of low mood in response to events in life, the disorder refers to a prolonged and more severe duration of a negative emotional state. Depression is in so far commonly diagnosed that Seligman already referred to the disorder as the "common cold" of psychiatry in 1973 (McLeod & Soppard, 2015; Seligman, 1973). The frequency of diagnosis has increased since then. Currently, on a global level, major depression accounts for more disability than any other disorder (Saveanu & Nemeroff, 2012). It ordinarily lasts 4-12 months. But without treatment, the chance of recurrence is high (Bear et al., 2015). In order to properly treat such a disorder, it is important to understand its causes of emergence. Various theories have been created relating to potential underlying mechanisms in the body. False ideas around the causes are thriving which prevents a clear consensus as to how the disorder could be defined. One of such is that apparently many scientists and health care professionals view depression as either a biological or an emotional concept and these concepts subsequently provide the framework for describing the causes of depression (D. Lam, 2000). Yet, depression does not have merely psychological causes, e.g. negative thinking, or biological causes, e.g. a disturbance of brain chemicals, for there is an interaction between factors deriving from both disciplines in the development of such a brain disorder suggesting the two disciplines to be connected (Kroes et al., 2011; Raison & Miller, 2011) Still, the myth forms a basis for the approach to an inquiry into the origin of mood disorders. Now, the focus lies primarily on the involved biological mechanisms. In this chapter two main hypotheses that are implicated in mood disorders are discussed together with factors that are likely to be involved in the cause of depression.

Monoamine hypothesis of mood disorders

The first theory is the *monoamine hypothesis of mood disorders.* In the 1960s, reserpine was introduced as a treatment for high blood pressure. Interestingly, a correlation was found between patients using reserpine and developing major depression (Park et al., 2018). This was linked to the monoamine-depleting activity of the drug. Its work of action led to the suggestion for affective disorders to be related to a disturbance in diffuse modulatory systems, including noradrenergic, serotonergic, cholinergic and dopaminergic systems (Bear et al., 2015). This is because reserpine acts as an adrenergic uptake inhibitor by binding to the vesicular monoamine transporter and thereby blocking uptake of the neurotransmitter into the vesicle. This leads to depletion of catecholamines from storage vesicles (Mandela et al., 2010). Inhibition of catecholamine pumps leads to the blockage of serotonin (5-HT), norepinephrine (NE) and dopamine (DA) uptake into presynaptic storage vesicles. Due to this interference, the 5-HT and the central catecholamines are depleted by cytoplasmic monoamine oxidase (MAO), an enzyme that breaks down catecholamines and serotonin, from central and peripheral synapses (Shamon & Perez, 2016). This process slows down activity of the peripheral nervous system inducing, for instance, a decrease in heart rate and blood pressure (Zhu et al., 2019).

There was another drug introduced, namely iproniazid, which was supposed to be a treatment for tuberculosis. This drug caused a notable elevation of mood instead which can be explained

by its inhibiting effect on MAO activity (Bear et al., 2015). As a result, the monoamine neurotransmitters were prevented to be broken down and remained available. A third discovery involved the antidepressant imipramine. The primary mechanism of action for imipramine is to inhibit reuptake of NE and 5-HT and thereby elevate their levels in the brain and promote their activity in the synaptic cleft (Boks, 2014). All this logically lead to the idea that mood is closely linked to the level of secreted monoamine neurotransmitters. This resulted in the introduction of antidepressants targeted at the serotonergic, dopaminergic and noradrenergic systems (Delgado, 2000). First, highly effective tricyclic antidepressants were the most available type of antidepressants. They act on multiple neurotransmitter pathways through blockage of presynaptic 5-HT and NE reuptake as well as as competitive antagonists of postsynaptic histamic, α-cholinergic and muscarinic receptors (Moraczewski & Aedma, 2020). However, tricyclic antidepressants are currently largely replaced by reuptake inhibitors that are more selective and overall better tolerated with the occurrence of less side-effects. (Didiano et al., 2014; Harmer et al., 2017; Hawton et al., 2010). These are developed for more selective inhibition of 5-HT and NE reuptake and reduction of the anticholinergic and membrane stabilising effects (Harmer et al., 2017). The latter reduces the risk of them being weakly tolerated for various side-effects can occur, and being perilous in overdose (Cleare et al., 2015; Hawton et al., 2010).

Despite their nearly immediate effects at synaptic transmission, the antidepressant action of the drugs takes a few weeks to develop (Bear et al., 2015). Selective 5-HT reuptake inhibitors (SSRIs) are recommended by most guidelines (Cleare et al., 2015). With the increasing interest in SSRI treatment, attention was raised to the 5-HT1A autoreceptors. These have a inhibitory feedback response to 5-HT release (Altieri et al., 2013). With repetitive SSRI treatment the functional sensitivity of the receptors is decreased. This is why it is suggested that the delay in onset of antidepressant action might be representing the time required for autoreceptor desensitisation. This ultimately leads to a greater availability of 5-HT in the synapse (Artigas et al., 1996; Harmer et al., 2017). Interestingly, dysregulation of 5-HT1A autoreceptors is commonly observed in depression (Albert et al., 2011).

Recently, cognitive impairment in depressed patients has been widely reported (Levada & Troyan, 2017). This includes deficits in attention, learning and memory, processing and motor functioning (Lam et al., 2014). It is suggested that depression and cognitive dysfunction have a similar neuropathological basis (Papazacharias & Nardini, 2012). Studies found that reduction of synaptic plasticity in the prefrontal cortex, amygdala, ventral striatum and hippocampus may be an important factor in the pathogenesis of depression and cognitive dysfunction due to depression (Darcet et al., 2016; Szczêsny et al., 2013). Various factors are play a role in neuroplasticity. Besides monoamines, factors like insulin-like growth hormone (IGF-1) and brain-derived neurotrophic factor (BDNF) are considered to have a stimulating effect on neuroplasticity. Consequently, research is done into such factors and cognitive dysfunction in depressed patients. Regarding IGF-1, results suggest that it enhances the activity of the noradrenergic system and therefore increase neuroplasticity (Bitar et al., 2000). Moreover, a literature study found that lower peripheral IGF-1 levels are linked to decreased neuroplasticity and vice versa which may result in clinic cognitive dysfunctionalities that are observed in major depression. IGF-1 plasma levels may even serve as a prediction for

depression in the future. (Levada & Troyan, 2017). Correlations are found between lower and higher levels of IGF-1 in the brain and an elevated risk of developing depression (Chigogora et al., 2016). IGF-1 is therefore an interesting factor to involve in a study into depression.

Extensive research at a molecular level brought attention to another factor, BDNF. This is because BDNF is also involved in neural formation, guidance and survival as well as synaptic plasticity in an adult brain. Research demonstrated that chronic infusion of BDNF in the rat midbrain induces an increase in monoamines, particularly 5-HT levels in all forebrain regions, DA levels region-specifically and NE levels to a lesser extent (Siuciak et al., 1996) Serotonin and catecholamines are important for the modulation and shaping of neuroplasticity (Avery & Krichmar, 2017; Bear & Singer, 1986; Kasamatsu et al., 1979; Kraus et al., 2017; Nitsche et al., 2009; Shepard et al., 2015; Voss et al., 2017). For 5-HT this is demonstrated by a study in an adult rats. BDNF infusion in the brain produced vigorous sprouting of serotonin nerve terminals and stimulated regrowth of damaged serotonergic fibres (Mamounas et al., 1995; Naert et al., 2011). The role of BDNF in relation to monoamines is therefore an interesting factor to study for the potential causes and treatments of affective disorders. BDNF levels are also negatively affected by stress which will be elaborated on in the next paragraph for besides the monoamine hypothesis, a second theory is implicated in depression that connects the disorder to stress.

Diathesis-stress hypothesis

Mood disorders seem to run in families. There is evidence for mental illnesses to be genetically predisposed. One study tested this using polygenic risk scores. The conclusion drawn from the findings suggested that subjects with both genetic vulnerability and a relatively high occurrence of personal life events showed a higher risk for developing depression. This analysis fits within the second model for the disorder (Colodro-Conde et al., 2018). That is, the *diathesis-stress hypothesis* (Beck & Bredemeier, 2016; Malerstein, 1968). The medical term *diathesis* relates to genetically, environmentally or a combination of both genetically and environmentally determined predisposition for a specific disease. An important peripheral neuroendocrine stress response system where genetic and environmental influences to converge and cause mood disorders is the Hypothalamo-Pituitary-Adrenal (HPA) axis. Exaggerated activity of the HPA system is associated with anxiety disorders and depression which often coexist. This system is presented in *figure* 1. The paraventricular nucleus (PVN) in the hypothalamus secretes corticotropin-releasing hormone (CRH), also known as CRF, which stimulates the release of

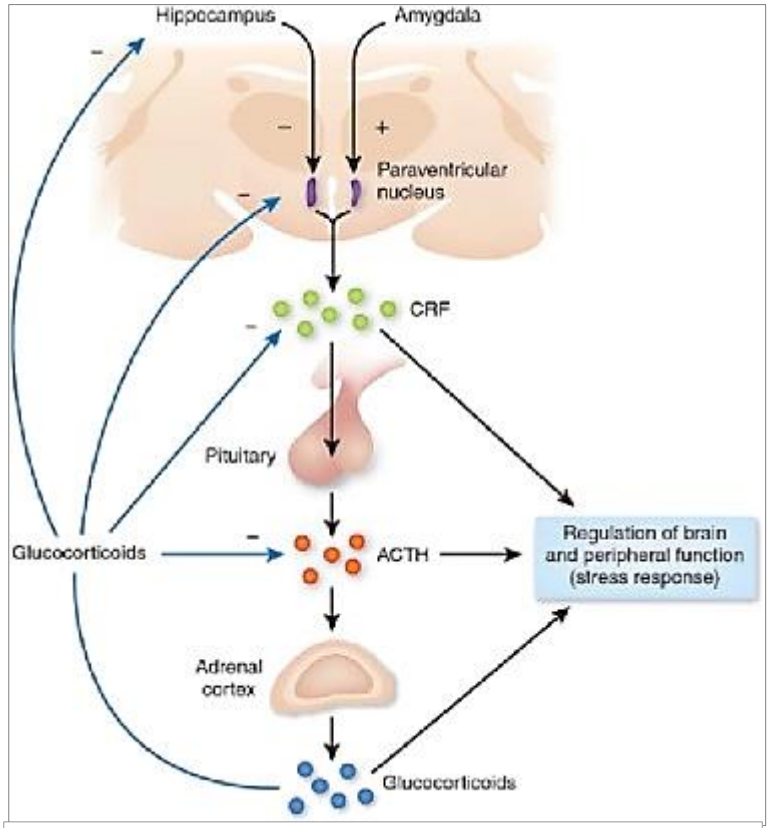

Figure 1 Regulation of the HPA Axis: CRH drives the ACTH release from the pituitary and ACTH stimulates glucocorticoid release from the adrenal cortex. Via mediation of GR in the hippocampus this exerts negative feedback on the hypothalamus and pituitary. Picture source: Liyanarachchi et al., 2017.

ACTH by the anterior pituitary. ACTH then stimulates the adrenal cortex to secrete corticosteroids, i.e. cortisol. This process is inhibited via a negative feedback loop. Activation of glucocorticoid receptors (GR) located in relatively dorsal parts of the brain – the hypothalamus and pituitary – and the hippocampus, leads to the negative feedback of the HPA axis (Jacobson & Sapolsky, 1991). Hence, normally an increased level of corticosteroids represses CRH secretion by the hypothalamus. In many depressed patients, this negative feedback is disrupted which explains observed elevated cortisol levels in the blood and saliva and CRH in the cerebrospinal fluid (Bear et al., 2015; Bhagwagar et al., 2005; Halbreich et al., 1985). Hippocampal response to cortisol is diminished. One study into the relation between the HPA system and depression involved the administration of an antagonistic compound with a high binding affinity to human CRH1 receptors which are present throughout the central and peripheral nervous systems, in patients who had a major depressive episode. A significant decrease in depression and anxiety scores was observed. The pharmacological principle of CRH1-receptor antagonism was therefore suggested to have therapeutic potential to be used as a treatment and prevention of diseases involving exaggerated central CRH activity, like depression (Zobel et al., 2000). Thus, research suggests that a hyperactive HPA system could be the cause of depression. Besides body peripheral functions, the active HPA system, CRH, ACTH and cortisol have potent effects on the brain. This can be elaborated upon using curious findings that explain the disruption of the negative feedback loop of the HPA axis at a molecular level.

As earlier discussed, reduced neuroplasticity is often associated with affective disorders. Glucocorticoids have a role in neurogenesis, neuronal survival, learning and memory (Herbert et al., 2006). Interestingly, a negative correlation is found between the number of GR in the hippocampus and development of affective disorders. With more GR, individuals are better equipped to respond to stressors as an adult and decreased hippocampal expression of GR is associated with increased stress responses in adulthood (Bear et al., 2015). The regulation of the GR number in the hippocampus is linked to several factors of which a few will be discussed. Firstly, GR are a product of gene expression for they are proteins. Secondly, monoaminergic systems may have a stimulatory effect on GR expression. Other neurotransmitters like glutamate and gamma-aminobutyric acid (GABA) may have positive effects on GR expression as well (Craft & Perna, 2004; Dishman, 1997). In addition to those, environmental factors play a role too, e.g. early childhood experience. The role of these factors is demonstrated in a rat model. Maternal care like grooming in young rats is a form of early sensory experience that regulates the amount of gene expression for GR. In adult rats that received much maternal care, hippocampal GR are more highly expressed. Due to the higher level of GR, those rats showed a reduction of anxiety-like behaviour compared to rats that did not receive much maternal care (Champagne, 2013). Rats that received much maternal care also showed a lower level of CRH in the hypothalamus. An increased level of CRH in the brain and a decreased feedback inhibition of the HPA system are associated with increased stress responses and can make the brain more vulnerable to develop depression (Jiang et al., 2019). Monoaminergic systems, the second factor listed, are instead stimulated by maternal care, which is negatively associated with depression. Serotonergic inputs in the hippocampus, for instance, are activated by tactile stimulation (Bear et al., 2015). Similarly, in humans, monoaminergic systems are stimulated by sensory experience. One study

demonstrated that urinary 5-HT is increased after stimulation like massage therapy (Ellingsen et al., 2016; Field et al., 2005). Furthermore, 5-HT induces a long-term increase in GR gene expression (Laplante et al., 2002). All this explains why poor childhood experience is often related to a reduction in GR (Bustamante et al., 2016). One risk factor for developing mood and anxiety disorders as an adult, besides genetic factors, therefore is childhood maltreatment (Bear et al., 2015).

Furthermore, BDNF is an interesting factor for its connection to stress and the HPA system as well. Research indicates that synaptic plasticity is affected by chronic stress and depression. Interesting findings were found in both rodent and human studies. Some used brain imaging in depressed persons to show a reduction in volume of the brain regions that play a role in emotion, mood and cognition, e.g. the prefrontal cortex and hippocampus, which would suggest disrupted connectivity and atrophy (MacQueen & Frodl, 2011; Price & Drevets, 2010). Other experiments demonstrated a synaptic loss in the same brain regions (Duman & Aghajanian, 2012; Kang et al., 2012). A similar result is seen in rodent brains where BDNF is decreased by chronic stress in rodents displaying symptoms of depression (Castrén, 2014; Duman & Monteggia, 2006). Other studies in mouse models found that inhibition of BDNF is correlated with a decrease in the synapse number of the hippocampus and medial prefrontal cortex and was accompanied by increased anxiety-like behaviours displayed by the mice (Z. Y. Chen et al., 2006; Liu et al., 2012). The BDNF inhibition derived from a methionine, Val66Met, polymorphism in the BDNF gene that is also in humans associated with an increased susceptibility for depression (Duman et al., 2016). Stress is also found to induce a decrease in neuron formation in the adult hippocampus and cause hypertrophy of neurons in the amygdala and nucleus accumbens (Miller & Hen, 2015; Roozendaal et al., 2009). Not all brain regions are affected to the same extend which suggests that some areas are more susceptible to the effects of stress than other areas. These effects may contribute to the change in behaviours regulated by these regions, namely motivation, reward and emotion as well as aforementioned mood and cognition (Harmer et al., 2017). Prevention or reversal of such effects could have an antidepressant function.

Though more factors are involved in the cause of depression, not all can be discussed in this paper. Antidepressant drugs remain to be a widespread treatment for depression. However, there is a growing interest in exercise. Many people like to exercise for it has many benefits, among which improvement of mental health is included. There is evidence for exercise to be beneficial for physical fitness, cognitive functioning, self-image and it may reduce symptoms of anxiety (Taylor et al., 1985). In order to understand how it could serve as a treatment, one must first learn the definition and effects of exercise on both physical and mental aspects.

Chapter 2 Exercise

Exercise has been known to stimulate physical fitness and general health. Moreover, for many people exercise positively affects wellness. Exercise has many benefits of which a number will be discussed in this chapter. First, however, exercise should be defined. Physical activity is bodily movement produced by skeletal muscles resulting from energy expenditure. In daily life, it involves sports, household and other activities. Exercise requires physical effort. It is a planned, structured and repetitive subset of physical activity that generally includes increasing the heart rate and improves or maintains physical fitness (Caspersen C, Powell K, 1985; Oxford Languages, 2020). It starts with skeletal muscle contraction using adenosine triphosphate (ATP) for energy. The transfer of a high-energy phosphate of phosphocreatine replenishes the ATP supply of a muscle. There is ATP and phosphocreatine readily available for about 15 seconds of intense exercise. Subsequently, ATP must be acquired from energy stored in nutrients through metabolism. This is done via two types of energy systems that are distinguished by the terms *aerobic* and *anaerobic* exercise. The aerobic pathway is the most efficient one for ATP production using glucose, carbohydrates and fatty acids as substrates. If the need for oxygen in a muscle fibre exceeds the supply, glucose metabolism shifts to anaerobic pathways. This involves the conversion of pyruvate into lactate at the end of glycolysis instead of the conversion into acetyl CoA and entrance to the citric acid cycle. Anaerobic metabolism, compared to aerobic metabolism, is a rather quick process of ATP production. However, it yields less ATP per glucose. Moreover, exercise depending on anaerobic pathways can generally not be sustained for a long period of time and it leads to a state of metabolic acidosis. During exercise, most people use a combination of both aerobic and anaerobic metabolism (Silverthorn, 2015). The kind of sports that are aerobically performed are for example hiking, running, swimming and cycling. These are more continuous, steady sports that occupy at least a few minutes. Anaerobic exercise involves more high intensity training, like sprinting, jumping and weightlifting.

Research in exercise physiology has yielded interesting but contradictory results regarding its effect on stress, depression and other mental parameters. It is shown that people who exercise regularly are less likely to develop clinical depression than those who do not exercise at a regular basis (O'Neal et al., 2000). It is however, difficult to find any causation in this correlation. This is because it is not clear whether those who exercise are less depressed because they exercise or that they exercise more because they are less depressed. Besides, more factors could be involved. For example, not everyone has a liking for exercise and some experience mood elevation as a result of the social interaction included in exercise or in participation in an experiment on the effects of exercise. A careful analysis of the results found in performed studies is required to learn about the effects of exercise on mood disorders. For instance, the levels of multiple hormones that affect metabolism change during exercise. This involves for instance, cortisol and glucagon (Hill et al., 2008; Silverthorn, 2015). Also, effects on 5-HT are observed (Valim et al., 2013). Such findings will be elaborated on in the next chapter focussed on the link between exercise and depression and how exercise could serve as a treatment.

Chapter 3 Exercise and depression

As mentioned in the previous chapters, exercise is known for many beneficial effects. In this chapter, a number of intriguing effects will be discussed that are of interest in exercise serving as a potential treatment for depression. A recent study in 17,839 U.S. adults found by means of a questionnaire that people who performed a combination of aerobic and anaerobic exercise reported lower levels of symptoms of depression compared to people who did not exercise (Bennie et al., 2019). Much research is done using experiments aiming at a reduction of depressive symptoms with aerobic as well anaerobic exercise interventions (Stanton & Reaburn, 2014). Most experiments involving exercise and depression use aerobic interventions. However, a study by Martinsen et al. compared the antidepressant effects of aerobic and anaerobic training in a group of participants. They found no significant differences which suggests that the antidepressant effects may not be limited to aerobic exercise, but may instead be similar in anaerobic exercise (Martinsen et al., 1989). Overall, the evidence for the relation between exercise and depression is consistent. However, the underlying mechanisms remain to be unclear and are therefore divided into multiple hypotheses.

Monoamine hypothesis

According the promising monoamine hypothesis, exercise leads to an increase in brain neurotransmitters that were discussed in the first chapter, namely serotonin (5-HT), norepinephrine (NE) and dopamine (DA). These monoamines are generally diminished in depression. Obtaining samples to measure neurotransmitters in the brain requires rather invasive procedures which is why not many results are provided yet in a human model, except for what can be studied form urinary and plasma samples. Monoamine levels in other samples are not entirely representative for levels in the brain, instead, they are overall negatively correlated with brain levels (Pietraszek et al., 1992). Acute exercise has been demonstrated to elevate the peripheral levels of the monoamine neurotransmitters (Basso & Suzuki, 2017; F. Chaouloff, 1989; Craft & Perna, 2004). Monoamine levels should, matter of course, not be too high for this could result in, for example, anxiety or extreme feelings of happiness (Volpi-Abadie et al., 2013). There is much more evidence supporting the idea that exercise affects the monoaminergic systems of which some will be discussed in the following paragraphs.

Serotonin

The first experiments on the relation between exercise and 5-HT levels were already performed in the seventies. The results showed that brain levels of 5-HT were increased with both acute and chronic aerobic exercise of rodents on a treadmill (Barchas & Freedman, 1963; F. Chaouloff, 1989; Romanowski & Grabiec, 1974). Effects were seen in the whole brain, but the strongest increase was found in mid-brain regions, rather than the brain cortex (Brown et al., 1979). Human studies gave similar results (Post & Goodwin, 1973; Young, 2007). What is more, in rats, treadmill running apparently increases tryptophan – the precursor to 5-HT – in the blood. In entering the brain, tryptophan competes with other large neutral amino acids (Höglund et al., 2019). A higher level of tryptophan in relation to the competitors allows tryptophan to enter the brain more rapidly which leads to an increased synthesis of 5-HT (Francis Chaouloff, 1997). Furthermore, in the rodent hypothalamus, exercise has also been linked to increased 5-HT turnover (A. Broocks et al., 1991). Broocks extended this finding to a confirmation of similar effects in a human model. Postsynaptic serotonin receptors were downregulated in correlation with the antidepressant effects of exercise in untrained, healthy

participants (Andreas Broocks et al., 1999, 2001). Evidently, in another human model, 5-HT serum levels were significantly increased with aerobic walking exercise (Valim et al., 2013). Both 5-HT and exercise are known to have stimulatory neurogenic effects (Kondo et al., 2015). It has even been reported that central 5-HT positively modulates neurogenesis that specifically occurs in response to running stimuli (Klempin et al., 2013). The exact mechanisms are, however, still unknown.

Norepinephrine

Subjects of studies by Dishman have reported a reduction in depression after physical activity. Dishman discussed the involvement of NE. He suggested that the reduction in depression may be due to how NE modulates brain-behaviour relationships (Dishman, 2013). This includes modulation of attention, motivation and reward (Prokopová, 2010). Interestingly, acute forced exercise in rodents depletes NE in the brain and has an inhibitory effect on 5-HT metabolism (Barchas & Freedman, 1963; F. Chaouloff, 1989; Stone, 1973). This would not suggest any experience of mood elevation. However, their study, also in a rodent model, provided evidence for chronic aerobic exercise – running wheel and treadmill training – increasing NE in brain regions that are activated during behavioural responses to stressors that evoke depression, namely the frontal cortex, hippocampus and the pons medulla (Dishman, 1997). A study by Greiwe et al. in a human model provided interesting results regarding the level of plasma NE in individuals that had trained aerobically, i.e. endurance training on a treadmill, for 10 weeks and an untrained control group. A comparison between these results showed that the NE plasma levels of the trained group were significantly higher than those of the untrained group after exercising (Greiwe et al., 1999). Thus, whereas acute forced exercise lead to the opposite effects, chronic exercise may stimulate NE and lead to increased arousal and attentiveness as well as motivation and mood and could therefore be beneficial for depressed patients (Moret & Briley, 2011; Ranjbar-Slamloo & Fazlali, 2020).

Dopamine

Exercise is also known to affect the DA system in the central nervous system (CNS). DA has been associated to both the motivation for and the rewarding effects of exercise (Greenwood et al., 2011; Y. M. Park et al., 2016). An interesting link is found with the levels of DA and its metabolites in the rodent brain. After a single session of exercise, the levels in the hippocampus, prefrontal cortex, midbrain as well as pons-medulla were significantly elevated (Meeusen et al., 1997, 2001; Meeusen & De Meirleir, 1995). However, other rodent studies showed that dopamine levels only increase once a threshold intensity of exercise is reached (Wang et al., 2000). This is seen in a human study as well. Here positron emission tomography (PET) was used to visualize the neurochemical changes in the brain. The subjects were scanned after either rest or 30 minutes of treadmill running at 85% of their age-predicted maximal heart rate. Consistent with the rodent studies, DA was not increased after acute exercise implying that the participants had no yet reached the threshold intensity (Basso & Suzuki, 2017; Hattori et al., 1994). Regarding the effects of chronic exercise on DA, another rodent model can be consulted. Rats subjected to food-reinforced running-wheel exercise for eight weeks showed upregulated concentrations of DA in brain homogenates, even though DA receptor densities were compensatorily downregulated (de Castro & Duncan, 1985; Lin et al., 2018). These findings suggest that exercise of the certain threshold intensity and/or chronic exercise stimulate the DA system and its role in motivation and reward as well as cognition and coping with stress (Aizawa et al., 2020).

IGF-1

IGF-1 is a factor that, as previously discussed, is associated with cognitive impairment which is commonly observed in depressed patients. Depressive mood and cognition are regulated by brain regions that are also responsive to IGF-1 production and physical exercise (Levada & Troyan, 2017). Various studies found that physical activity has a stimulating impact on IGF-1 secretion (Bang et al., 1990; Eliakim et al., 1998). Literature suggests that an increase in IGF-1 levels of approximately 15% higher than pre-exercise levels can be achieved with high-intensity exercise around the lactate or anaerobic threshold. This increase lasts for up to 20 minutes after exercise termination (Bang et al., 1990; Cappon et al., 1994; Schwarz et al., 1996). One rodent study demonstrated the involvement of IGF-1 in increases in hippocampal functioning induced by acute exercise. In that study, both spatial memory and hippocampal IGF-1 mRNA levels were enhanced after five days of voluntary wheel running. Moreover, blockage of the IGF-1 by means of an IGF-1 receptor binding antibody in the hippocampus eliminated the improvement of spatial memory retention. This suggests that IGF-1 may stimulate exercise-induced advancements in long-term memory (Basso & Suzuki, 2017; Ding et al., 2006).

Exercise is found to stimulate neurogenesis in the adult hippocampus. Studies by Carro *et al.* demonstrated how IGF-1 is involved. They found that exercise stimulated IGF-1 uptake from the bloodstream into specific brain areas among which the hippocampus is included. By means of a blocking IGF-1 antiserum they blocked the entrance of circulating IGF-1 which resulted in complete inhibition of increases in the number of new neurons in the hippocampus induced by exercise (Carro et al., 2001). Their results indicated exercise protects the brain from and prevent brain damage through an increase of IGF-1 uptake into the brain (Trejo et al., 2001). Exercise is therefore recommended by these studies as a preventive measure against neuronal loss which is also observed in depression. IGF-1 remains to be an interesting factor for its plausible role in depression, regulatory role in various neuronal processes as well as stimulating effect on other neurotrophins among which BDNF is included.

BDNF

As discussed in the first chapter, adequate levels of BDNF are associated with maintenance of normal cognitive function and mood. Impairments are instead associated with cognitive dysfunction and depression symptoms. Another main regulator of neurogenesis, BDNF, has been the compound of interest for many studies on the effects induced by exercise. Apparent results involve a significant increase in plasma BDNF concentrations induced by acute aerobic exercise in both healthy individuals and individuals suffering a neurological or psychiatric condition (Goekint et al., 2008; Gold et al., 2003; Gustafsson et al., 2009; Laske et al., 2010; Ströhle et al., 2010). Ströhle et al (2010), for example, found that 30 minutes of moderate-intensity exercise lead to a significant increase of BDNF levels in individuals with a panic disorder, whereas the levels observed in normal controls showed no changes. Panic disorder patients already had lower baseline BDNF concentration than healthy participants. Moreover, the increased BDNF levels tend to be greater after high-intensity compared to low-intensity aerobic exercise (Ferris et al., 2007; Goekint et al., 2008; Winter et al., 2007). These results suggest that the therapeutic efficacy of exercise may be linked to the enhancement of BDNF in the patients. Future research should, however, examine whether BDNF concentration will normalize with training programs and whether this will lead to reduction of mood disorder symptoms (Deboer et al., 2012).

Recently, a study was performed in the exercise-induced stimulatory effects on dendrites in hippocampal regions of young rat brains (Serra et al., 2019). They observed that juvenile exercise led to increased levels of hippocampal BDNF. They also examined whether these effects were influenced by stress hormones because chronic stress can promote HPA-axis activity and inhibit BDNF release in the brain (Li et al., 2008; Maghsoudi et al., 2014). Nonetheless, they found no significant change in corticosterone levels and cortical and hippocampal ACTH levels which is why they presumed that the exercise-induced neuronal effects they observed were not associated with changes in levels of BDNF, ACTH and corticosterone in the brain (Serra et al., 2019).

Stress and the HPA axis

With exercise as a physical stress, homeostasis is challenged. As a consequence, the autonomic nervous system and HPA-axis are activated in response to this stressor in order to maintain the homeostasis (Mastorakos et al., 2005). CRH secretion by the hypothalamus is stimulated and leads to activation of the HPA axis and glucocorticoid, e.g. cortisol, production (Stranahan et al., 2008). In depressed patients, feedback inhibition of the HPA axis is disrupted causing the axis to be hyperactive. Studies on cortisol and exercise support the idea that moderate to high intensity exercise induces an elevation of circulating cortisol levels. Acute low intensity exercise, however, contrastingly results in a decrease of circulating cortisol levels (Hill et al., 2008). Another curious report discussed that running is found to protect the hippocampus from a decrease in glucocorticoid receptors in animals experiencing chronic mild stress (Zheng et al., 2006).

Cortisol is thought to be a mediator between chronic psychosocial stress and depression and the association with cognitive dysfunction. Though both exercise and chronic stress increase cortisol secretion, chronic stress has a negative impact on neuroplasticity, cognition and well-being, whereas chronic exercise is considered to have beneficial effects (C. Chen et al., 2017). This is why it is suggested that exercise might add to a normalization of the activity of the HPA-axis that is disrupted in depressed patients (Portugal et al., 2013; Wegner et al., 2014). Gerber *et al.* (2020) performed a study in psychiatric patients in which they examined the impact of aerobic exercise on cortisol and change in depression in association with cortisol response through a correlational analysis. They found nor a change in acute cortisol reactivity from baseline to post-exercise intervention nor in cortisol reactivity in participants who performed six weeks of aerobic exercise training. Besides, symptoms of depression did not change in correlation to change in cortisol reactivity. Thus, according to those results, aerobic exercise was not associated with stress reactivity (Gerber et al., 2020). More research is required to find out what treatments would be efficient to normalize HPA-axis functioning.

Thermogenic hypothesis

The thermogenic hypothesis reports the rise of core body temperature that follows exercise to be responsible for the reduction of feelings of depression. Experiments in animal models have provided results valid for an acute tranquilizer effect of exercise. They have shown small temperature rises in either the brain stem or whole body that result in effects typical of a rather relaxed state. That is, a decrease in muscle spindle activity as well as synchronized electrical activity in the brain cortex (Deboer et al., 2012; DeVries, 1981; Pitts, 1969). This was measured by means of a stereotaxic instrument and recording of the impulse pattern of fine filaments (C. von Euler & Söderberg, 1956; Curt von Euler & Söderberg, 1957). DeVries reviewed on studies on the chronic effects in a human model. He found using electromyography (EMG), that

walking, cycling, jogging and bench stepping from 5 to 30 minutes at 30% to 60% of maximum intensities reduced neuromuscular tension and produced the tranquilizer effect. Therefore, he supposes that appropriate types, durations and intensities of exercise can be significantly effective (DeVries, 1981). However, research on the thermogenic hypothesis is contradictory. Some studies provide evidence for a positive correlation between an increase of body temperature and a decrease in feelings of anxiety. Still, this is unsupported or even refuted by other research (Mikkelsen et al., 2017). The link between the rise of core body temperature and depression remains to be thoroughly explored.

Endorphin hypothesis

Among the neuromechanisms that are hypothetically involved in mood-elevation due to exercise, endorphin is often cited. The endorphin hypothesis derives from the relation of endorphins to an overall sense of well-being and positive mood. However, some believe elevation of mood to be independent from secretion of endorphin (F. Chaouloff, 1989; Craft & Perna, 2004). Moreover, urinary and plasma levels might not be representable for the levels in the brain (Markoff et al., 1982). Nevertheless, an increase in plasma endorphin levels is observed in individuals following acute and chronic exercise which means that endorphin secretion could still be associated with mood changes and feelings of depression. (Carr et al., 1981; Morgan, 1985). Interestingly, endorphins are also found to affect monoamine metabolism in the brain. A mouse model demonstrated a decrease in DA levels in the striatum induced by endorphins. However, in the cortex and brain stem an increase of 5-HT and NE levels was observed. Furthermore, the reduction of endogenous DA in the striatum induced by α-methyl-ρ-tyrosine was lessened in mice treated with γ-endorphin. (Noma et al., 1981). There is a phenomenon called runner's high. This positive mood change that occurs with exercise is often suggested to be caused by increased endorphin secretion (Craft & Perna, 2004). However, injection with naloxone, an opiate antagonist, did not reverse the running-associated elevation of mood. This indicates that endorphins would not be involved with runner's high (Markoff et al., 1982). In short, not all findings regarding the role of endorphins in exercise and mood are consistent, thus this topic should be studied more.

Distraction hypothesis

The distraction hypothesis suggests that exercise can be beneficial for persons suffering a depression for it may distract a person from worries and negative thoughts. Exercise has been demonstrated to be more effective than the use of more self-focused activities, e.g. journal keeping (Craft & Perna, 2004; Smith, 2011). Exercise is also compared to other distracting activities, like relaxation and social contact. However, the results have not been conclusive. Exercise was more effective than some activities, but similar to other activities (Klein et al., 1984). Here, individual differences could be an interesting factor to look into for the effects of exercise on mood may not be the same for each level of physical fitness. Besides, not everyone likes exercise and some may prefer another activity which could affect mood.

Self-efficacy hypothesis

Exercise may also exert antidepressant effects through enhancement of self-efficacy. Self-efficacy relates to one's belief in his capabilities to succeed in a situation (Bandura et al., 1999). Bandura also discusses how people suffering a depression may feel incapable of producing positive desired results and coping with their feelings of depression. Research into this hypothesis is primarily done with a focus on improving physical self-efficacy and efficacy to regulate exercise behaviours. The relationship between self-efficacy and exercise is limitedly

studied. However, the yielded results demonstrate that for depressed persons, participating in an exercise program was positively linked to increased feelings of coping self-efficacy and therefore inversely related to symptoms of depression (Craft, 2005). Another study found that besides the enhanced self-efficacy due to exercise, initiation and maintenance were, in turn, also stimulated by self-efficacy (McAuley et al., 2008). Such findings form an interesting basis for a process of improvement of self-efficacy in conjunction with decreasing symptoms of depression by the use of exercise.

Discussion

In conclusion, the development of depression depends on multiple factors. The two main hypotheses discussed in the paper related to disruptions in the monoaminergic systems and the diathesis-stress hypothesis. In many depressed patients, reductions in monoamine levels are observed. Monoamines are associated with mood as well as cognitive function. Disturbances in the regulation of monoamines may therefore induce feelings of low mood, depression and cognitive dysfunction. Antidepressant drugs act on these disturbances. Exercise is found to have an effect on serotonin, norepinephrine and dopamine. Overall, an increase in these compounds is observed following exercise. Nevertheless, stimulation of monoaminergic systems by exercise probably depends on the intensity of the exercise intervention.

Many other factors are involved, including BDNF and IGF-1. These are interesting factors involved in neuroplasticity and research should continue looking into the apparent stimulation of these factors by exercise and whether a training program can normalize their concentration and whether it will lead to reduction of mood disorder symptoms. A follow-up review could look into other factors often mentioned in the literature, e.g. glutamate and GABA, which may also be involved in mood disorders (Craft & Perna, 2004; Dishman, 1997; R. Meeusen et al., 1997).

The diathesis-stress hypothesis involves an individual's vulnerability to develop depression based on his genetic and/or environmental predisposition. This may be due to disruptions of the HPA axis and an often observed decrease of glucocorticoid receptors in mainly the hippocampus. The effects of exercise on this system remain to be equivocal. More clarity on the exercise-glucocorticoid relationship is required to gain more knowledge about the beneficial and harmful effects of chronic stress and exercise. Results found in the effects of exercise at different intensities on cortisol levels is promising and should be elaborated as well as the study into potential treatments that could normalize HPA axis activity. Also, the interaction between the compounds or combination of theories discussed in this paper would be interesting to look at for multiple hypotheses could be applied in the study of mood disorders. On the whole, there is sufficient evidence for establishment of the benefits of exercise. Its mechanism of action, however, remains largely undetermined.

Although more research is required to determine which mechanisms are important moderators of the effects of exercise, it is probable that a combination of biological, psychological and sociological factors are involved in the relationship between exercise and depression. This is why current treatment for depression includes not only antidepressant drugs, but psychodynamic therapy and cognitive behavioural therapy as well. Previous research primarily focussed on aerobic exercise interventions in their study of the effects of exercise on mood, cognition and anxiety. Research on anaerobic exercise interventions is still limited. Moreover, individual differences may play a role too in effectiveness of exercise as a treatment. It remains to be studied whether an exercise treatment program for depression is as effective for a patient that does not like to exercise as it is for a patient that does like to exercise. Besides, levels of physical fitness vary between individuals. Low muscular strength, for example, is suggested to be associated with an increased risk of developing depression (Volaklis et al., 2019). This implies that differences in strenuosity of exercise would be required in order to

achieve the desired effect for an individual. It would therefore probably be more convenient to adjust the program to a patient’s preferences of activity and level of physical fitness.

Afterword

The maximum length of this thesis could not comprise all there is to discuss on mood disorders, exercise and how they are associated for there is much more interesting information to share.

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