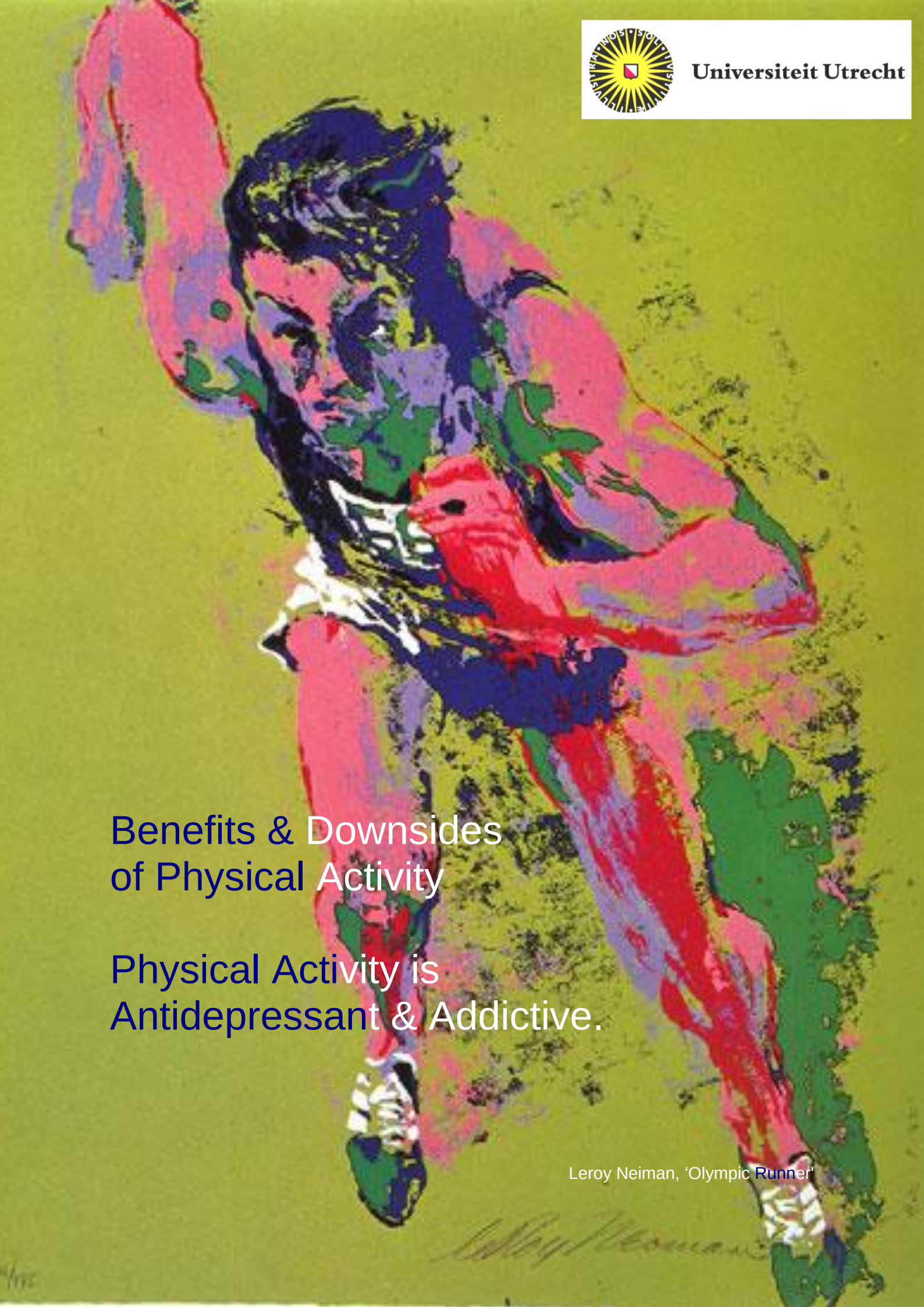

Universiteit Utrecht

Benefits & Downsides of Physical Activity

Physical Activity is Antidepressant & Addictive.

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Abstract

Physical activity has been found generally as pleasant and good for one's health. It is known to have a positive impact on nearly every system in the body. Regular exercise will improve the cardiovascular system, facilitates weight control, will create greater bone mineral density and it will decrease the risk for cancer, stroke and diabetes. Regular exercise can enhance and protect brain function and it has been found to have an antidepressant effect. Therefore physical activity is investigated to be used as a potential treatment for depression. It was found that physical activity can increase transmission of monoamines in the brain thereby correcting any imbalances seen in depressed patients. It also has an effect on the hypothalamic pituitary adrenal axis to reduce the effects of daily stressors which can be a cause of depression. In addition, it can increase the expression of BDNF in the hippocampus to facilitate neuronal growth and dendritic sprouting. Many other genes are activated important for regulating plasticity, metabolism, immune function and degeneration processes. Physical activity and anti-depressant drugs seem to have most prominent effect when used together. However, physical activity has traditionally been seen as having only positive influence for all people, but when taken to extremes, physical activity can become addictive and compulsive-like behaviour. This behaviour is called exercise dependence (ED). Traditionally, definitions of dependence were only restricted to ingestion of psychoactive substances stated in the DSM-IV. However, the concept of addiction is changing. There is becoming more emphasis on how certain behaviours may cause long-term damage to the brain the same way as drugs of abuse do, resulting in addiction. This is for instance seen when physical training causes neurochemical and morphological adaptations in brain reward pathways and hippocampus that are also shared by addictive drugs. In addition, physical activity can cause tolerance and withdrawal symptoms which are behaviours comparable to the DSM-IV of substance abuse. Neurochemically similar long term effects are seen, showed for instance with the activation of ΔFosB. Also positive reinforcement of addiction is seen in for instance when regular runners experience the runner's high and negative reinforcement is indicated by several withdrawal symptoms. Therefore ED should be seen as a clinical disorder in its own right as almost 3% off all active people exhibit this extreme behaviour. A better understanding of the neurochemical and morphological effects of physical activity in the brain could constitute a basis for developing novel treatments for depression and drug addiction. Linking molecules to mood and physical activity should continue to be investigated in the future and the research field of depression and addiction should increasingly work together.

Table of Content

1. Introduction

The objective of this thesis is to discuss the benefits and downsides of physical exercise on the well-being of humans. In particular physical exercise can serve as treatment for depression. On the other hand when physical exercise is taken to extremes, addiction to exercise, called dependence (ED) can occur. Most articles describe one of these aspects of physical exercise, however the impact of physical exercise on both sides of the spectrum should be further investigated and are therefore both discussed in this review.

Physical activity can either be muscular strength and isometric anaerobic or cardio respiratory and aerobic exercise. Aerobic exercise is for instance running wheel activity for rats and mice or long distance running for humans in which oxygen is metabolized to produce energy. Anaerobic exercise can for example be weight lifting, in which energy is provided without the use of inspired oxygen. In most cases these forms of physical activity have generally been found as pleasant and good for one's health. It has an impact on nearly every system in the body. Regular exercise will improve the cardiovascular system, facilitates weight control, will create greater bone mineral density and it will decrease the risk of cancer, stroke and diabetes.[1] In addition to positive effects on the body, it also has positive effects on the mind. It was already demonstrated in 2003 that there is a positive correlation between good cardiovascular fitness and high measures of global cognitive function.[2] Researchers had found that regular exercise can enhance and protect brain function. This is for instance seen in older adults who regularly exercise and therefore are more protected against diseases like Alzheimer's disease and dementia.[3, 4] Exercise can even be a treatment for traumatic brain injuries where patients suffer from decreased memory capacity and executive function that limit independence.[5] However, a very interesting upcoming field is the fact that people who regularly exercise have a lower risk in developing depression (DSM-IV is shown in figure 1.1).[6] Moreover, physical exercise has recently been found to have an antidepressant effect in patients suffering from major depressive disease (MDD).[7] To summarize, there are several benefits regarding physical activity and more importantly, it can be used as an anti-depressant treatment. The hypothesis considered in chapter 2 is therefore: '*Physical activity can be used as a treatment for depression.*[7]

Figure 1.1. DSM IV Criteria for Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure:

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms do not meet criteria for a Mixed Episode.
C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition (e.g., hypothyroidism).
E. The symptoms are not better accounted for by Bereavement, i.e., after the loss of a loved one, the symptoms persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

Even though physical activity has generally been seen as only beneficial, when taken to extremes, physical activity can become a compulsive and addictive-like behaviour in humans and animals. This phenomenon is referred to as 'exercise dependence' (ED). This compulsive behaviour of excessive overtraining has not been widely accepted to be a psychological disease. However, dependence should not be restricted to the ingestion of drugs and can include behavioural addictions. The acute effect of pleasure felt when taking drugs or felt with natural rewards is due to several factors including enhanced dopamine (DA) release in the Nucleus Accumbens (figure 1.2). In addition, y-Aminobutyric acid, opioid peptides, serotonin, acetylcholine, endocannabinoids and glutamate systems play an important role in addiction.[8] Traditionally, definitions of dependence were only restricted to ingestion of these psychoactive substances also stated in the DSM-IV (figure 1.3). However, the concept of addiction is changing. There is becoming more emphasis on how certain behaviours may cause long-term damage to the brain the same way as drugs of abuse do, resulting in addiction. This is for instance seen when physical training causes neurochemical and morphological adaptations in brain reward pathways and hippocampus that are also shared by addictive drugs. Therefore, extreme physical activity will be discussed in this thesis showing it to be compulsive and addictive behaviour. The neurochemical and functional changes in the brain after addictive drugs and exercise will be compared and discussed. To support this observation the following hypothesis is stated and discussed in

chapter 3: *'Natural rewards such as physical activity can be addictive*'. Investigating this phenomenon will eventually help understand the neural pathways of drug addiction and establish excessive physical activity as a psychological disease. This is important as a substantial amount of people suffer from ED.

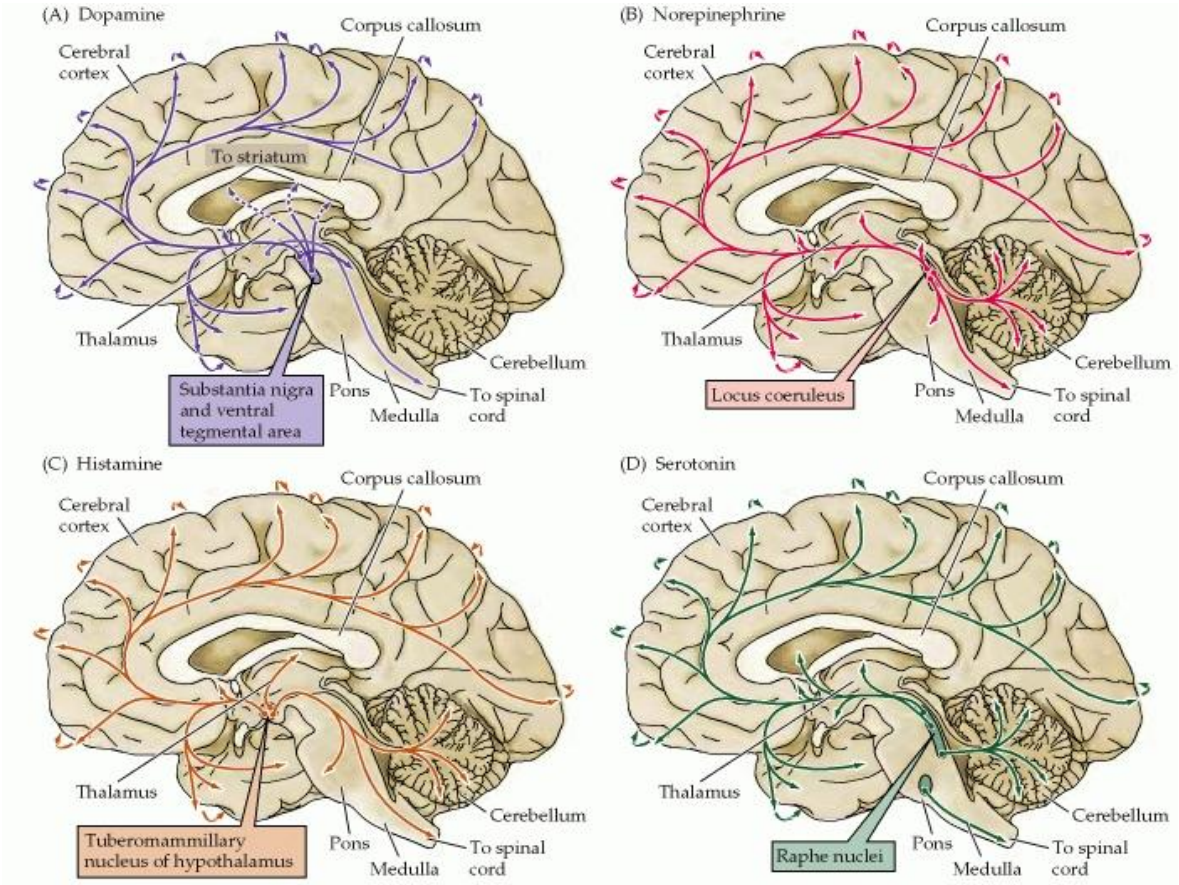

Figure 1.2. The monoamine circuits are very important for the rewarding and motivational aspects of drugs and have an influence on most parts of the brain. The dopamine circuit for instance has projections from the ventral tegmental area, the nucleus accumbens and parts of the frontal lobe. This reward circuit is altered by drug abuse and can even be altered in non-drug compulsions. (Copied from Purves, Neuroscience, 4th edition)

In the literature different definitions exist regarding addiction, mostly sharing certain basic components common to all addictive behaviours.[9] In this thesis, the following definition of addiction will be used: 'A repetitive habit pattern that increases the risk of disease and associated personal and social problems'.[9] There will also be referred to the DSM-IV of addiction (figure 1.3). Addictive behaviours are often experienced subjectively as loss of control, the behaviour contrives to occur despite volitional attempts to abstain or moderate use. Typical for an addict is the importance of short-term rewards and immediate gratification, which often have deleterious long-term effects. High relapse rates are typical when trying to change the addictive behaviour.

The phenomenon called 'cross-sensitization' will also be discussed regarding exercise dependence. Cross-sensitization is increased behavioural sensitivity of one drug after pre-exposure to another drug. Not a lot of research has been done whether there can be behavioural cross-sensitization between a natural reward and an addictive drug, though it is very likely to occur. So does running initiate the abuse of other drugs? In addition to being addictive itself, physical activity can also trigger substance abuse. For instance, running increases ethanol preference.[10]

The combination of exercise dependence and eating disorders will also be discussed in chapter 3. When for instance rats are put on an activity based anorexia-model, animals tend to show excessive running in running wheels and in addition lose weight rapidly. These animals will even go on with running when their weight is life threatening. In addition, studies have shown a clear correlation between addiction for exercise and compulsive control of weight.

So physical activity can be used as a treatment for depression, but when taken to extremes it can turn into an obsessive and addictive-like behaviour. This phenomenon is referred to as 'exercise dependence', but should more be seen as a clinical disorder in its own right. A better understanding neurochemical and morphological effects of physical activity in the brain could constitute a basis for developing novel treatments for depression and drug addiction.

Figure 1.3. DSM IV Criteria for Substance Dependence

Pattern of drug abuse causing significant harm or suffering, as characterized by three or more of the following:

1. Tolerance.
2. Withdrawal symptoms.
3. Drug use in larger amounts or during longer periods than initially intended.
4. Difficulty in restricting drug use.
5. Great deal of time devoted to procuring and consuming drugs, recovery from drug use.
6. Important social or professional activities given up in favour of drug-related activities.
7. Drug use continued despite knowledge of adverse consequences.

2. *Benefits* of Physical Exercise

Physical activity has been found to have a positive impact on nearly every system in the body including the cardiovascular system, it facilitates weight control, it will create greater bone mineral density and it will decrease the risk for cancer, stroke and diabetes.[1] *Regular exercise can also enhance and protect brain function and it has recently been found to have an antidepressant effect.*[7, 10] *Therefore, physical activity will be investigated to become a general treatment for depression. This will be either with or without the combination of anti-depressant drugs and psychotherapy. Several researchers have investigated these beneficial effects with animal studies on neuronal pathways and human clinical trials have been done to confirm the therapeutic effects of physical exercise.*[11]

Major depressive disorder

Major depressive disorder (MDD) is recognised as a mood state, clinical syndrome and psychiatric condition. MDD is becoming a large global burden of disease. It is the leading cause of disability and affects more than 340 million people worldwide. Approximately 16% of all people in the United States will suffer from depression throughout their lives.[12] MDD has an estimated economic burden in the USA of $83.1 billion per year, which includes direct treatment costs and indirect costs associated with depression in the workplace.[13] One of the core symptoms of MDD are depressed mood, anhedonia (meaning the inability to enjoy normal natural rewards), irritability, difficulties in concentrating and abnormalities in appetite and sleep. The official diagnosis of depression are mostly done using the diagnostic criteria stated in the Diagnostic and statistical manual of mental disorders (DSM-IV) (figure 1.1). In addition to depression, patients are at higher risk to develop other diseases like coronary artery disease or type 2 diabetes.[14] But visa versa, especially when chronic or life threatening, medical illness can be a psychological stressor in itself and it may trigger MDD.[14] Therefore it is logical that depression is more prevalent in medical patients than in healthy people. Depression can complicate the diagnosis of possible other medical conditions or vice versa. Despite the big prevalence of depression, not a lot is known about its pathophysiology, because of its heterogeneous appearance. However several brain areas regarding emotion, reward and executive function are likely to be involved. These limbic areas like the prefrontal cortex seem to be decreased in volume in patients with MDD.[15] This decrease has given rise to the hypothesis that depressed patients have decrements in neurotrophic factors such as brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF and neurotrophin-3 (NT3). Neurotrophic factors are important proteins involved in the development of the nervous system and the survival and maintenance of neurons in the adult brain. Antidepressants may work indirectly to increase the level of neurotrophic factors in an attempt to restore brain volume and function. However, how most anti-depressants exactly work is not yet understood. Another hypothesis states that an imbalance regarding monoamine levels is the cause of MDD. Anti-depressant drugs such as iproniazid and imipramine have antidepressant effects as they increase central serotonin or noradrenaline transmission. However, the cause of depression is far from being a simple deficiency of central monoamines. Also a dysfunction of the hypothalamic-pituitary-adrenal axis (HPA-axis) has been found to occur in depressed patients. Stress, as indicated before, can be an initial cause of depression, which increases the activity of the HPA-axis and the level of cortisol in the blood as an indication of chronic stress (chronic hypercortisolemia).

Today treatment for depression are antidepressant drugs as tricyclic drugs, SSRIs (Monoamine reuptake inhibitors) and tranylcypromine (monoamine oxidase inhibitors), but also electroconvulsive seizures, psychotherapy and deep brain stimulation. Because of the heterogeneity of the disease, not all treatments work for all patients. As physical exercise improves several aspects of brain function, it could be a new treatment, used for all MDD patients (summary found in table 2.1).

Criterion	Major depressive disorder
Lifetime risk	1 in 6
Diagnosis and monitoring	Subjective–qualitative: patients must show a depressed mood or anhedonia, as well as assorted other symptoms, for at least 2 weeks, and these symptoms must disrupt normal social and occupational functioning Patients monitored through standardized questionnaires
Aetiology and risk factors	Stressful life events (such as loss of loved ones or financial or professional crises) Genetic risk (heritability ≈ 40%) Disease genes unknown; can be idiopathic, a side effect of a drug (such as interferon-α or isotretinoin) or secondary to systemic illness (such as Cushing's syndrome or stroke, among many others)
Treatments	Monoamine reuptake inhibitors (such as tricyclic drugs, SSRIs, NRIs or SNRIs) Monoamine oxidase inhibitors (such as tranylcypromine) 'Atypical' agents (such as bupropion or mirtazapine) Electroconvulsive seizures Psychotherapy Deep brain stimulation Exercise promotes recovery
Pathogenesis	Abnormal activity of the HPA axis (hypercortisolism or hypocortisolism)? Alterations in neurotrophic signalling? Abnormal hippocampal neurogenesis? Deficits in brain reward processing? Abnormal cognitive styles (negative thinking)?

Table 2.1. Major depressive disorder: the pathogenesis shows different hypotheses on how depression comes to be. (Copied from Krishnan et al. 2008)[16]

Human studies: *Psychology of exercise*

Human clinical studies have consistently found a positive association between physical activity and mental health, such as better emotional status, reduced depression and anxiety and enhanced psychological capability for dealing with chronic stress.[17, 18] Several researchers compared psychotherapy treatment to physical activity as a treatment and consistently found both therapies to significantly reduce depressive mood.[19] A different study suggested that an aerobic training program offers additional benefits to psychiatric patients receiving psychotherapy.[20] Also significant lower relapse rates were found in patients using antidepressants in combination with physical exercise or exercise alone after six months.[20] However, due to the poor quality of much of the research done, the effectiveness of exercise in reducing symptoms of depression could not be determined. Human epidemiologic studies clearly show the beneficial effects of physical activity on physical and mental health. However, the effect size of antidepressant drugs seem to be much larger, but better

controlled trials should show the same effect for treatment with physical activity. Also additional clinical studies on humans are needed because mostly all research done on humans has been retrospective.

There are different hypotheses explaining the positive feelings regarding physical training as a therapy for MDD. Bandura et al., postulated that confidence in one's ability to exercise is very much related to a person's actual ability to exercise.[21] It has indeed been found that adoption and maintaining of an exercise program is related to self-efficacy.[21] Another theory indicates that exercisers gain confidence when they become skilful and this translates into other areas of their life, including management of their depressive symptoms. This suggests that the antidepressant effects of exercise may be mediated by improved self-evaluations. Ironically, even though depression can be partially treated by being physically active, the disease itself is a barrier for adopting an active life style. Several symptoms such as loss of energy, fatigue, diminished pleasure and feelings of worthlessness make it hard to start exercising. Also fear, lack of knowledge and previous negative experiences with physical exercise can withhold a patient to start being active. It is important to know what the reasons are for a patient not to have an active lifestyle. An appropriate approach to overcome these barriers is very important for every other individual. When these barriers are overcome, the patient is likely to keep up training schedules. This positive cycle will contribute to a decrease of depression.

Animal studies: *Monoamines*

By empirical screening for drugs against depression, substances such as iproniazid and imipramine were found to have an antidepressant effect. There are still speculations about how these drugs work. As mentioned before, MDD may be caused by an imbalance of monoamine neurotransmitters levels of serotonin, norepinephrine and dopamine. If deregulations in central monoamine systems trigger or maintain MDD, a successful treatment might work by correcting these imbalances. In line with this hypothesis, researchers think that iproniazid and imipramine increase central serotonin or noradrenalin transmission and thereby decrease depressive symptoms. Several lines of evidence suggest that physical exercise also increases the transmission of monoamines, therefore acting the same way as anti-depressant drugs are thought to work. Serotonin is one of the monoamines to have increased levels during physical exercise. This is for instance seen in animals were physical activity elevates the levels of tryptophan, the amino acid precursor of serotonin in the blood and spinal fluid.[22] This increased level of monoamines during physical exercise has also been seen in humans.[23] In addition, exercise decreases levels of amino acids that compete with tryptophan for the uptake into the brain.[23] This will thus increase the levels of tryptophan and enhance serotonin synthesis, thereby correcting the possible imbalances of the central monoamines.

Interestingly, brain cells that induce the monoamine norepinephrine are activated immediately after physical activity in experimental animals, such as rats and mice. This means these cells are also involved.[24] Therefore, chronic exercise possibly leads to increased levels of norepinephrine and its metabolites. This increase in norepinephrine during exercise is important to consider, because depletion of brain norepinephrine may be a key feature stated in one of the hypotheses regarding the pathophysiology of depression.[25] Norepinephrine is associated with positive effects on mood, giving a first indication towards the anti-depressant effects of physical exercise. Levels of dopamine are also elevated during physical exercise. Dopamine has been known to play a role in MDD regarding the

motivational problems and anhedonia seen in patients. A number of researchers proposed that these symptoms may reflect deficits in the reinforcing effects of reward thus an under activation of the brain reward systems.[26] Increasing the levels of dopamine by physical exercise might have a positive effect on this deficiency.

The role of these monoamines are important for the establishment of MDD, and the effects of exercise on mood via these monoamines are a step forward in understanding the positive effects of physical exercise. But this monoamine hypothesis for depression is inadequate, because only two third of patients of MDD have benefit of antidepressant drugs showing the heterogeneity of the disease.[27] Thus the cause of depression is far from being a simple deficiency of central monoamines. The mechanism of action of a treatment cannot be seen as the opposite of disease pathophysiology. The fact that physical activity and anti-depressant drugs increase central monoamines may only improve the symptoms and do not act on the primary cause of depression.[28] This may also indicate that the treating mechanisms of physical activity in MDD patients do not only work via monoamine levels as almost all patients of MDD benefit from increased physical activity as it elevates mood and enhances cognitive function in all depressed patients. Other hypotheses regarding MDD give rise to different mechanisms by which physical activity acts on depressive mood.

Hypothalamic-pituitary-adrenal axis

Another theory explaining the cause of depression focuses on the so called hypothalamic-pituitary-adrenal-axis (HPA-axis). This neuroendocrine feedback system consists of the hypothalamus, pituitary and the adrenal glands. As stress can be an initial cause starting a depressive period, it activates the HPA-axis, thereby increasing the level of stress hormones, such as cortisol in the blood in humans (corticosterone in rodents). The hypothalamus and the hippocampus can inhibit the release of these stress hormones, however when the system is deregulated it can result into chronic hypercortisolemia, meaning that there are excessive levels of cortisol in the blood even when real stressors are absent (figure 2.2). The increase in cortisol in part mediates decreases in neurotrophins levels (such as BDNF), the extent of neurogenesis and the complexity of neuronal processes in the hippocampus. This can be one of the causes for depression and in 50% of all MDD patients this HPA-axis is known to work abnormal, however hypercortisolemia is less common.[25] Today, glucocorticoid and corticotrophin-releasing factor receptor antagonists are currently being tested in clinical trials to potentially treat chronic hypercortisolemia and therefore the depressive symptoms.[29]

Rats, mice and other rodents are all willing to run in a running wheel voluntarily. Rats will even bar press for wheel access and will also develop conditioned place preference to environments previously paired with a running wheel. This suggests that they are very motivated to run and this indicates that running is rewarding for these animals.[30] However, running can also be seen as a stressor even when it is voluntary. Running will activate the sympathetic nervous system which will result in epinephrine production and also the activation of the HPA axis. This will eventually result in glucocrticoid production, the same as for other stressors. Running poses a threat to homeostasis and is therefore a stressor itself even when no other psychological indicators of threat or fear are present. Although this type of exercise also stimulates the HPA axis initially, adaptation occurs relatively rapidly by negative feedback systems (figure 2.2).[31] As running uses the same neuroendocrine stress axes as other stressors, many interactions exist. Running can thereby increase and reduce the effects of other stressors. In the long run, the balance between the HPA axis activation

and inhibition with voluntary running is likely to be shifted, and the consequence of such a shift could determine the decreased response to other stressors.[32] This will eventually help the body to better cope with stressors by blunting the effects. This was also found in a study by Campeau et al. 2010, who showed that rats had reduced HPA axis response to lower-intensity stressors such as saline injections, but not to more intense stressors such as predator odour exposure after 6 weeks of voluntary running.[33] Important to notice is that the effects were only found in rats with a history of wheel running of 6 weeks of more, indicating that the physiological benefits of physical exercise mostly appear after some period and relatively stable and slow-developing plastic changes are responsible for the HPA axis response attenuation. In addition, the study showed that even though a longer period of regular exercise is needed, it is not necessary to exercise on a daily basis. Intermittent access to the running wheel over 6 weeks resulted in a similar HPA axis response reduction as rats that had access daily.[34] This is consistent with human reports of runners indicating that several weeks of mild exercise are generally required to have health benefits.[35]
So the abnormalities of the HPA axis found in depressed patients may be reduced in the long run by decreasing the effects of the HPA axis with physical exercise. Running and other physical exercise counteracts mild stressors in life by constraining the HPA axis response to low intensity stressors that occur frequently over the course of a day. If cortisol levels rise after each stressor experience, this could potentially be harmful to health. The ability to limit cortisol release, by regular exercise over a long period, could be a reason why exercise provides stress resilience and health benefits such as decreased risk for depression.[34] Interestingly, this change in the HPA axis is also likely to be involved in the addictive properties of physical exercise explained in chapter three.

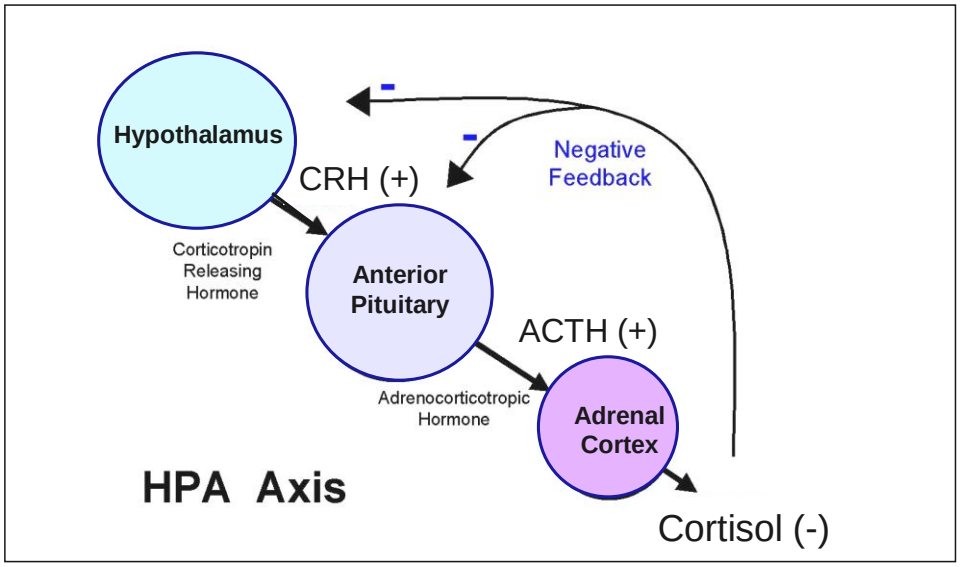

Figure 2.2. Hypothalamus pituitary adrenal axis is an important system for regulating stress. Cortisol in the blood regulates as a negative feedback system. Stress- induced hypercortisolemia leads to the central down-regulation of glucocorticoid receptors, impairing cortisol's negative feedback and enhancing levels of corticotrophin-releasing hormone (CHR) and adrenocorticotrophic hormone (ACTH) and eventually increasing cortisol levels.

Brain derived neurotrophic factor and the hippocampus

The observation that in patients with MDD the brain volume of limbic areas seem to be decreased, led to the neurotrophin hypothesis, which states that stress impairs the brain's ability to generate new cells and supports the survival of existing cells (table 2.3).[15] Therefore it is hypothesized that factors regulating the birth and health of neurons across neurotransmitter systems, called neurotrophins, instead of abnormalities in levels of neurotransmitters, underlie the pathophysiology of depression. Antidepressants may work to increase the level of neurotrophic factors in an attempt to restore brain volume and function. One of the most important neurotrophic growth factors is called BDNF (brain derived neurotrophic factor). Antidepressant drugs can up-regulate this protein, linking BDNF to depression.[36] BDNF is well known for its protective function within the brain and is mostly found in adult limbic structures. It is present with highest concentration in the hippocampus. This molecule is important for the ability to protect neurons, to increase neuronal plasticity, to enhance learning, and to assist in the overall maintenance of the brain. Physical exercise has been found to increase the amount of BDNF in rats and therefore it promotes these positive actions on neurons as well as dendrites. The increase in BDNF is robust, rapid and sustainable even after small amounts of activity. In humans, physical activity has been found to increase the levels of BDNF in serum. In animal studies, increased gene transcription in hippocampus especially in the dentate gyrus was found.[8] Here BDNF has been found to mediate synaptic plasticity.[37] Even in aged rats, BDNF increase was found after running in running wheels. As the incidence of depression is known to be higher in the elderly population, it is important to know whether BDNF can mediate brain plasticity in these patients. Especially when treatment in the elderly is difficult as brain noradrenergic and serotonergic levels and function often decline with age it is important to find alternative treatments such as physical activity.[38]

The hippocampus is very important for learning and memory and it deteriorates early in neurodegenerative diseases like Alzheimer's disease. Today it has been widely accepted that atrophy and cell loss occurs in two major sites in the brain of chronic depressed patients: the subgranular zone of the dentate gyrus and in the subventricular zone of the hippocampus.[39] Stress, a key factor implicated in the cellular pathology of depression, can decrease BDNF levels in the hippocampus, thereby down-regulating neurogenesis.[8] This decreases the ability to learn and impairs memory seen for instance, when BDNF is blocked within the rat brain, animals show impairments in memory and learning.[40] All commonly used anti-depressive treatments increase neurogenesis in the hippocampus, such as ECT, tricyclics and SSRI.[10] However, why new neurons might restore mood is largely unknown. Interestingly, the brain region showing the earliest and most sustained neurotrophic up-regulation in response to exercise is the hippocampus.[1] Thus, physical activity as well as anti-depressants can prevent this decrease of BDNF, thereby protecting the hippocampus.[1] A study on middle aged individuals indicated that their activity level was predictive of higher levels of verbal memory in a sample of 1919 participants. Other activities investigated, like game playing, attending religious services or playing a musical instrument were not predictive of memory performance.[41]

In addition, running can protect the hippocampus against the loss of neurons when rats are subjected to mild chronic stressors. In line with the previous paragraph which states that running helps to deal with mild stress, it also directly protects the hippocampus.[42] When neurons in the hippocampus of animals are exposed to chronically high levels of circulating glucocorticoids they will retract their dendrites, and show reductions in the density of

dendritic spines. However, in the brains of runners, dendritic branching in the hippocampal neurons has actually been shown to increase, as has the density of dendritic spines. This occurs despite high levels of circulating corticosterone. These morphological alterations are indicative of enhanced synaptic function of the hippocampus due to the increase of BDNF.[32]

Neuroplasticity roles
Enhanced synaptic transmission
Activity dependent regulation
Encodes LTP
Improves learning
Stimulates synaptic protein synthesis
Neurotrophic roles
Promotes survival in culture and in vivo
Promotes neurite extension
Promotes differentiation
Neuroprotective roles
Protects against ischemic insults
Protects against axotomy
Neurogenesis
Increases the number of neurons
Increases dendritic branching
Increases density in dendritic spines

Table 2.3. The neurotrophic factor, BDNF, participates in numerous functions in the brain and is best known for its roles in neuroplasticity and neuroprotection. (Copied from Cotman, 2002)[1]

Bjornebekk et al., 2005, analyzed an animal model of depression, the Flinders Sensitive Line (FSL) rats and the control Flinders Resistant Line (FRL) rats, to find the biological underpinnings of depression and the effect of wheel running on the hippocampus. They found that the in 'depressed' FSL had a lower level of proliferated cells in the dentate gyrus compared to control FRL as well as lower expression of BDNF. In the 'depressed' FSL strain wheel running had an antidepressant effect as indicated by the immobility time during the forced swimming test, a commonly used test to see how animals respond to uncontrollable stress, used for screening potential efficacy of antidepressant treatments.

This antidepressant effect was seen even though the FRL strain showed a higher daily running activity than the FSL strain. After 5 weeks of running, cell proliferation was increased in the FSL rats but not in the FRL rats. The cell proliferation in the hippocampus correlates to the antidepressant effect seen in these rats.[43] In addition, they found that in the depressed animals, running increased levels of mRNAs encoding Neuropeptide Y (NPY) and the NPY-Y1 receptor, which was correlated to increased cell proliferation.[43, 44] It has been suggested that NPY has a role for promoting proliferation of neuronal precursor cells possibly mediated by the Y1 receptor.[44] It is widely distributed within the nervous system with high concentrations in the limbic and cortical areas. Several clinical and experimental studies suggested that NPY has a role in the pathophysiology of depression as NPY levels are decreased in plasma and cerebrospinal fluid as well as the frontal cortex and caudate nucleus of depressed patients.[45, 46] When NPY or an NPY-Y1 agonist is infused into the cerebral ventricle it induces antidepressant like effects, showing the anti-depressant effects of physical activity.[44]

The fact that the antidepressant effect could not be demonstrated in the 'non-depressed' rats is in line with the findings that mood in non-depressed people is not affected by antidepressant drugs. However this animal model for depression is still questionable as

depression is a heterogeneous disease in humans and not all symptoms can be accurately modelled in animals. It still remains a challenge to recapitulate a long lived multidimensional syndrome such as depression in animal models.

Exercise induced gene transcription in the hippocampus

In addition to BDNF, other genes that are involved in neuronal activity seem to be increased in the hippocampus during exercise such as vascular endothelial growth factor (VEGF) and nerve growth factor (NGF), which also have antidepressant and pro-neurogenic properties in rodents (figure 2.4).[47] Overall, other areas of the brain also have up regulated gene transcription, but the hippocampus is one of the main brain areas able to generate new neurons. In addition, the amount of neurogenesis in the hippocampus is a measure for the effectiveness of anti-depressant drugs. The up regulation of gene transcription shows that exercise can increase the ability of neurons to change structure and increase their synapses. Healthy neurons are known to have synaptic connections with thousands of others neurons. These activated genes are associated with membrane trafficking, vesicle recycling and synaptic plasticity, all important for neuronal connectivity. Neurons can increase the strength and number of synaptic connection eventually promoting brain activity and cognition. Thus, exercise may enhance neuronal maintenance and growth through numerous increased gene transcription.

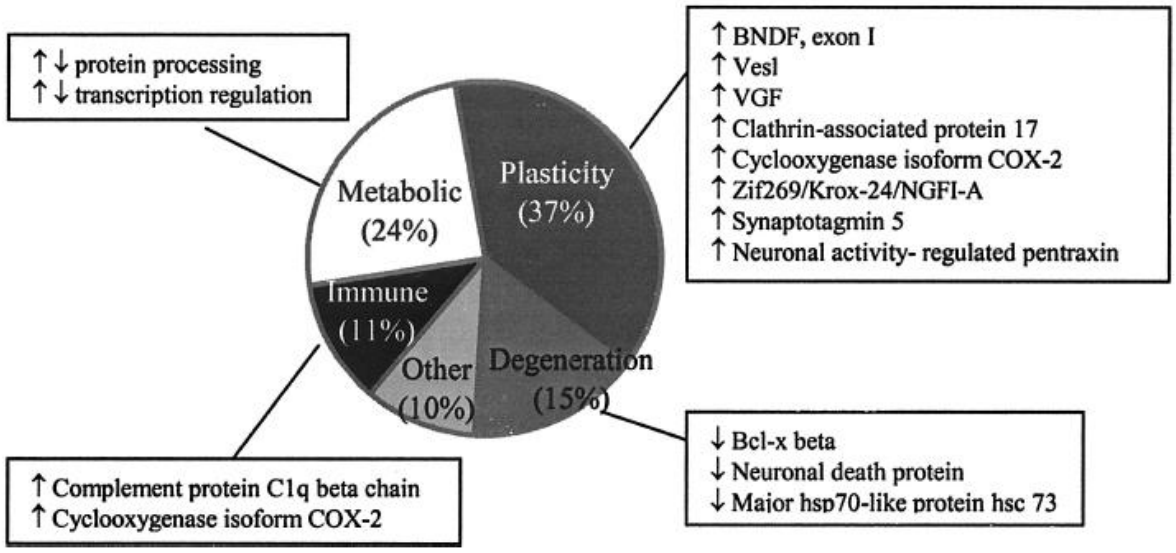

Figure 2.4. Already after 3 weeks of daily physical activity, exercise induces the transcription of numerous genes. These genes are important for regulating plasticity, metabolism, immune function and degeneration processes. (Copied from Cotman, 2002)[1]

Vascular changes and angiogenesis

In addition to up regulation of multiple genes, aerobic exercise increases vascular changes, including an increase in oxygen saturation, which promotes angiogenesis and it increases cerebral blood flow (CBF). Increased oxygen saturation and angiogenesis, meaning the formation of new blood vessels, may significantly affect brain function, resulting in behavioural improvements and memory. This increase in CBF can go up to 30% from rest to maximal exercise. Middle and anterior cerebral arteries that supply the prefrontal, frontal, temporal and parietal lobes show a particular increase in CBF.[5]

Long term increase of CBF or oxygen utilization subsequently increases angiogenesis within the cortex.[48] Angiogenesis induced by exercise may significantly affect brain function, resulting in better health and behavioural improvements. However, more research has to be done on this subject.[5]

Physical activity combined with antidepressants

An increase in BDNF level and the induction of adult hippocampal neurogenesis can be seen as a measure for the effectiveness of the antidepressant activity of a certain treatment.[16] Both antidepressant drugs and physical exercise seem to increase BDNF levels in the brain. Blockade of hippocampal neurogenesis inhibits the therapeutic-like effects of most antidepressant treatments in rodent models.[16] Interestingly, when animals receive both treatments, the maximal effectiveness is reached much earlier than when only one of the treatments is used. Russo-Neustadt et al. 2001., showed that general physical activity and antidepressant treatment in rats each lead to increased transcription of the BDNF gene in the hippocampus. They also showed that animals receiving a combined treatment had an increase in hippocampal BDNF mRNA well above baseline. They suggested that combined treatments may provide a wider margin of BDNF mRNA expression enhancement than either one alone.[36, 49] They concluded that the combination of behavioural and pharmacological therapy is considered the most effective clinical intervention for depression. Also Cotman et al. 2002., had the same results. They stated that a combination of the antidepressant tranylcypromine with voluntary wheel running produced additive increases in BDNF mRNA. Normally antidepressants work only after 2 weeks to reach maximal effectiveness. The increase of BDNF due to the antidepressants is also seen only after 2 weeks. But when the two treatments are combined the maximal effectiveness is already reached after two days, seen by the increase of BDNF.[1] Maybe it is possible that antidepressants and physical activity converge at a cellular level to promote brain function. Thus, physical activity may decrease the required time for antidepressants to become effective, again making physical activity an important clinical feature.

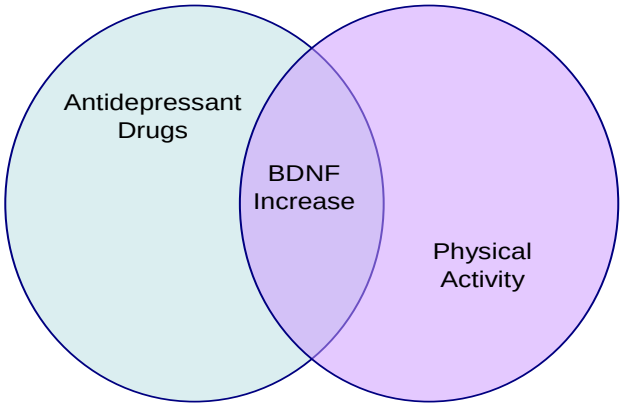

Figure 2.5. When antidepressant drugs are combined with physical exercise during the same period, maximal effectiveness is reached earlier shown by the levels of BDNF, a common measure for the effectiveness of antidepressant activity.[1]

To summarize, physical activity has a positive impact on nearly every system in the body. It will improve the cardiovascular system, facilitates weight control, will create greater bone mineral density and it will decrease the risk for cancer, stroke and diabetes.[1] Many of these conditions are impaired in patients with MDD. In addition, physical activity changes brain plasticity and has a protective function.[7] Animal models have shown that exercise reduces the damage of brain injury as well as the onset of instance Alzheimer's disease and

dementia.[3, 4] In depressed patients, physical activity increase brain health and can be used as a treatment. No other behavioural or pharmaceutical treatment can make such claims. In addition, to investigate and understand the mechanisms by which physical activity treats depression can help to better understand the pathophysiology of this heterogeneous disease. And even though there is no unified theory of depression physical activity seems to fit most hypotheses and can therefore be regarded as a substantial new treatment for all depressed patients.

Physical exercise as a treatment for depressions seems to be a very important addition to already existing anti-depressant drugs. Especially the combination of physical exercise and antidepressant drugs seem to be the most effective therapy. It has also been found that either aerobic or anaerobic exercise is effective regarding elevated brain function.[20, 50] In addition, physical activity has additional benefits such as lower medical costs, few if any adverse effects, it is readily available and can be sustained indefinitely (unlike other treatments for MDD). It can be used as a prevention of recurrence of symptoms as well, therefore physically active people have lower relapse rates for depression than in active people.[25]

However the next logical question remains 'how much exercise is needed to get the best results?' It is already known that exercise effects on executive function are not dose-dependent. So a better fitness does not directly give larger cognitive gains. Yet smaller gains in fitness increases cognitive function. However the exercise-cognition effect threshold is not known and gives conflicting findings, so further investigation is needed. It is also very important to note that the patient should self-select their level of exercise intensity. This way the greatest improvements are made. If individuals are given a pre-described training schedule that is of a too high demand the task is perceived to exceed an individual's ability, anxiety and frustration are likely outcomes. The expectations of the patient's performance are very important to give mood enhancement due to the exercise.[51] Still, large randomized intervention trials are necessary to examine this question. However, in the face of the next chapter of this thesis the old adage 'everything in moderation' seems to be in order when prescribing physical activity for brain health.

3. *Downsides* of Physical Exercise

Natural behaviours such as eating, drinking, sexual behaviour and physical exercise can activate brain reward systems and as a consequence, all organisms engage in these behaviours to receive the reward. Drugs of abuse can also activate these brain reward areas in addition to other brain areas. Traditionally, definitions of drug dependence were only restricted to ingestion of psychoactive substances as stated in the DSM-IV (figure 1.3). However, as drugs of abuse use the same neuronal systems as natural rewards do, they are increasingly showing to be very similar. The traditional symptoms for addiction, which include withdrawal, tolerance, repetitive behaviour and excessive behaviour, can also be applied to natural rewards such as excessive exercise. Therefore, the following question arises: 'Can natural rewards be addictive?' In this following chapter this question will be addressed regarding physical activity, because when taken to extremes, physical activity can develop into compulsive or addictive-like behaviour, seen in for instance in injured athletes that continue their training in spite of unhealthy consequences.[52]

The following hypothesis is stated: 'Natural rewards such as physical activity can be addictive', because dependence is not restricted to the ingestion of drugs and by widening the boundaries of dependence such behaviours as physical activity can be described as behavioural addiction. In the following chapter this hypothesis will be discussed and natural rewards and drug of abuse will be compared.

Definitions and conceptualization

Excessive exercise was for the first time described by Baekeland et al., in 1970 when they found that middle aged men were 'overcommitted' to sports and continued to run despite injuries.[53] They found this phenomenon because they could not recruit people for their study on the effects of exercise withdrawal on sleep deprivation. These men did not want to give up training even when they were given a fair amount of money.[53] Since this first report, there has been increased interest in this phenomenon of excessive exercise. Subsequently, in literature several definitions and assessments have been used such as 'commitment to run', 'obligatory exercise', 'exercise addiction', 'exercise dependence', 'exercise abuse' and 'morbid exercise'. All these terms refer to exercising which has been taken to extremes. In this thesis the term 'exercise dependence' (ED) will be adopted, which categorizes 3% of all exercising individuals that have a high risk of becoming a victim of compulsive physical activity.[9, 54] However, no mutual agreement exists when a person becomes a victim of ED and whether this disease actually exists. Inadequate conceptualization of exercise dependence was and is a major methodological problem within this research field. This has led to great discussion within the literature. Definitions of exercise dependence were sometimes based on behavioural factors such as exercise frequency or duration, but also on psychological factors such as compulsive behaviour and physiological factors such as tolerance and withdrawal symptoms. In addition, different methods have been used investigating ED, including qualitative interviews, case studies and self-report questionnaires.[9] During time, the conceptualization of ED has changed in literature. First, exercise dependence was seen as a so called 'positive addiction', because several positive psychological and physiological benefits are produced with physical exercise (chapter 2). This 'positive addiction' was seen as an enjoyable activity that produces extreme pleasure (called the runner's high) and the general thinking was that exercise makes us just 'feel

good'. However, soon several negative side-effects were seen in a certain population of committed exercisers. The positive feelings described by the 'positive addiction' theory showed to be the reinforcement to keep engaging in this behaviour, making it addictive-like. Therefore the 'negative addiction' theory was introduced, showing the downsides of physical activity.[55, 56] This was a very important development, because exercise in general is defined as only a health-related behaviour.[55] Several people who were committed runners indicated that running was the most important thing in their lives. Also several withdrawal symptoms occurred when they were deprived of exercise. These are both criteria that meet the DSM-IV for addictive behaviour shown in figure 1.3. Thus running controlled their lives as they lost perspective on life and exercise. This cannot be seen as positive behaviour.[9]

When excessive exercise was more and more seen as a negative behaviour, it was noted that exercise dependence is not very different from the chemical-dependence process, seen in addictive drugs, because the same behavioural aspects occur. First, the individual needs daily exercise to cope with life in general. Second, when a training session is missed various withdrawal symptoms occur and third the pleasurable feeling, euphoria, felt during or after a running-session could only be maintained by increasing the dosage indicating a mechanism of tolerance. These are again behaviours that meet the DSM-IV criteria for addiction, showing the similarities between substance dependence and ED.

Several measurements were developed to assess the negative dependence to running like the Negative Addiction Scale (NAS) and the Running Addiction Scale (RAS).[57] The NAS scale was based on motivational, emotional and behavioural characteristics seen in excessive exercisers. The RAS assessed characteristics such as withdrawal effects and the need to exercise. Also 'stress relief' was defined as how running can help cope with life stressors and 'adherence to training' which showed maintenance of training in spite of obstacles. However, these scales were not sufficient enough to bring the 'negative' and 'positive addiction' theories together, so a scale was designed to describe both phenomenon of exercise dependence. Exercise behaviour had to be seen more as a continuum, which ranges from healthy to pathologic and addictive.[58] This of course, shows a major difference between substance dependence and ED. The use of drugs is always unhealthy, but natural rewards are generally positive and can only become unhealthy after pathologic and addictive use. Three distinct profiles were assigned to group different runners: the first is 'healthy neurotic', including runners that exercise to achieve the benefits of physical exercise. The second group are 'compulsive' runners, which are runners that exercise to fulfil compulsive needs to have a sense of control in their lives. And the third group are the 'addicts' whose exercise sessions were dominating their lives. The difference was made between people who were committed to exercise and people who behaved as addicts. Committed exercisers organize exercise round their lives, while the addicts organizes their life round exercise, as the addicted exerciser claims physical activity is the most important thing in their lives, again one of the criteria of the DSM IV. This classification of runners raises the following question: What is healthy behaviour and when does running become addictive and compulsive? This seems to be a hard question as the shift between a casual user to an addict is still not precisely known in substance dependence. Such transition from controlled to compulsive drug seeking behaviour is also seen in non-drug rewarding behaviours. By definition, the transition from controlled to compulsive reward seeking behaviours is a hallmark characterizing addiction. However, people who are physically active show a continuum from healthy to addictive behaviour, making the point of transition even harder to find. Interestingly, a study on the duration of access to a rewarding stimulus is an important factor for the transition from a low to a high consumption pattern. In one study this was done with

cocaine administration for 1 or 6 hours per day in a self administration paradigm with rats. The rats receiving only access for 1 hour did not increase administration, however the rats that had longer access dramatically increased their dosage per day.[59] The same principle was seen in rats that received limited access to running wheels. The rats that received longer access to the running wheels shifted from low to high running wheel activity, while the rats with shorter daily running wheel access did not increase their running wheel activity.[60] This study indicates that the transition from moderate to high reward consumption is similar for cocaine administration as for wheel running, indicating that there is probably a common mechanism.

In summary, through the years researchers found the essential features of exercise dependence such as withdrawal symptoms and impaired functioning on social physical and psychological health. In addition, tolerance, adverse consequences and lack of control are also important features describing ED. Knowing these features gave important advance for the measurement of ED and the exercise dependence scale (EDS-R) was described using the DSM-IV criteria of substance abuse (figure 3.1).[61] In addition, another scale was made called the Exercise Addiction Inventory (EAI) developed for a quick inventory on exercise addiction.[54] This scale is based on six basic components: Salience, mood modification, tolerance, withdrawal symptoms, conflict and relapse. Salience means that exercising is the most important activity in the person's life and dominates normal thinking (craving). Mood modifications are the subjective reports on how people feel when they are exercising and this feeling may be used as a coping strategy. Conflict refers to the conflicts a person has with people around them or with their job regarding exercise training. A study on 200 participants using the EAI showed that 3% of all individuals who exercise were at high risk for developing ED.[54] These two last conceptualizations permitted good identification of individuals that are at risk for developing ED and therefore better research could be done.

Figure 3.1. The Exercise Dependence Scale (based on the DSM IV criteria).

Consistent with the DSM-IV criteria for substance dependence, exercise dependence was operationalzed and measured as a multidimensional maladaptive pattern of exercise, leading to clinically significant impairment or distress, as manifested by three or more of the following:

1. Tolerance: either a need for increased amounts of exercise to achieve the desired effect or a diminished effect occurs with continued use of the same amount of exercise.
2. Withdrawal: manifested by either the characteristic withdrawal symptoms for exercise (e.g., anxiety, fatigue) or the same (or closely related) amount of exercise is taken to relieve or avoid withdrawal symptoms.
3. Intention Effect: exercise is often taken in larger amounts or over a longer period than was intended.
4. Lack of Control: a persistent desire or unsuccessful effort to cut down or control exercise.
5. Time: a great deal of time is spent in activities necessary to obtain exercise (e.g., physical activity vacations).
6. Reductions in Other Activities: social, occupational, or recreational activities are given up or reduced because of exercise.
7. Continuance: exercise is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the exercise (e.g., continued running despite injury).

Inadequate conceptualization of exercise dependence was and is a major methodological problem within this research field. In addition, usually one form of exercise, namely running or jogging, has been addressed in the literature. Other forms should be investigated more. However, in spite of the ongoing debate, the knowledge on exercise dependence has greatly expanded during time. And the new definitions and measurements of behavioural addictions have started to emerge, which suggest that there are certain basic components common to all addictive behaviours and therefore all rewarding activities are potentially addictive.[9] This conceptualization is very important to place behavioural addictions in the field of dependence. Nevertheless, there is strong evidence for the existence of ED despite ongoing debate whether or not it warrants recognition as a clinical disorder in its own right. Because of this focus on the conceptualization of ED, not a lot attention has been given to the underlying mechanisms of ED, therefore they are largely unknown. Understanding the biological mechanisms may help to discover treatment for patients with ED. In the following paragraphs the most plausible mechanisms of ED are discussed in addition to the comparison with the known mechanisms of substance addiction.

Affect regulation hypothesis

Humans can become addicted to drugs, because of the hedonic feeling drugs can produce. This positive reinforcement is the first theory on how the initiation of addiction comes to be. As drugs give such as pleasurable feeling, one cannot stop using it. Physical activity in humans and animals is a rewarding behaviour. Marathon runners can for instance experience the so called 'runner's high', a very pleasurable state, felt during excessive running. This phenomenon is described as an euphoric state resulting from long distance running, however it does not occur after every training. This euphoric feeling resulting from regular exercise is an example of the rewarding properties of running which supports the 'positive reinforcement theory'. Another theory on drug addiction called the 'negative reinforcement theory' states that the removal of the drug makes you feel bad, and the need for this drug makes it addictive. This negative reinforcement can be a reason to keep engaging in an addictive behaviour. Abstinence from running causes withdrawal symptoms, anxiety and depression. Reduction of anxiety and depression seemed to be one of the primary running motives in a group of regular exercisers.[62] Another study showed that the main motives for exercise in a group of 30 ED patients was stress reduction.[63] These studies thus support the negative reinforcement theory regarding drugs of abuse. Both theories of positive and negative reinforcement are seen in drug addiction, but can also be applied to ED, because on one hand, exercise dependence could increase positive mood in individuals that are depressed but also in healthy individuals (seen with the runner's high). On the other hand, exercise could decrease negative feelings. In this last situation, exercise dependence would be a mean to cope with daily life stresses, also seen when physical activity is used as a treatment for depression. Tomkins presented these two theories in a model called 'the affect regulation theory' which postulates that running serves as a 'positive affect enhancer', for people who run to increase positive feelings and a 'negative affect reducer', for people who run to reduce their distress.[63] In the following paragraphs the biological mechanisms of the so called runner's high and the withdrawal symptoms are discussed supporting the affect regulation theory by explaining the negative and positive reinforcements of ED.

'The 'Runner's high': *Opioid theory*

Physical activity is a strong natural reward. Rats and mice, for example, choose to run spontaneously on running wheels, and will learn to lever-press for access to a running wheel. They will also develop conditioned place preference to environments previously paired with a running wheel.[64] Likewise, in humans it is clear that physical exercise has positive effects on mood, however the biological mechanisms of the hedonic feelings called 'the runner's high' is not precisely known. Subjectively it has been described as pure happiness, elation, a feeling of unity with one's self or nature, endless peacefulness, inner harmony, boundless energy and a reduction in pain sensation. These personal descriptions are similar to the claims of distorted perception, atypical thought patterns diminished awareness of one's surroundings an intensified introspective understanding of one's sense of identity and emotional status made by people who describe drug or trance states.[65] However, not all distant runners come to experience the runner's high and not during every training session this feeling occurs. This has led to the question when and how this emotional state arises. The neurochemical mechanisms of mood changes caused by exercise have barely been investigated so far but different hypothesis are present in the literature. The leading hypothesis is called the 'endogenous opioid theory' which suggests that region specific effects of opioids known as endorphins in fronto-limbic brain areas are involved in the processing of affective states and mood. Dopamine and opioid networks are part of the neurocircuitry reward system in the brain and are thought to be responsible for addictive behaviours in humans.[66] Previously this 'endogenous opioid theory' hypothesis was reinforced by increased levels of endorphins measured in blood plasma and cerebrospinal fluid after running to calm the sympathetic nervous system and to relieve the body form pain coming from the exercise itself.[67] Administration of an opioid receptor antagonist like naloxone will blunt the feeling of the runner's high.[68] Actual conformation of this theory was recently published when researchers used a positron emission tomography (PET) ligand activation study with the non-selective opioidergic ligand 6-0-(2-[^{18}F]fluoroethyl)-6-0-desmethyldiprenorphine to determine relative changes in ligand binding after running and correlated this with euphoria rating. They found a decreased availability of opioid receptors mostly in the prefrontal and limbic/paralimbic brain areas. Opioid binding was inversely correlated with the euphoric feelings of the runners.[69] These findings were a support for the 'opioid theory' of the runner's high and suggested region-specific effects in frontolimbic brain areas that are involved in the processing of affective states and mood, but are also important for a person to weigh the pros and cons of engaging in particular behaviours. Impairment of this brain region is predicted to result in drug craving and impaired decision making (also known as the impulsivity theory). The feelings of euphoria felt during running can lead to unhealthy exercise and decision making in humans and animals seen in for instance athletes continuing their training program in spite of their injuries.[57] However, these researches could not determine which opioid receptor was involved, and no increased activity was seen in the nucleus accumbens, a very important region for reward related feelings. Later in time, other researchers did show increased activity in the nucleus accumbens and the mechanisms behind this increase of dopamine and norepinephrine. Exercise increases serum calcium levels, which can be transported to the brain to activate the rate limiting enzyme for catecholamine, which is important for the synthesis of dopamine and norepinephrine.[5]

Interestingly, a recent study showed that opioid tolerance and physical dependence can occur after chronic exercise. This suggests that regular exercise can reduce the sensitivity to opioids, consequently requiring higher doses of exercise to achieve the same effects.[70] This

explains the tolerance effect seen in ED one of the DSM IV criteria for substance dependence.

However, not all researchers believe the opioid theory, because opioid release alone is to general to explain the euphoric state and this hypothesis is too simplistic. Researchers still even debate on whether the euphoric feeling actually exists.[65] In another study, it was found that physical exercise increased the plasma levels of anandamide and hence activated the endocannabinoid system in humans.[71] Therefore these researchers have investigated the involvement of the endocannabinoid system (maybe in addition to the brains opioid systems) as another option explaining the runner's high. This seems plausible as the activation of the endocannabinoid system reduces pains sensations and alters emotional and cognitive processes.[65] It was found that when the major central cannabinoid receptor CB1 is knocked-out, animals exhibited 30-40% less running activity than control animals, showing the direct or indirect involvement of the endocannabinoid system. It is known that CB1 blockade and CB1 receptor deletion reduces reward driven behaviours. Thus the endocannabinoid system has been linked to the central reward system in the brain showing it is probably involved in the feelings of euphoria felt during chronic exercise.[72] The precise mechanism of the endocannabinoid system or other brain systems on exercise has not yet been explained. As discrepancies in the literature exist, it is probable that different rewarding mechanisms in the brain work elegantly together producing the euphoric feeling during distance running. This seems likely as for instance there is a close interaction between dopamine and the endocannabinoid system in structures that are implicated in the brain's reward system. For instance, the dopamine D1 and D2 receptors are colocalised with the CB1 receptor. It has been shown that the cannabinoids alter dopaminergic activity in the medial forebrain bundle and increase the firing rates of dopaminergic neurons in the ventral tegmentum, substantia nigra and the medial forebrain bundle. In addition, endocannabinoids induce a selective release of dopamine in the shell of the nucleus accumbens through CB1 receptors, which also suggests that the activation of endogenous cannabinoids could be a reason for ED.[65] Interestingly, endocannabinoids also seem to increase the release of endogenous opioids in brain regions involved in processing pain signals.[73] The receptors of cannabinoids and opioids are co-localized in brain areas involved in pain processing.[73] Endogenous opioid-dependant antinociception produced by long term voluntary running is known to persist for hours after the end of the active period. Physical activity therefore increases the nociceptive thresholds in both humans and animals.[74] This indicates the involvement of opioids through the endocannabinoid system which increases reward and decreases pain sensitivity. So different rewarding mechanisms in the brain work together producing the so called runner's high. Even though there is still a debate on how euphoric feelings come to be regarding physical activity, it is clear that an euphoric state is felt when running distances and long term consequences in emotional behaviours are seen which could explain the addictive properties of physical exercise. Probably the endocannabinoid system, the dopamine system and the opioid system are all involved and somehow work elegantly together during physical activity.

Withdrawal symptoms

As discussed in the previous chapter, depressive symptoms are more prevalent in sedentary people than in physically active individuals.[6] In addition, physical activity can be used as a treatment for depression. However, when physically active people, in particular people suffering from ED, stop their training sessions they can show symptoms of depression. Human studies have found that when committed runners have to stop with their training scheme they can display several withdrawal symptoms demonstrated by increased anxiety, restlessness, sexual tension, fatigue and impaired sleep. These symptoms are similar to hallmarks of withdrawal in substance abusers, mood disturbances such as depression and anxiety.[75] There is even a direct correlation between the amount of exercise and the intensity of the withdrawal symptoms. Kanarek et al, investigated in an animal study the relationship

between the intensity of running and the severity of withdrawal symptoms. Physical dependence was measured by injecting the rats with 1.0 mg/kg of the opioid antagonist naloxone, and observing them for symptoms of precipitated withdrawal. There seemed to be a direct positive correlation when animals were put on a restricted feeding schedule and received access to running wheels.[52] In humans withdrawal is described as the sensations experienced when stopping an addictive behaviour and can take the forms of physiological or psychological disturbances. As depressive symptoms are relieved with regular exercise, these symptoms reoccur when training is stopped, making it less likely to give up an active lifestyle. As mentioned before, this is in line with the 'negative reinforcement theory' which states that the removal of a drug of abuse makes you feel bad, and the need for the drug makes it addictive. The withdrawal symptoms seen in physically active people can form a reinforcer for addiction.

As stated before, many studies indicate that withdrawal symptoms occur when runners are deprived of their daily training, although to date, little is known about the biological processes that underlie these symptoms. One theory postulates that 'sickness behaviour', meaning psychological stress that is seen with increased cytokine IL-6, for instance following an infection with influenza, has comparable symptoms that are associated with exercise withdrawal in ED. Cytokines like IL-1 and IL-6 are immunotransmitters that act as messengers between the immune system and the brain and are important modulators of mood. These cytokines modulate complex human central nervous system functions including serotonergic, noradrenergic neurotransmitter systems and the stress-related HPA-axis, which all promote changes in brain neuronal activity and can influence behaviour. As seen in chapter two, physical exercise has an influence on the HPA axis to help the body better cope with moderate stressors and therefore decreases the risk of depression.[33] In addition, exercise is known to have a profound influence on cytokines. Typically IL-6 is the first cytokine present in the circulation as increased levels were seen after exercise without muscle damage. IL-6 is both pro and an anti-inflammatory cytokine, although in the case of exercise, data suggest it is anti-inflammatory.[76] IL-6 decreases the effects of other inflammatory markers, which explains why physically active people have lower baseline levels of inflammatory markers.[76, 77] As IL-6 has effects on complex brain function, overproduction or intolerance of IL-6 during exercise, is hypothesized to be implicated in the cause of ED.[78, 79] Exercise might have a transient decrease in negative effect, but the exercise itself is the underlying cause of ongoing behavioural disturbances in ED, as it concurrently results in excessive production of IL-6. When IL-6 levels are over produced, for instance seen when there is an inability to cope with an excessive exercise load (the initial trigger of ED). This will activate neuroendocrine pathways, which are associated with behavioural and psychological disturbances of exercise withdrawal and the induction of sickness behaviour. This sickness behaviour induces the urge to exercise again to be relieved from negative feelings. As a new training increases the overproduction of IL-6, sickness behaviour occurs again. Showing that negative feelings after removal of a drug or in this case exercise, is part of the addictive mechanism (figure 3.2). Interestingly, the increase of cytokines such as IL-6 and IL-1 are also associated with the pathophysiology of depression described in chapter two.[80] The symptoms occurring after exercise withdrawal are similar to the depressive symptoms seen in MDD. The increase in cytokines might generate these depressive symptoms in both depression and exercise withdrawal and can be relieved by exercise in both MDD and ED.

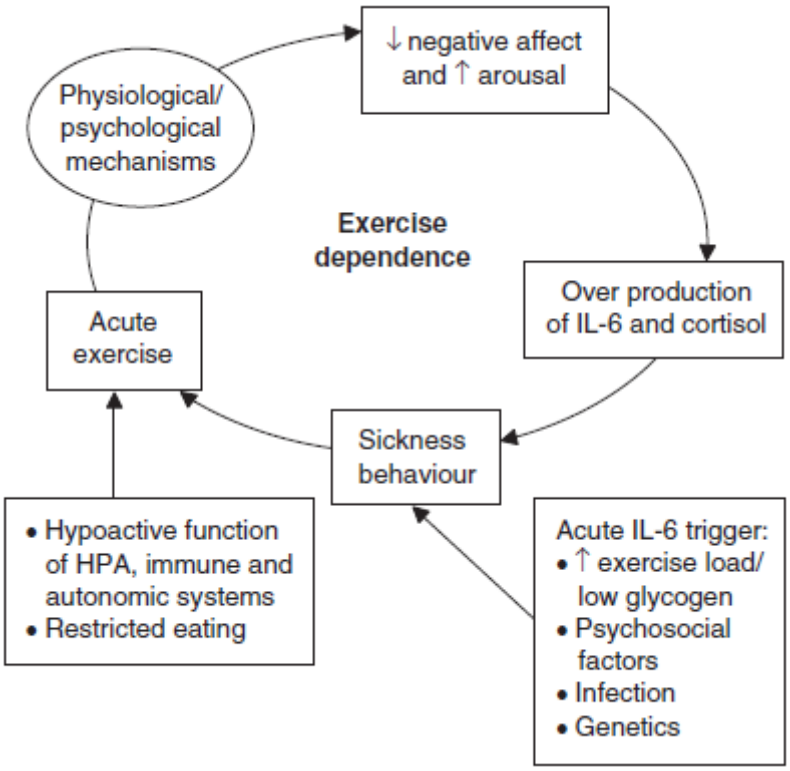

Figure 3.2. This graph shows a conceptual model for the psychobiological mechanisms of exercise dependence. Also the reduced activity of the HPA axis represented in the previous chapter to be antidepressant. In both MDD and ED sickness behaviour seems to increase depressive symptoms and exercise relieves these negative feelings. (Copied form Hamer et al. 2007)[63]

In addition, IL-6 can induce the production of cortisol as seen the previous chapter.[77] Cortisol levels seem to play a role in decreasing depressive symptoms but it also plays a role in substance addictions, seen for instance in the associations cortisol and alcohol craving during withdrawal and may also be implicated in the addiction for excessive exercise.[8] So activating the brain stress systems through cortisol seems to contribute to the negative reinforcement associated with withdrawal states and relapse. Interestingly, the combination of exercise and restricted eating may also reinforce the over production of exercise-induced IL-6. This shows direct biological evidence for overlap between eating disorders and ED (figure 3.2). More about the connection between excessive exercise and eating disorders will be discussed below. Understanding the impact of IL-6 and sickness behaviour may eventually lead to the development of successful treatment strategies of ED and/or MDD. In addition, IL-6 may become a reliable biological marker for blood research of people suffering from ED. However, sickness behaviour is one theory regarding withdrawal symptoms and more research is needed on whether this theory is conclusive.

Brain reward pathways

Physical activity in humans and running in running wheels with rats is known to have a rewarding effect seen in the so called 'runner's high' in humans and conditioned place preference in chambers paired with the running experience in rats. This rewarding effect is due to the activation of the mesolimbic reward pathway including the dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens. This pathway has been implicated in both the pathophysiology and treatment of depression, anxiety and substance abuse disorders.[64] As physical exercise has a protective affect on depression and

on other mood disorders it might work through common neurobiological mechanisms: Physical exercise causes neurochemical and morphological adaptations in brain reward pathways, amygdala, cerebral cortex and hippocampus that also are shared by addictive drugs. This is for instance seen in the altered gene transcription for several factors involved in reward and dopaminergic neurotransmission in the mesolimbic reward pathway. In the VTA the levels of mRNA for Tyrosine Hydroxylase (TH) were increased by physical activity after six weeks in comparison to inactive rats. This increase of TH mRNA is also seen during drug abuse.[81] TH is the enzyme which is responsible for catalyzing the conversion of DOPA the precursor for dopamine. Dopamine is in turn a precursor for norepinephrine (NE) and epinephrine. It was therefore shown that chronically exercised animals have increased levels of norepinephrine and serotonin (5-HT) in several brain areas, as compared to controls.[82] In addition, wheel running decreases the dopamine receptors D2 mRNA in the rodent accumbens which is similar to the effects observed in repeated morphine and cocaine consumption.[64] In the caudate putamen, similarities in the increase of dynorphin mRNA levels was found after long distance running in running wheels and after cocaine administration in addictive-prone Lewis rats. The expression of dynorphin mRNA levels is regulated by dopamine.[83] This stimulation of endogenous opioid peptides seems to exert analgesic effects and may also produce the addictive behaviours seen in ED showing a common mechanism of induction. However, inconsistencies still exist on this topic in the literature.[84] Therefore, the comparison between natural rewards such as physical activity and drugs of abuse is still difficult. However, throughout the years, substantial evidence has been shown to support the idea that drugs of abuse have mostly the same effect on rewarding brain areas as natural rewards such as physical activity has and that dopamine plays a substantial role in both drugs of abuse as in physical activity. As dopamine release increase motivation, it could therefore be a powerful promoter of engaging in physical activity. Anyhow, these changes in neuroplasticity could alter opioidergic or dopaminergic neurotransmission in the mesolimbic reward pathway and could account for the altered sensitivity to drugs of abuse (cross sensitisation) often observed following repeated voluntary wheel running. This finding might suggest that it is possible to substitute drug taking behaviour with a naturally rewarding behaviour such as physical activity.[52]

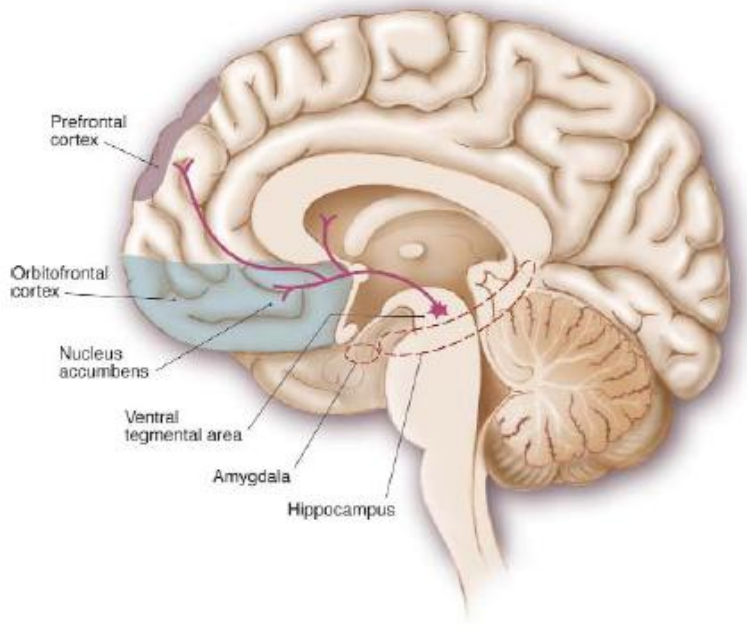

Figure 3.3. The reward circuit consists of the ventral tegmental area, nucleus accumbens, and parts of the frontal lobe linked by dopamine that even non-drug compulsions may alter in the long run. Both drugs of abuse and natural rewards increase dopamine in the nucleus accumbens which might generate cross-sensitization. (Copied from Holden et al., 2001.)[85]

Increase of ΔFosB in brain reward pathways

The long term affects of drugs of abuse are clearly visible in drug addicts as they have a hard time regaining a normal life style and have high relapse rates. In patients with ED similar behaviour is seen. Neurochemically, several effects of long term drug abuse have been reported and the key molecule seems to be ΔFosB. This molecule is part of the Fos family and is a component of the long lasting AP1 transcription factor.[86] These AP1 complexes are proposed to mediate some of the long lasting effects of drugs of abuse that underlie addiction.[86] Unlike other Fos-like proteins, which have very short half-lives, ΔFosB accumulates in a region specific manner in the brain after its transcription, because it is a very stable molecule. ΔFosB levels are increased in the reward pathways of the brain, particularly in the nucleus accumbens and in the dorsal striatum, due to drug use and after withdrawal, the levels are relatively persistent until they return to baseline. ΔFosB is proposed to be the 'molecular switch' that initiates and maintains addiction.[87] Physical exercise can also induce increased levels of ΔFosB in the brain reward pathways identical to drugs of abuse, however it is not known whether these levels persist after withdrawal. Even though the levels of ΔFosB return to baseline after drug withdrawal, the effects of drugs can be persistent, indicating other sustained molecular changes.[88] As ΔFosB acts manly as a transcription factor (AP-1) its effect on neuronal function is mediated through the regulation of other genes that persist long after drug exposure or physical exercise ceases. Perhaps ΔFosB sensitizes a neural circuit related to compulsive behaviour, and sustained molecular changes in the brain explain the reason why drug abusers and ED patients have high relapse rates. These induced behavioural changes may promote increased and compulsive reward seeking behaviour. The finding that drug reward and a natural reward induce same molecular adaptation within the same neuronal cell type suggests that the two may act via some common mechanism, which could be the increase of for instance monoamines (dopamine), endogenous opioids or the endocannabinoid system.

Genetics

It is clearly shown that ΔFosB is implicated in addictive behaviours as animals with an genetically modified overexpression in of ΔFosB in the striatum and accumbens showed increased sensitivity and preference for cocaine as well as increased preference to run.[88, 89] As these inbred mice show similar responses to seeking reward from an addictive drug and wheel running, indicates that possibly the same genes are involved in the addictive properties of natural rewards, probably induced by the AP-1 complex. These examples of genetically modified mice given above have similar responses to reward seeking from either addictive drugs or by engaging into physical activity. It could therefore be possible that similar genes that give predisposition to drug addiction also give a predisposition for exercise addiction such as an overexpression of the FosB-gene. Finding candidate genes that may influence addictive behaviours is a challenge. There are for instance animal models that are drug prone called the Lewis strain whereas the Fischer strain is not, although both were derived from the Sprague-Dawley strain.[90] Genetic differences between these models can help to develop candidate genes for addiction. Interestingly, the Lewis rats who are addiction prone, develop high rates of running wheel activity when given access to a running wheel, which is not seen in the Fischer strain.[91] Visa versa, the mice of the 129 mouse strain, do not have a preference for alcohol or other addictive drugs nor do they develop high wheel running activity.[75] This is an indication for the fact that animals that have a genetic predisposition for developing an addiction also have a predisposition for developing high running wheel activity. However, there is no absolute correlation as there also exist mouse

strains, such as Balb/c and C3H that do develop high running wheel activity but do not have a predisposition for alcohol addiction.[75] There is still research needed on the impact of genetic background in inbred rodent strains on addiction to running and to addictive drugs. In addition, creating more genetic rodent models for addiction or ED could help to better understand the underlying mechanisms.

Cross-sensitization

Another interesting phenomenon seen with addictive drugs is called 'cross-sensitization'. This means that an addictive drug induces the use of another drug. A common feature of addictive drugs is that they increase the level of dopamine in common neuronal pathways and in particular the nucleus accumbens and this may initiate cross-sensitization (figure 3.3).[75] This supports the hypothesis of common neural pathways for the behavioural response to most addictive drugs. Not much research has been done on whether there is behavioural cross-sensitization between a natural reward and an addictive drug. It is however very likely to occur as natural rewards also significantly increase the amount of dopamine in the nucleus accumbens. In addition, cross sensitization might occur via the increase of ΔFosB particularly in the nucleus accumbens and in the dorsal striatum. This finding that drug reward and a natural reward induce same molecular adaptation within the same neuronal cell type suggests that the two may act via some common mechanism, but also indicates that cross sensitization might occur via increased ΔFosB and the genes it activates. This is also shown with animals with an genetically modified overexpression in of ΔFosB in the striatum and accumbens that showed increased sensitivity and preference for both cocaine as well as running wheels.[88, 89]

Recent research found this cross-sensitization between running wheel activity as a natural reward and alcohol consumption. Researchers gave addiction-prone Lewis rats the choice between water and ethanol. After these rats reached high and stable ethanol intake, they were subjected to ethanol withdrawal for 2 weeks. During these weeks one group was given access to running wheels and the other group was not. Finally, the animals were given access to the bottle of ethanol again together with running wheel access and the other group only got access to the ethanol bottle. Animals that were given access to running wheels increased their ethanol intake significantly in comparison to the control rats. In conclusion, this study showed that running increases ethanol preference in rats.[10] It is comparable to the increased intake of ethanol when rats received in addition small amounts of morphine.[92] Interestingly, it has also been shown that food restriction increases the preference for addictive drugs.[93] This is also seen in the Activity based anorexia model (ABA) which shows dramatic increase in running wheel activity when food is restricted to one hour per day.[52] This phenomenon will be further discussed in the next paragraph.

The increase in ethanol due to free access to running wheels is an example of a behavioural interaction between non-drug induced and drug induced reward seeking behaviour. As cross-sensitization is suggestive of a common neuronal neurobiological background, these studies show how similar drugs of abuse and natural rewards as physical activity are.

The link between exercise dependence and eating disorders

Throughout the years it has become increasingly clear that in addition to physical exercise people can benefit from dietary interventions. For instance a study showed that the 'hunger hormone' ghrelin coming from the gut, which normally induces increased food intake, can also produce antidepressant-like responses.[94] In addition, increased neurogenesis in the hippocampus was found in mice on dietary restriction. This also included increased BDNF

expression.[95] However, little is known about the similarities of the mechanisms which underlie these factors or how they may interact and influence brain function. Both behaviours can be taken to an extreme seen in for instance in the eating disorder called anorexia nervosa (AN) and in exercise dependence. Anorexia nervosa can occur together with excessive exercise when not only excessive food deprivation but also extreme physical exercise becomes a serious problem. These compulsive behaviours have a reinforcing property on each. The similarities between eating disorders and exercise dependence were first described by Yates, Leehey and Shisslak in 1983.[96] They showed that compulsive runners have striking similarities to anorexic patients regarding family background, socioeconomic status and personality characteristics such as expression of anger, perfectionism and high self-expectation, tendency for social isolation, tolerance of pain and physical discomfort, and a tendency towards depression. Yates et al. even proposed that compulsive running is a male analogue of anorexia nervosa, but a better definition would be that AN and ED are 'sister activities', as these diseases have very similar etiological and psychological characteristics.[9] Because these diseases are so similar, diagnosis becomes difficult in particular when ED patients also lose unhealthy amounts of weight due to excessive training. ED is mostly diagnosed if AN is excluded. The biggest difference is that with ED patients the exercise is an end in itself and the dieting and weight loss is used to improve performance, while with AN patients the exercise is used as a means towards losing weight or balancing calories and is associated with a morbid fear of fatness.[97]

The activity based anorexia model (ABA) has been proposed as an animal model for anorexia nervosa. It is a phenomenon where rats are put on a restricted feeding schedule (RFS) and only receive food for one hour per day. In addition, they have access to running wheels present in their cages and over time they dramatically increase in wheel running activity. These animals can even be trained to lever press for access to the running wheels indicating high motivation.[98] Interestingly, when rats are set on a restricted feeding schedule alone, they quickly adapt to this diet, eventually increasing their body weight. However, putting them on a diet and adding a running wheel, they decrease food intake and body weight dramatically until they die of starvation. These rats compulsively engage in physical activity where a reduced drive to acquire other biologically relevant natural rewards important for survival such as food are neglected. In addition, when access to the running wheels is denied, the animals tend to exhibit withdrawal symptoms. For this reason the ABA-model can perhaps also be used as an animal model for exercise dependence in addition to a model for AN.[52] Interestingly, Anorexia nervosa has a high comorbidity with drug addiction. This provides further evidence of a common neurobiological basis for AN, ED and substance addiction and the use of the ABA model for all three mental disorders.[52]
However, it is important to keep in mind that this excessive exercise is only present when animals receive food for only one hour per day. The link between starvation and excessive activity was explained in another study on animal research suggesting an association between the HPA axis activity and food restriction that induces increased physical activity, mediated through body fat levels. This creates a cycle by reinforcing self-starvation via reward mechanisms, which has relevance in relation to anorexia nervosa and increased physical activity.[63] The ABA model clearly shows the complex interplay between stress, exercise and diet, and how deregulation of the factors that control physiological homeostasis can lead to metabolic imbalances and deregulation of mood resulting in depression or withdrawal symptoms, in addition to extreme physical activity. In line with the deregulation of mood due to a changed metabolic status, it is shown that peptides such as orexin and ghrelin

might have an antidepressant role, particularly during conditions of low caloric intake. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress for instance seen in the ABA model.[94]

To summarize, in humans and animals physical activity is a natural reward and can become a compulsive and addictive-like behaviour when taken to extremes. However, still discrepancies exist in the literature whether this behaviour is an addiction. This ongoing discussion is due to different factors. One problem has been the conceptualization of exercise dependence. Because of different definitions and methods used to determine ED, studies differ in outcome reinforcing the different opinions within the literature. However, each of these attempts of conceptualization on exercise dependence brings the behaviour more and more into the field of dependence.

Traditionally the term 'addiction' was confined to the use of substances. Nowadays that concept is changing. More evidence points towards the concept that any rewarding behaviour can initiate compulsion and eventually become addictive. The general idea is that the brain does not distinguish between the sensation of reward induced by a chemical or an experience. Addiction used to be defined as dependence on a drug shown by craving, tolerance and withdrawal. However, not all drugs of abuse show these symptoms and some natural rewards do. Cocaine for example, is very addictive but causes little withdrawal. Patients getting morphine as a painkiller during hospitalization can stop taking the drugs without being addicted. Physical activity, showed in this chapter, does fit the DSM IV criteria of substance abuse as it for instance causes withdrawal symptoms, tolerance and craving. This indicates that physical activity certainly can become a maladaptive and addictive behaviour in some people thereby widening the boundaries of the concept of addiction.[85]

During time, several hypotheses have been proposed in the literature explaining the addictive properties of physical activity. The hypothesis of Tomkins was discussed and he presented two theories in a model called 'the affect regulation theory' which postulates that running serves as a 'positive affect enhancer', for people who run to increase positive feelings and who try to experience the so called runner's high and a 'negative affect reducer', for people who run to reduce their distress and to reduce withdrawal symptoms.[63]

Several neuroadaptations were found to be particularly similar between drugs administration and physical activity in the reward circuit of the brain shown by ΔFosB and increased gene transcription of dopamine. The finding that drug reward and a natural reward induce same long term molecular adaptation within the same neuronal cell type suggests that the two may act via some common mechanism, which could be the increase of dopamine in the nucleus accumbens. The runner's high felt after long distance running resembles a high felt after drug taking and showing the positive reinforcement physical activity can have. In addition, the withdrawal symptoms felt when training schedules are stopped resembles withdrawal due to drugs of abuse. This negative effect reinforces the behaviour stated in the negative affect hypothesis. Different hypothesis exist regarding the biological mechanisms of exercise dependence, but none are complete. However, most of these hypotheses show the mechanisms and insight on how this behaviour can become a serious addiction and how addiction works in general. It is still to be very important that exercise addiction will be further investigated not only to understand it biological mechanisms, but also to search for new

treatment strategies. It will also help to understand biological mechanisms of addiction to drugs better.
Finally, exercise dependence seems to have similar mechanism as anorexia nervosa. Both diseases show compulsive behaviour and can exist together. Understanding the biological mechanism of ED might help to partially understand AN as well.
So to conclude, new biological insight and new definitions and measurements of behavioural addictions have started to emerge, which suggest that there are certain basic components common to all addictive behaviours and therefore theoretically all rewarding activities are potentially addictive.

4. Discussion

Both the antidepressant and the addictive properties of physical activity have extensively been reviewed, because generally literature focuses on one of the two aspects. In summary, physical activity should generally be used as a treatment for depression. However, it can turn into an obsessive behaviour. This obsessive behaviour is called exercise dependence and should be seen as behavioural addiction. It is very important to realize that there are two sides of physical activity. A better understanding of the neurochemical and morphological effects in the brain caused by physical activity could constitute a basis for developing novel treatments for both depression and drug addiction. This interesting concept shows the typical connection of physical activity between these two devastating diseases.

Depression

Depression is a big problem in our society. For instance, in the U.S. approximately 16% of the population will suffer from MDD. Therefore, society loses a fair amount of money dealing with this disease. In the United States the economic burden of depression, including direct treatment costs, mortality costs of suicide and indirect costs in the workplace, is estimated at $83.1 billion per year.[99] To deal with depression, different antidepressant drugs are available today, but none of them will have effects on all patients as it is a heterogeneous disease. Because depression has a great impact on society it is important to find novel treatments. Researchers should look beyond the conventional treatments specified on only monoamines, cortisol, BDNF and the hippocampus, but to other treatments such as physical activity which not only has influence on all these areas of depression mechanisms, but has many other areas which it has an effect upon. In addition, physical exercise has a positive effect on all MDD patients in contrast to most antidepressant therapies. Also using physical exercise in combination with antidepressant drugs gives a quicker antidepressant result than one of these treatments alone.

Future research regarding physical activity and depression

Even though it has been proven that physical activity is a proper treatment for depression, still a lot of research needs to be done. As depression appears to be associated with several subtle cellular and molecular alterations in a complex neural network, it is a heterogeneous disease and the mechanisms causing it are still under investigation. Similar, the antidepressant working of physical activity is also largely unknown and deserves attention. When physical activity will be incorporated as a more general treatment, it may help to understand some features of depression. Due to the poor quality of many studies, also the effectiveness of exercise in reducing symptoms of depression could not precisely be determined. Better research is now done as recent investigations are currently trying to eliminate any form of potential bias by selecting a reasonable placebo control regarding physical activity, which have previously consisted of non-exercisers, non-ED exercisers or individuals with or without eating disorders, concealing the method of randomization and adequate blinding of outcome assessments. Large clinical trials need to be done to confirm the treatment capacities of physical exercise. Also treatment adherence is under the investigation regarding physical activity to make treatment and prevention more efficient. For instance, this is done by involving a social coach, providing a home-based exercise program,

individualizing each patient's exercise program and implementing a behavioural intervention to reduce barriers to exercise.

In conclusion, physical exercise deserves to be considered and applied as a viable stand-alone or adjunct treatment for depression. Its importance is generally underestimated. Not only can it help to treat depression, it can also help to prevent relapse and it is beneficial for almost every other system in the body. For instance, in western society diseases like obesity are becoming increasingly prevalent. Not only is obesity life threatening in itself, it has a high comorbidity with depression. To solve these problems, physical exercise should be promoted by health care providers as for instance more than 60% of all the adults in America do not engage in the recommended amount of activity. If they would, almost every field of the medical world benefits, because physical exercise will not only help to overcome MDD, regular exercise facilitates weight control, will improve the cardiovascular system, will create greater bone mineral density and it will decrease the risk for cancer, stroke and diabetes. This will lower medical costs and lower unemployment due to medical reasons. Children should be obligated to at least practise sports for two times a week and continue this throughout their adulthood. The community should encourage health care providers to talk routinely to patients about incorporating physical activity into their lives. If more money would be invested to get people to exercise, these costs will be balanced through lower medical expenses.

Exercise dependence

However, approximately 3% of all physically active people will develop exercise dependence.[9] Discrepancies in the literature regarding this estimate exist, because of the different identification measurements. Anyhow, still a fair amount of people are at risk. When sports are going to be promoted more, the amount of people suffering from ED will also increase. Therefore this subject should be taken very seriously as it will become increasingly problematic. General recognition of ED as a behavioural addiction is of great importance and therefore it should be taken up into the DSM IV for psychiatric diseases. One of the most challenging aspects of this research field is to accurately identify ED using universally agreed measures and diagnostic criteria. Not only will this help to recognize people with ED, it will also help to easier compare different studies.

In this thesis the question was addressed whether natural rewards such as physical activity can become addictive. Theoretically all rewarding behaviours could potentially be addictive when taken to extremes, especially in a world were natural rewards are easy to gain. Therefore unnatural amounts of rewarding activities can easily be obtained. This is seen in for instance Western society were food is available everywhere and sports are very popular. In actual practice, especially physical activity has been shown to become addictive. This is because it has influence on various brain areas but also on the general physiology of an individual. All these changes together give potentially powerful addictive properties.

The deceiving aspect of natural rewards becoming addictive is that natural rewards are seen as positive and not harmful. Drugs of abuse corrupt the normal circuitry of rewarding and adaptive behaviours causing long term drug-induced neuroplastic changes.[8] Physical activity taken to extremes can create the same long lasting changes in the brain, therefore it should be seen as potentially harmful.

The paradox of physical activity

Figure 4.1 shows in a diagram the two sides of physical activity. It illustrates how depression and addiction are connected through physical exercise. The paradox of exercise is that this behaviour was traditionally been seen as having only benefits for all people. However, when exercise is taken to extremes, addiction can occur. If an athlete is forced to stop training, due to for instance an injury, depression is likely to occur. Visa versa, when a person is depressed, physical activity can serve as a treatment, mostly together with anti-depressant drugs. Staying physically active is very important for a healthy lifestyle, but exercise schedules should not be neglected or used extensively. Ironically people at risk for addiction have a tendency towards depression as well, indicating some malfunctioning of the brain reward systems of these individuals.[96] This nicely illustrates the connection between the two diseases through physical activity. Not just all natural rewards are interconnected in this through depression and addiction, showing that physical activity has a substantial influence not only on brain functioning but also on other biological processes, making it a powerful behaviour. This is for instance supported by the fact that physical activity alone can overcome the anhedonia in MDD patients.

Typically, in anorexia nervosa, both depression and excessive exercise come together in addition to extreme deprivation of food. Because mood disorders and substance abuse share high comorbidity and perhaps overlapping neural substrates, it is possible that common neurobiological mechanisms underlie the protective effect of physical activity against these various stress related psychiatric disorders.[64] This indicates some common malfunctioning of the brain reward systems of these individuals.

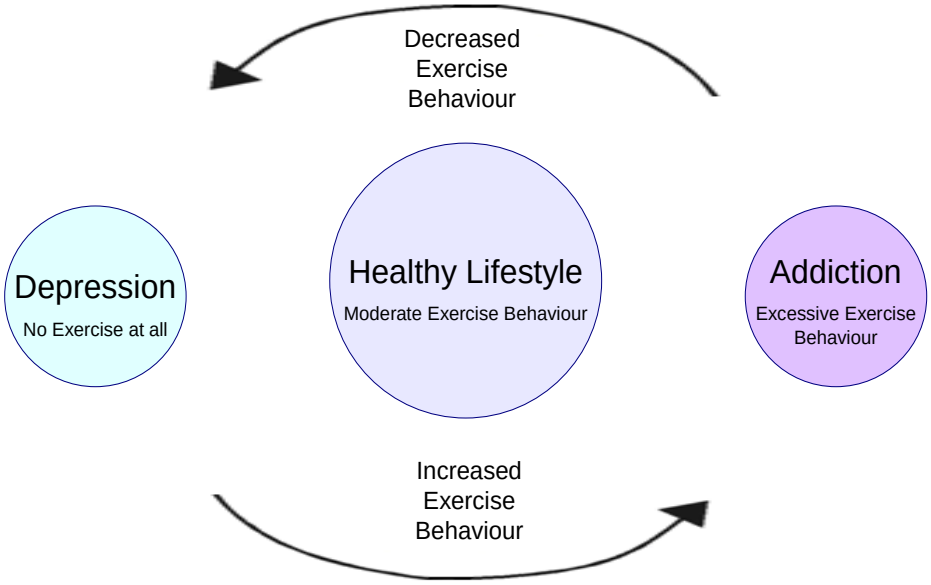

Figure 4.1. Shows how depression and addiction are connected through physical exercise. Exercise can be used as a treatment for depression however, when exercise is taken to extremes, addiction can occur. This indicates some common malfunctioning of the brain reward systems of these individuals. Not just all natural rewards are interconnected by depression and addiction, showing that physical activity has a substantial influence not only on brain functioning but also on other biological processes, making it a powerful behaviour. Understanding the changes made in the brain by physical activity may help to understand how depression and addiction come to be. In addition, this graph shows the importance of balancing the intake of natural rewards.

This connection between depression, addiction and physical exercise is also seen in the structural rearrangements such as dendritic branching, and fluctuations in the size of the nerve cells in the hippocampus, accumbens, prefrontal cortex and the ventral tegmental area, both after administration of addictive drugs and antidepressant treatments, including running. Understanding of the neurobiological basis of addiction and antidepressant drugs is of importance to finding new treatments. In addition, understanding the neurochemical and morphological effects in the brain of physical activity could constitute a basis for developing novel treatment for depression as well as drug addiction.

Future research regarding physical activity and addiction

Many questions regarding drug addiction and exercise dependence remain. The neurobiological and behavioural interactions between natural reward and drug-induced reward still need to be revealed. A big problem regarding this research is the different conceptualizations of exercise dependence and the use of different mouse models. This way, inconsistencies between studies exist, which makes comparison and creating proper overviews difficult. Better understanding of the behavioural pharmacology in voluntary running could potentially provide insight into how to treat drug abuse and to treat exercise dependence. In addition, the precise interaction between the different brain reward systems connected by for instance dopamine, opioids and endocannabinoids should be investigated to unravel for instance the runner's high. Also, the effects on the level of transcription factors, growth and trophic factors are to be further investigated. Which proteins have a role in mediating the structural rearrangement processes in the brain? Additional research will be necessary in order to reveal whether the observed changes in gene transcription following repeated voluntary exercise include changes common to many rewarding stimuli or represent unique effects specific to exercise.

Very interesting is the comparison between ED and other diseases such as anorexia nervosa, but also between for instance cachexia, a disease with an anorexic phenotype seen in end stage cancer. In this disease, an increase in the concentration of IL-6 is seen. This is comparable to the IL-6 change seen in ED which creates sickness behaviour and is probably responsible for one of the addictive properties of physical exercise. The ABA model in rats could bridge the gap between these different diseases and maybe create new treatment strategies. Additional research is needed to examine the inflammatory consequences of prolonged physical activity and to determine the role of inflammation in negative mood and fatigue, also found in other diseases.

ΔFosB, and the various molecular pathways it regulates, could be a suitable target for interesting new research and the development of pharmacological treatments for a range of disorders. What are the other neuronal changes that outlast the ΔFosB signal so that addiction becomes life-long? Maybe ΔFosB can be used as a biomarker to assess the state of activation of an individual's reward circuitry as well as the degree to which an individual is addicted both during the development of an addiction and its gradual waning during extended withdrawal or treatment. Linking molecules to mood and physical activity should continue to be investigated in the future and the research field of depression and addiction should increasingly work together.

5. Abbreviations

ABA model	Anorexia based activity model
ACTH	Adrenocorticotrophic hormone
BDNF	Brain derived neurotrophic factor
CBF	Cerebral blood flow
CHR	Corticotrophin-releasing hormone
DA	Dopamine
DSM-VI	Diagnostic and Statistical Manual of Mental Disorders
EAI	Exercise Addiction Inventory
ED	Exercise Dependence
EDS-R	Exercise Dependence Scale
FRL	Flinders resistant line
FSL	Flinders sensitive line
HPA-axis	Hypothalamic-Pituitary-Adrenal Axis
IL-6	Interleukin-6
LH	Lateral hypothalamus
MDD	Major depressive disorder
NAc	Nucleus Accumbens core
NAs	Nucleus Accumbens shell
NAS	Negative addiction scale
NE	Norepinephrine
NGF	Nerve growth factor
NT3	Neurotrophin-3
PFS	Prefrontal Cortex
RAS	Running addiction scale
RFS	Restricted feeding schedule
TBI	Traumatic brain injury
VEGF	Endothelial growth factor
VGF	Nerve growth factor
5-HT	Serotonin

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