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Exercise as a treatment strategy in mental disorders

Alterations in reward and stress processing as potential mechanisms of action

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Für meine Eine

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1. Summary / Zusammenfassung

1.1. Summary

The World Health Organization recommends regular physical activity for the maintenance of physical and mental health. These recommendations are based on a large number of epidemiological studies that found positive cross-sectional and longitudinal associations between physical activity and mental health. Regarding the therapeutic effects of exercise interventions in individuals with mental disorders, there is a heterogenous picture. While beneficial effects of exercise in Major Depression (and partly in anxiety disorders) were subject to several reviews and meta-analyses, there appears to be less evidence for other groups of mental disorders, e.g. substance use disorders.

Several psychological and neurobiological mechanisms have been proposed to underlie the positive effects of exercise, e.g. enhanced neural plasticity, improved coping, self-efficacy, and mood enhancement. Additionally, stress reactivity and reward processing are important candidates. Dysfunctions in reward and stress sensitivity accompagny several mental disorders, and exercise modulates the perception of and behavioural responses to rewarding and stressful stimuli.

Hence, the aims of this dissertation are twofold: first, to systematically review clinical studies in terms of the therapeutic effects of exercise in different mental disorders, especially substance use disorders which were neglected in the literature so far. Second, to use functional magnetic resonance imaging (fMRI) to investigate exercise-induced alterations in reward processing and stress reactivity.

For the first complex, two systematic literature reviews were performed. One compared evidence from different groups of mental disorders, the other one

focused on substance use disorders. While meta-analyses revealed small, but clinically relevant positive effects of exercise in the treatment of depression and smoking, evidence from randomized-controlled trials is sparse for most other groups of disorders. Many studies also suffer from severe methodological limitations. Therefore, more systematic research is necessary (especially adequately powered randomized-controlled trials) before exercise can be recommended as a general treatment for mental disorders. Since individual psychological and social parameters seem to fundamentally impact exercise outcomes, studies also suggest that more emphasis should be placed on the interactional aspect of exercise interventions, instead of purely focusing on physiological aspects.

For the investigation of reward processing and stress reactivity as central mechanisms of action, two fMRI paradigms were applied to highly trained and sedentary young men, half of which had been randomized to exercise on a treadmill at moderate intensity for 30 minutes, while the other half performed “placebo” exercise. A psychosocial stress task (the Montreal Imaging Stress Task) and a monetary incentive delay task were then used to elucidate the effects of habitual exercise training, previous acute bouts of aerobic exercise, and their interactions. In both paradigms, the acute effects of exercise were stronger than chronic effects. More precisely, participants who had exercised prior to the fMRI experiments showed a decreased neural response of the ventral striatum during reward anticipation and feedback of reward in the monetary incentive delay task. Furthermore, a diminished cortisol stress response to the psychosocial stress task was found, combined with higher tonic brain activation in the bilateral hippocampus

and lower tonic brain activation in the anterior cingulate cortex. Additionally, positive affective changes during exercise correlated with lower hormonal stress responses to the stressor.

This suggests that acute exercise induced an activation of the dopaminergic reward system and the hypothalamus-pituitary-adrenal axis, which had a sustained effect (i.e. more than one hour after exercise cessation) on phasic activation of the respective system. In the HPA axis, this mechanism is well known as non-genomic negative feedback and can be integrated into the theoretical framework of the cross-stressor adaptation hypothesis. For the dopaminergic system, our results support the tonic-phasic dopamine hypothesis.

In contrast, we found no or little differences between trained and untrained men. Transferring this finding to the context of mental disorders, the results suggest that positive long-term outcomes of exercise interventions may in large part rely on accumulated acute effects. As a consequence, exercise could be used as an active coping strategy to deal with substance craving or upcoming stressful situations. Yet, the results need to be replicated in patient samples, using disorder-specific stimulus material (e.g. substance-use related cues or phobic situations as a stressor). Furthermore, future studies in clinical populations should pursue the question whether disturbed reward sensitivity or abnormal stress reactions seen in clinical populations can be reversed by exercise. To summarize, the findings of this thesis provide an overview on exercise as an (adjunct) treatment for mental disorders and depict a number of gaps in the literature. Additionally, it adds to the understanding of mechanisms by which acute exercise influences reward and stress sensitivity.

1.2. Zusammenfassung

Auf der Grundlage zahlreicher epidemiologischer Quer- und Längsschnittstudien, die einen negativen Zusammenhang zwischen körperlicher Aktivität und psychischen Störungen belegen, empfiehlt die Weltgesundheitsorganisation (WHO) regelmäßige körperliche Aktivität zur Prävention psychischer Störungen. Studien bezüglich der therapeutischen Effekte von Sport bei psychischen Störungen ergeben hingegen bislang kein homogenes Bild. Während beispielsweise für Depression bereits Meta-Analysen vorliegen, wurden andere Gruppen psychischer Störungen mit ebenfalls hoher Prävalenz (z.B. Suchterkrankungen) bisher nicht systematisch beleuchtet.

Als Wirkmechanismen von Sport werden unter anderem eine erhöhte neuronale Plastizität, Stimmungsverbesserung und Steigerung der Selbstwirksamkeit diskutiert. Darüber hinaus stellt die Modulation der Belohnungsverarbeitung und Stressreaktivität einen interessanten Ansatzpunkt dar, weil einerseits beide bei psychischen Störungen typische Dysregulationen aufweisen, und andererseits durch Sport erheblich beeinflusst werden, wie in zahlreichen (vor allem tierexperimentellen) Studien gezeigt wurde.

Diese Dissertation soll einen systematischen Überblick über Sportinterventionen bei psychisch Kranken geben, und zwar vor allem in jenen Störungsgebieten, die bislang in der Literatur vernachlässigt wurden, z.B. substanzgebundenen Störungen. Zusätzlich sollen mit Hilfe funktioneller Bildgebung die neuronalen, aber auch subjektive und psychoneuroendokrine Veränderungen von Belohnungs- und Stressverarbeitung untersucht werden, die durch Sport hervorgerufen werden.

Zur Beantwortung des ersten Themenkomplexes wurden zwei systematische Literaturübersichten angefertigt, deren erste sich auf den Vergleich der vorliegenden Evidenzgrade für den Einsatz von Sport bei unterschiedlichen Störungsgruppen konzentriert, die zweite auf substanzgebundene Störungen. Während für Depression und Rauchen kleine, aber klinisch bedeutsame Therapieeffekte durch Sportinterventionen nachgewiesen werden konnten, mangelt es in den meisten anderen Störungsgebieten an randomisiert-kontrollierten Studien. Ein Großteil der bisher veröffentlichten Studien zeigt deutliche methodische Schwächen. Daher ist weitere Forschung unerlässlich, bevor Aussagen darüber getroffen werden können, bei welchen Störungsbildern welche Art von Sport eine wirksame Therapieoption darstellt. Soziale und psychologische Komponenten der Sportinterventionen stellen sich zunehmend als bedeutsam für deren Wirksamkeit heraus, so dass diesen künftig größere Aufmerksamkeit zuteil werden sollte.

Für die Untersuchung zweier mutmaßlich zentraler Wirkmechanismen von Sport bei psychischen Störungen, nämlich die Veränderung der Belohnungsverarbeitung und der Stressreaktivität, wurde eine funktionelle Magnetresonanztomografie-Studie durchgeführt. Hochtrainierte und untrainierte Männer bewegten sich entweder für 30 Minuten bei moderater Intensität auf dem Laufband oder erhielten eine Placebo-Sportintervention. Anschließend wurden ein psychosozialer Stress-test (Montreal Imaging Stress Task) sowie ein Belohnungsparadigma (Monetary Incentive Delay Task) durchgeführt. Das Studiendesign ermöglichte die getrennte Betrachtung von habituellen und akuten Sporteffekten, sowie von deren Interaktionen.

In beiden Experimenten zeigten sich akute Effekte von Sport, wohingegen sich trainierte Probanden nicht oder nur kaum von untrainierten unterschieden. Männer, die sich 30 Minuten auf dem Laufband bewegt hatten, zeigten eine deutlich verminderte neuronale Antwort im ventralen Striatum während der Antizipation und des Feedbacks von Geldgewinnen. Ebenso fiel die Cortisol-Stressantwort im Stresstest bei Probanden der Laufbandgruppe geringer aus, verbunden mit einer stärkeren tonischen Hippocampus-Aktivität und einer verringerten Aktivität des anterioren Cingulums. Dies weist darauf hin, dass der stressmindernde Charakter von Sport auf negatives Feedback der Hypothalamus-Hypophysen-Nebennieren-rinden-(HPA) Achse zurückzuführen ist. Die Ergebnisse lassen sich im theoretischen Rahmen der „Cross-Stressor Adaptation Hypothese“ und der „Tonisch-phasischen Dopamin-Hypothese“ diskutieren und legen nahe, dass langfristig positive Effekte von Sportinterventionen bei psychischen Störungen zum Teil auf akkumulierte akute Effekte zurückgehen. Diese könnten somit gezielt als Coping-Strategie zur Stressreduktion oder Rückfallprophylaxe eingesetzt werden. Zunächst müssen jedoch weitere Studien die Ergebnisse an Patienten-Stichproben replizieren und der Frage nachgehen, ob Sport kurz-oder langfristig störungs-assoziierte Dysregulationen des Belohnungs- und Stressverarbeitungssystems verbessern kann.

Zusammenfassend gibt diese Dissertation einen Überblick über Sport als Behandlungsoption bei verschiedenen psychischen Störungen, zeigt Lücken in der bisherigen Forschung auf, und trägt zum Verständnis der Wirkmechanismen von Sport in diesem Zusammenhang bei.

2. Theoretical Background

2.1. Introduction

According to the World Health Organisation (WHO), high-income countries are facing an increasing number of lifestyle-related diseases such as diabetes, cardiovascular diseases, cancer and mental disorders, which constitute an enormous burden of disease to the societies and the individuals. Among the most prominent risk factors, physical inactivity constitutes "*the fourth leading risk factor for global mortality*" (WHO, 2010). For the prevention of these non-communicable diseases and depression in adults, the WHO recommends a minimum of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity per week. Similarly, the American College of Sports Medicine (ACSM) recommends to be physically active on a moderate-intensity level for at least 30 minutes on at least 5 days per week, supplemented by 2-3 sessions of non-aerobic (resistance) exercise to increase muscular strength, and coordination / flexibility exercises (Garber et al., 2011).

In line with these recommendations, exercise and physical activity are more and more present in the media as an effective and cheap approach to avoid physical and mental illness (Hauschild, 2013; Lenzen-Schulte, 2013).

Therapeutic effects of exercise interventions have been shown especially for Major Depressive Disorder (MDD), where a large number of well-controlled clinical trials have been published (see Chapter 3 & 4), followed by meta-analyses estimating effect sizes and elucidating exercise characteristics which contribute to these therapeutic effects.

However, evidence is unequally distributed across different groups of mental disorders. Narrative and systematic reviews mostly concentrate on depression and anxiety (e.g. Stathopoulou, Powers, Berry, Smits & Otto, 2006; Ströhle, 2009). So far, studies on other groups of mental disorders have not been systematically compared. More specifically, substance use disorders (SUD) are another highly prevalent group of mental disorders which cause immense social and economic damage (Drogen & Suchtbericht, 2013; Wittchen et al., 2011). Despite well-established pharmacological and psychological interventions, long-term outcomes and abstinence rates are modest, intensifying the search for complementary treatments. Although exercise interventions have been suggested to be a promising approach in SUD, there appears to be only little scientific evidence in this field.

Furthermore, the mechanisms of action by which exercise exerts positive effects in patients with mental disorders are not well understood. Amongst other mechanisms discussed in section 2.3., some studies suggest that especially the responsiveness to reward and stress is disturbed in several mental disorders (Ginty, 2013). Physical activity and exercise on the other hand particularly modulate these components (see sections 2.3.3. and 2.3.5.). For instance, chronic exercise has been shown to induce certain alterations in psychoneuro-endocrinological markers (Wilmore, Costill & Kenney, 2008), e.g. increasing hypothalamus-pituitary-adrenal (HPA) axis drive, and at the same time reducing peripheral cortisol sensitivity, thus protecting cells from potential damage by high levels of cortisol (see Article IV).

The investigation of reward processing, on the other hand, is especially interesting because it is related to several mental disorders. Preclinical studies showed that exercise itself has rewarding properties and largely induces plasticity in the brain reward system (see sections 2.3.3. and Articles II & III), acting on anhedonia and the rewarding properties of different drugs. Thus, the investigation of neural correlates of reward processing and exercise in humans is of particular interest.

In the following sections, a brief introduction to exercise and physical activity will be given, and evidence for a role of physical activity in the prevention of mental disorders will be reviewed. Subsequently, the rationale for exercise interventions in mental disorders will be discussed, along with the most prominent psychological and neurobiological mechanisms of action. Among these mechanisms, reward and stress will be illuminated in greater detail. Finally, the research questions for this dissertation thesis will be outlined.

2.1.1. Exercise and Physical Activity

At first, some terms and definitions used in the following sections shall be briefly defined: Physical activity and exercise are sometimes used synonymously, but refer to different aspects of motor behaviour. **Physical activity** in a wider sense describes all kinds of movements and muscle action that increase energy demand above the resting state. This includes different domains of life, e.g. work, transportation, housekeeping, playing and exercise. **Exercise** in a narrower sense can be defined as a series of planned, purposeful body movements with different aims, e.g. increasing or maintaining fitness or strength, improving well-being, or

promoting health and relaxation. Depending on the physiological characteristics, two broad categories of exercice should be mentioned. **Aerobic exercise** involves all types of exercise which allow sufficient oxygen supply to aerobically metabolize carbohydrate into energy. This usually represents low or moderate intensities which can be maintained over a longer period of time. Typical examples are long-distance running, walking, rowing, swimming, or cycling. At higher exercise intensities, the metabolism is no longer able to sufficiently supply the muscles with oxygen, resulting in the additional recruitment of anaerobic glycolysis. After a short period of time, this results in an accumulation of lactate and exhaustion. **Anaerobic exercise** is for example found in short-distance running (sprint) or resistance exercise. Thus, the expression *"moderate physical activity / exercise"* usually refers to solely aerobic exercise. The threshold for the transition from aerobic to anaerobic metabolism depends on a subject's **aerobic capacity**, often refered to as **fitness**. This describes the functional capacity of the cardiorespiratory system and the ability of the body tissues to take up oxygen from the blood (**VO_2max**). Several factors influence a person's aerobic fitness, especially genes, lifestyle habits, the amount and type of physical activity, and health parameters.

In the following sections, the temporal dimension must also carefully be considered. **Acute effects** refer to physiological or psychological changes that are induced by single bouts of exercise and last up to a couple of hours. **Chronic effects** in contrast require adaptations which occur over longer time periods, associated with regular exercise training.

2.2. Physical Activity, Exercise and Mental Health

2.2.1. Epidemiological Studies on Physical Activity and Mental Health

In the WHO guidelines cited above, the prevention of depression is explicitly mentioned. Indeed, a number of epidemiological studies from different countries have shown that there are cross-sectional associations between physical activity and different mental disorders, especially mood and anxiety disorders (Goodwin, 2003; Harvey, Hotopf, Overland & Mykletun, 2010; Stephens, 1988; Ströhle et al., 2007; ten Have, de Graaf & Monshouwer, 2011). This held true for self-reported symptoms (Stephens, 1988) as well as clinically diagnosed disorders (e.g. Goodwin, 2003; Ströhle et al., 2007). Additionally, negative associations between levels of physical activity and substance use disorders were found (Lampinen, Heikkinen & Ruoppila, 2000; Ströhle et al., 2007; ten Have et al., 2011). While some studies only found effects in *regular* PA (i.e. > once a week), Harvey et al. (2010) as well as ten Have et al. (2011) reported negative associations for *any amount* of leisure-time physical activity, with social engagement and social support being important mediating factors.

Apart from these cross-sectional correlations, there is evidence for longitudinal associations between physical activity and mental health: Over a time span of four years, Ströhle and colleagues (2007) found lower incidences of any mental disorder (especially dysthymia, anxiety disorders, and somatoform disorders) in subjects engaging in regular physical activity. Irregular physical activity, compared to no physical activity, reduced the incidence of any substance use disorder (SUD) and posttraumatic stress disorder (PTSD). For any amount of physical activity, a significantly lower risk of agoraphobia/panic and somatoform disorders, but a

higher risk of bipolar disorder was found (Ströhle et al., 2007). In older adults, baseline levels of physical activity as well as reductions of physical activity over the years were associated with depressive symptoms 8 years later (Lampinen, Heikkinen & Ruoppila, 2000). ten Have (2011) found a lower incidence of any mood or anxiety disorder (esp. Major Depressive Disorder, MDD) in subjects who were physically active (at any frequency) across a 3-years-period. None of these studies reported sex differences, yet a study by Mikkelsen et al. (2010) found lower incidence rates of depression in physically active women, but not in men over a course of 26 years (Mikkelsen et al., 2010).

2.2.2. Potential Causal Chains

Despite large sample sizes and mostly prospective designs, the major limitation of these studies is their correlational nature which does not allow causal conclusions. Even though in these studies, it seems self-evident that mental health is a *consequence* of regular physical activity, other causal chains must be considered. As Stephens (1988, p. 44) states, "*good mental health is probably not a sufficient condition for initiating exercise, [but] it may very well be a necessary one, at least with regard to anxiety, depression, and self-esteem*". Individuals with sub-clinical mental health problems or high levels of life stress may prospectively be less prone to engage in physical activity than others. This assumption is supported by studies reporting an increased risk for a sedentary lifestyle in subjects with self-reported or clinically diagnosed depression at study baseline (Roshanaei-Moghaddam, Katon & Russo, 2009; Stavrakakis, de Jonge, Ormel & Oldehinkel, 2012). Alternatively, physical activity and mental health may be determined by common third variables.

Indeed, multitudinous studies found that sex, age, education, marital status, socioeconomic status, and physical health influence both mental health and the levels of physical activity (ten Have et al., 2011), but in all above-listed studies, the association between physical activity and mental health remained significant when these and other possible confounders were controlled.

Also, certain personality variables such as higher extraversion and conscientiousness and lower neuroticism have been found to be linked both to mental health (Malouff, Thorsteinsson & Schutte, 2005), but also to more regular exercise behaviour (de Moor, Beem, Stubbe, Boomsma & de Geus, 2006; Rhodes & Smith, 2006) and may therefore mediate the relationship between physical activity and mental health.

Genetic factors largely explain differences in adult exercise behaviour (Stubbe, Boomsma & de Geus, 2005; Stubbe et al., 2006). A large Dutch twin study (de Moor, Boomsma, Stubbe, Willemsen & de Geus, 2008) replicated cross-sectional and longitudinal correlations between leisure-time exercise and self-reported anxiety and depression, and revealed no *causal* relationship between these variables. Instead, common genetic factors were found to underlie both physical activity and depression/anxiety. Candidate genes are for example genes underlying highly heritable personality traits such as extraversion, neuroticism, or novelty seeking which are linked to both physical activity and mental health (de Moor et al., 2006; Rhodes & Smith, 2006). Another hypothesis is that the acute rewarding or aversive effects of exercise may depend on genetic variation in the opioid and dopamine systems (Stubbe, Boomsma & de Geus, 2005), predisposing individuals towards a more or less sedentary lifestyle.

2.2.3. Exercise as a Treatment Strategy in Mental Disorders

Additionally to the preventive action that may be inherent to physical activity, there is evidence that patients with mental disorders can benefit from exercise interventions. In a large representative community sample, persons with affective, anxiety, or substance abuse/dependence disorders who were physically active reported a higher health-related quality of life than those who were inactive (Schmitz, Kruse & Kugler, 2004). In addition, one longitudinal epidemiological study described that subjects diagnosed with one or more mental disorders at study baseline were more likely to recover from these disorders during the next three years, when they engaged in regular physical activity during leisure time (ten Have et al., 2011). This effect was found especially for anxiety disorders.

Apart from these epidemiological studies which did not systematically introduce exercise interventions, there is a growing body of evidence from clinical studies using exercise as an (adjunct) treatment for mental disorders. This evidence is reviewed in Articles I & II. Beforehand, potential mechanisms of action will be discussed that make exercise interventions a promising approach for mental disorders.

2.3. Mechanisms of Action

Physical activity and exercise can be considered as very complex interventions with multitudinous neurobiological and psychological facets. On a temporal dimension, physiological and psychological reactions during and after a single bout of exercise also have to be distinguished from long-term adaptations that occur after a period of regular training. In the following sections, anxiolysis, mood enhacement, social support, self-efficacy, and alterations in brain plasticity, reward processing and stress reactivity will be reviewed as mechanisms that are especially relevant for the context of mental health, along with underlying biological correlates. Two important remarks shall be made in advance:

First, all psychological factors and all transmitters, peptides and hormones discussed in the following sections largely influence each other and have complex interactions (Bergman, 2013; Dishman et al., 2006). Thus, their potential distinct role illustrated here may result in a simplified picture, yet is essential for understanding the neurobiological basis of behavioural changes.

Second, animal studies allow to investigate the neurobiological basis of exercise on a cellular level (mRNA expression, neurotransmitter secretion and reuptake, receptor density and occupation). However, there are limitations concerning their transferability to humans. Major limitations include that in several studies, the animals were deprived of physical activity when entering the experimental / control condition, and that running wheel access may be particularly stimulating and rewarding in an otherwise barren cage environment, which may lead to an overestimation of the rewarding properties of physical activity. Furthermore, some studies use exercise as a stress model (forced run or swim), which needs to be

carefully distinguished from studies investigating voluntary exercise, allowing the animal running wheel access and self-paced timing, intensity and duration.

On the other hand, human studies face the problem that neurotransmitter/ peptide/ hormone concentrations are mostly measured in the periphery using blood samples, or, more rarely, cerebrospinal fluid. These peripheral measures are known to not necessarily reflect neurotransmission in specific brain regions where they exert their antidepressant / mood-enhancing / stress-reducing action (e.g., Dietrich & McDaniel, 2004; Gustafsson et al., 2009). Unfortunately, it is mostly not possible to directly measure concentrations and turnover of neurotransmitters or their interactions in vivo in the human brain. Therefore, the neurobiological mechanisms discussed in the following sections deserve further investigation to better understand their effects and interactions in humans. More recently, neuroimaging techniques measuring cerebral blood flow (functional magnetic resonance imaging - fMRI) or receptor availability (positron emission tomography - PET) have advanced, allowing indirect conclusions on neurotransmission. For instance, studies showed high correlations between BOLD signal and PET signal in reward processing (Schlagenhauf et al., 2013; Schott et al., 2008), or between BOLD signal and external variables such as cortisol levels in stress research (Pruessner et al., 2008). Thus, future neuroimaging studies in humans will likely deepen the understanding of neurobiological correlates of exercise.

2.3.1. Anxiolytic Effects of Exercise

Anxiety is a symptom which is not specific for anxiety disorders, but common to several mental disorders and even to non-clinical populations. The anxiolytic

effects of exercise is well-documented and appears to be very robust for acute and chronic exercise, for aerobic, anaerobic and combined exercise, for short and longer bouts of exercise, different intensities, and different populations (Petruzzello, Landers, Hatfield, Kubitz & Salazar, 1991; Wipfli, Rethorst & Landers, 2008, see also Article I). The largest effects are found when exercise is compared to no-treatment, but even when compared to other complementary treatments (e.g. yoga, stress management therapy, meditation / relaxation, music therapy), this effect remains significant (Wipfli et al., 2008). In patients with panic disorder, exercise may help re-interpret the feared bodily symptoms (e.g. tachycardia, sweating) and habituate to them, comparable to interoceptive exposure therapy (Clark, 1986). In line with this, studies found that aerobic exercise reduced anxiety sensitivity (Broman-Fulks, Berman, Rabian & Webster, 2004; Smits et al., 2008) which is considered a vulnerability factor for the development and course of anxiety (and other) mental disorders.

Recent research illuminates the biological basis of the anxiolytic action of exercise. Apart from exercise-induced changes in the serotonergic and noradrenergic neurotransmission (which will be discussed in section 1.2.2.), a potential biological mechanism is the secretion of atrial natriuretic peptide (ANP) from atrial muscle cells during aerobic and anaerobic exercise. Studies suggest that the secretion of ANP is causally involved into the anxiolytic effects of exercise and negatively correlates with pharmacologically provoked panic symptoms (Ströhle, Feller, Strasburger, Heinz & Dimeo, 2006; Ströhle, Kellner, Holsboer & Wiedemann, 2001). Furthermore, the is evidence that ANP is a powerful modulator of hypothalamus-pituitary-adrenal (HPA) axis activity, acting as a corticotrophin-

releasing hormone (CHR)- inhibiting factor (Demiralay, Jahn, Kellner, Yassouridis & Wiedemann, 2010; Koopmann et al., 2013). In contrast to these well-documented acute effects, no differences were found between trained and untrained men with regard to baseline levels and acute exercise-induced ANP increases (Poveda et al., 1997).

2.3.2. Mood Enhancement and Antidepressant Effects of Exercise

Similarly to anxiety, exercise was shown to exert antidepressive effects in non-clinical and clinical populations, as concluded by a large number of reviews and meta-analyses (e.g. Cooney et al., 2013; Krogh, Nordentoft, Sterne & Lawlor, 2011; Rethorst, Wipfli & Landers, 2009, see also Article I).

It is a central assumption of exercise psychology is that physical activity enhances mood, concluded by innumerous studies and reviews (e.g. Reed & Ones, 2006; Yeung, 1996). Despite this widely popularized view, several studies reported negative affective responses to exercise (Petruzzello, Jones & Tate, 1997; Van Landuyt, Ekkekakis, Hall & Petruzzello, 2000). Apperently, mood-enhancing effects depend on the fitness level and initial mood state of the subject, as well as the exercise intensity (e.g. Hoffman & Hoffman, 2008; Petruzzello et al., 1997; Reed, Berg, Latin & La Voie, 1998; Tate & Petruzzello, 1995; van Landuyt, Ekkekakis, Hall & Petruzzello, 2000). A meta-analysis on 158 aerobic exercise studies (Reed & Ones, 2006) confirmed that the greatest and most generalizable effects were found when baseline affect was low, and when exercise doses were rather low (durations 7-35 min, low to moderate intensity). These effects lasted up to 30 min post-exercise. Only fitter subjects experienced mood improvement at moderate

and higher exercise intensities. This is in line with Ekkekakis and colleagues (2011) who suggested that affective responses during exercise are homogenously positive at lower intensities, become more heterogeneous at intensities close to the ventilatory threshold (i.e. at the transition between aerobic and anaerobic metabolism) and are mostly negative at high intensities (but usually followed by a positive rebound effect after exercise cessation). Self-selection of intensity and duration are important modulators of the affective responses to exercise (Ekkekakis, Parfitt & Petruzzello, 2011). Unequivocal results were reported concerning the long-term affective consequences of exercise which are difficult to assess, as, by definition, mood is a transient state (see Berger & Motl, 2000; Walter et al., 2013).

In search of the neurobiological basis of exercise-related antidepressant effects, changes in serotonin (5-HT) and norepinephrine (NE) transmission are potential mechanisms of action. Several antidepressants act on increasing serotonergic transmission by inhibiting the reuptake or breakdown of 5-HT, thus increasing extracellular concentrations. Some authors postulate that moderate levels of physical activity increase 5-HT levels in a beneficial way (Helmich et al., 2010). In humans, exercise was found to increase the availability of total and unbound tryptophane, a 5-HT precursor, in the blood (Fischer, Hollmann & de Meirleir, 1991; Melancon, Lorrain & Dionne, 2012), supporting the hypothesis that exercise enhances 5-HT synthesis. Further support comes from several animal studies illustrating the role of exercise-induced changes in serotonergic transmission in depression-like behaviours (e.g. learned helplessness) in rodents (Greenwood, Foley, Burhans, Maier & Fleshner, 2005; Greenwood et al., 2003). Likewise,

exercise has been proposed to increase the central availability of NE, which has so far only been shown in rat studies (as reviewed by Helmich et al., 2010). Recently, it has been proposed that exercise-induced changes in 5-HT and NE levels exert their antidepressant effects indirectly by enhancing neuroplasticity and regulating brain-derived neurotrophic factor (BDNF; Cotman & Berchtold, 2002; Helmich et al., 2010; Ivy, Rodriguez, Garcia, Chen & Russo-Neustadt, 2003; also see section 1.2.5.).

Apart from 5-HT and NE involved in mood regulation, endogenous opioids (EO) and endocannabinoids (EC) are discussed as underlying mechanisms for exercise-induced positive affect and euphoria (see section 1.2.4.).

2.3.3. Alterations in Reward Processing

Closely related to mood enhancement, a direct rewarding effect has been ascribed to exercise (Brené et al., 2007). Some authors even compare exercise to addictive substances which may lead to misuse or abuse (Hamer & Karageorghis, 2007; Landolfi, 2013). Several rodent studies found exercise-induced alterations in the mesolimbic reward system, involving endogenous opiods (EO), dopamine (DA) and endocannabinoids (EC). Rats engage in wheel running voluntary and develop a conditioned place preference, indicating rewarding properties of wheel running (Belke & Wagner, 2005; Brené et al., 2007, see also Article III). Furthermore, several studies indicate that the rewarding properties of cocaine, heroine, ethanol, and methamphetamine are altered by chronic and / or acute exercise (Smith & Lynch, 2011, see also Article III) and that exercise reduces acquisition (Smith & Pitts, 2011) and reinstatement (Smith, Pennock, Walker & Lang, 2012) of drug-

seeking behaviour. In humans, evidence is sparse on how acute and chronic exercise modulate reward processing. Although there is evidence that alterations of reward processing are a central characteristic of different mental disorders (Ginty, 2013), there is only indirect evidence from studies using exercise as an intervention in SUD (see Article II). The underlying neural mechanisms of altered reward processing in humans remain so far elusive.

Apart from dopamine which is a central neurotransmitter for the processing of reward and in SUD (see Articles II & III), EO and EC have been discussed as a potential mechanism of action, since they induce euphoria and anxiolysis. EO were called to account for the famous “runner’s high”, which is nowadays not undisputed (see Dietrich & McDaniel, 2004; Raichlen, Foster, Gerdeman, Seillier & Giuffrida, 2012). Actually, increases in peripheral β-endorphine (βE) levels were found after acute aerobic exercise at ≥ 50-60% VO_2max, and lower or unchanged baseline levels in endurance-trained subjects (see Goldfarb, 2013). However, it can not be inferred from these studies that peripheral levels reflect EO levels in the brain, because βE hardly crosses the brain-blood barrier (see Goldfarb, 2013). Indeed, a PET study revealed lower opioid receptor availability (i.e. supposedly higher EO release) in prefrontal and limbic/paralimbic regions after 2 hrs of running, which was correlated with self-reported euphoria (Boecker et al., 2008). It remains unclear if this effect can also be found at lower intensities and / or shorter exercise durations. Yet, the involvement of EO has a high clinical relevance, due to their eminent role in SUD and other mental disorders (see Tejeda, Shippenberg & Henriksson, 2012; Trigo, Martin-Garcia, Berrendero, Robledo & Maldonado, 2010),

their interactions with the DA and EC systems, and their up-regulating effect on the BDNF (Zhang et al., 2006; see section 1.2.4.).

Endocannabinoids (EC) are another candidate for exercise-induced reward modulation. In fact, the EC system of humans and other "*cursorial mammals*" is activated by exercise in a dose-dependent manner (Heyman et al., 2011; Raichlen et al., 2012; Raichlen, Foster, Seillier, Giuffrida & Gerdeman, 2013; Sparling, Giuffrida, Piomelli, Rosskopf & Dietrich, 2003). EC cross the brain-blood barrier easily and bind to receptors in the limbic system, basal ganglia, cortex, hippocampus, amygdala, hypothalamus, and cerebellum. They have synergistic effects with EO regarding analgesia (see Dietrich & McDaniel, 2004) and massive impact on dopamine signalling (Dietrich & McDaniel, 2004; Gardner, 2005), the regulation of the HPA axis (Hill & McEwen, 2010; Tasker, 2004) as well as BDNF secretion (Heyman et al., 2011), suggesting they play a multifaceted role for several key mechanisms discussed here. Dysregulations of the EC system were shown to be involved in several mental disorders (depression, anxiety, schizophrenia, see Marco et al., 2011). Importantly, there are close interactions between EO, DA and EC with regard to euphoria, mood, anxiolysis, and reward / pleasure (Gardner, 2005). The biological mechanisms discussed here can therefore not be seen separately, but exert complex interactions with each other.

2.3.4. Enhancement of Neural Plasticity

Brain-derived neuroptrophic factor (BDNF) is considered a powerful agent in plasticity, neuroprotection, and adult neurogenesis. Therefore, it is a central component for cognition which is impaired in most mental disorders. There is

evidence for an association between lower BDNF serum levels, structural brain alterations, and poorer cognitive and memory performance in the context of mental disorders, especially depression and schizophrenia (Garza, Ha, Garcia, Chen & Russo-Neustadt, 2004; Karege et al., 2002; Schmidt & Duman, 2007), although not all studies found disturbed peripheral BDNF release (Gustafsson et al., 2009). Cognitive benefits and antidepressant effects arising from physical activity and exercise are implicitly or explicitly attributed to BDNF by several studies (Bjornebekk, Mathe & Brene, 2005; Garza et al., 2004; Griffin, Bechara, Birch & Kelly, 2009; Pajonk et al., 2010). In healthy humans, evidence is mixed regarding the effects of acute exercise on BDNF serum levels: some studies found an increase in BDNF serum levels after short-term moderate aerobic exercise (Tang, Chu, Hui, Helmeste & Law, 2008), whereas others reported BDNF increases only at higher exercise intensities (Vega et al., 2006), or even failed to detect any acute BDNF level increases (Goekint et al., 2010; Laske et al., 2010; Ströhle et al., 2010). However, in depressed elderly women and patients with panic disorder, acute exercise induced a transient increase or normalization of BDNF levels, respectively (Laske et al., 2010; Ströhle et al., 2010).

In the long term, endurance training may increase peripheral baseline BDNF levels in healthy adults (Seifert et al., 2010), in contrast to strength training (Goekint et al., 2010). Other studies failed to detect baseline differences between untrained, endurance-trained, and strength-trained subjects (Schiffer, Schulte, Hollmann, Bloch & Struder, 2009) or even reported lower baseline BDNF levels in trained subjects (Currie, Ramsbottom, Ludlow, Nevill & Gilder, 2009; Nofuji et al., 2008).

In depressed patients who did not or only partially respond to selective serotonine reuptake inhibitor (SSRI) treatment, basal serum BDNF levels did not correlate with symptom improvement and remained stable throughout a 12-weeks exercise intervention (Toups et al., 2011). This suggests that an additional symptom improvement induced by exercise augmentation may be effective by mechanisms other than BDNF in pharmacologically pre-treated patients. Despite mixed evidence regarding adaptations in long-term exercise training and methodological considerations regarding the ratio of plasma / serum BDNF to brain BDNF, BDNF and other nerve growth factors (e.g the insuline-like growth factor; Trejo, Carro & Torres-Aleman, 2001) likely play a role in the antidepressant and neuroprotective action of exercise. Furthermore, BDNF metabolism is particularly mediated by NE and 5HT (Cotman & Berchtold, 2002; Ivy et al., 2003; see section 1.2.2.) and is strongly connected to the psychoneuroendocrine stress systems, especially the hypothalamus-pituitary-adrenal (HPA) axis (see section 2.3.5.).

2.3.5. Alterations in Stress Reactivity and Coping

One key mechanism for the protective / therapeutic action of physical activity suggested by many authors is the reduction of stress reactivity and the attenuation of deleterious consequences of chronic stress (Tsatsoulis & Fountoulakis, 2006a). In rodent studies on uncontrollable stress, regular exercise prevented learned helplessness and depressive / anxious behaviours (Greenwood, Foley, Burhans, Maier & Fleshner, 2005; Greenwood et al., 2003). In these studies, alterations of the serotonergic system played a major role. In humans, exercise was proposed to be an active coping strategy to deal with (experimental and real-life) stressors. For

example, better cardiovascular recovery was reported when the subjects exercised after a psychosocial stressor, even though exercise initially further increased cardiovascular activation (Chafin, Christenfeld & Gerin, 2008). The subjective ability to cope with stress was found to be improved after 10 weeks of supervised and unsupervised training (Steptoe, Edwards, Moses & Mathews, 1989), and longitudinal studies suggest that physical activity used as a coping strategy can buffer the negative effects of chronic medical conditions and severe life events (Arida, Cavalheiro & Scorza, 2012; Harris, Cronkite & Moos, 2006; Phillips et al., 2012).

Another facet of the stress-exercise relationship is the question whether exercise can lower the physiological reactivity to stress. Acute exercise itself constitutes some sort of stressor for the organism and activates the two major stress systems in the body, the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis (see Wilmore et al., 2008; Article IV). These activations depend on the duration and intensity of the exercise bout and are transient (Hackney, 2006; Wilmore et al., 2008), yet are related to certain after-effects such as a post-exercise hypotension (Pescatello & Kulikowich, 2001). As discussed in section 1.2.4., the EC and EO systems serve as important modulators of the HPA axis response (e.g. Inder et al., 1995; Tasker, 2004), additional to complex interactions between the HPA system and BDNF (Belke & Wagner, 2005; Kunugi, Hori, Adachi & Numakawa, 2010). Thus, these systems likely interact with regard to exercise-induced alterations in stress reactivity.

Several adaptations have been demonstrated that occur with regular exercise training, resulting in lower SNS and HPA responses to the same exercise workload

in trained compared to untrained subjects (Hackney, 2006; Sothmann et al., 1996). Within the theoretical framework of the cross-stressor adaptation hypothesis (Sothmann et al., 1996), it was assumed that trained subjects may be also less reactive to other stressors (see Article IV). This assumption was corroborated by studies reporting lower HPA stress responses in trained compared to untrained subjects (Rimmele et al., 2009; Rimmele et al., 2007; Traustadottir, Bosch & Matt, 2005). A meta-analysis on cardiovascular stress markers however found great heterogeneity between studies, concluding that on average, cardiovascular responses to stress were not attenuated in trained subjects (Jackson & Dishman, 2006). In contrast to long-term effects, acute exercise was shown to reduce cardiovascular responses to subsequent psychosocial stress (see meta-analysis by Hamer, Taylor & Steptoe, 2006). For the acute effects of exercise on HPA axis responses, there is no evidence in humans yet. However, studies suggest that altered sensitivity to cortisol feedback is one key mechanism of exercise-related changes in HPA axis regulation (Duclos, Corcuff, Pehourcq & Tabarin, 2001; Duclos, Gouarne & Bonnemaison, 2003; Petrides et al., 1994; Wittert, 2000). Although the peripheral mechanisms of adaptation to repeated and strenuous exercise are well-documented (decreased adrenal sensitivity to adrenocorticotropic hormone (ACTH) in highly trained men (Wittert, Livesey, Espiner & Donald, 1996), decreased tissue sensitivity to cortisol (Duclos et al., 2001; Duclos et al., 2003), it remains also unclear how exercise and exercise-related HPA activation impact on the neural processing of (subsequent) stressors. Furthermore, the interactions between psychoneuroendocrine and neural mechanisms in humans are unknown.

2.3.6. Changes in Self-Esteem, Self-Efficacy, and Locus of Control

Although not unanimous, there is cross-sectional evidence that higher levels of physical activity are associated with higher self-esteem, at least in men (McAuley, 1994; Tiggemann & Williamson, 2000). A theoretical framework for this relationship is provided by the *Exercise and Self-Esteem Model* (EXSEM; Sonstroem, Harlow & Josephs, 1994). A number of intervention studies confirmed the domain-specificity of this effects (i.e. exercise-related self-efficacy does not automatically generalize to other domains), and pointed out that besides physical changes associated with regular exercise (e.g., reduced weight, lower body fat, higher aerobic fitness and strength), self-efficacy is an essential mediator in the relationship between physical avtivity and physical self-worth (e.g. McAuley, Blissmer, Katula, Duncan & Mihalko, 2000).

Indeed, self-efficacy was found to be one of the most important predictors of the initiation and maintenance of regular physical activity (e.g. Jerome & McAuley, 2013), and evidence suggests that it is both a precondition and a consequence of physical activity (Elavsky et al., 2005; Hughes et al., 2010; Jerome & McAuley, 2013). In line, a large cohort study in healthy young adults confirmed a strong association between internal locus of control and exercise behaviour (Steptoe & Wardle, 2001). Studies also suggest that self efficacy can generalize, but it will be strongest for activities resembling the trained one. Furthermore, counselling can enhance generalization to other areas (Biddle & Mutrie, 2008, p.113), underlining the importance of coaching or therapeutic monitoring when physical activity is applied as a treatment strategy.

2.3.7. Social Factors

Apart from the biological and individual psychological mechanisms, group interaction, positive feedback, and social support (by trainers and course members) are crucial factors for positive exercise outcomes and adherence, reported especially in qualitative studies (e.g. Carless & Douglas, 2008, 2012). While an atmosphere of competition and critical evaluation are potentially detrimental, positive feedback, group cohesion and social support are not only crucial for exercise adherence, but likely constitute an important mechanism of action for the positive affective consequences of exercise.

2.4. Research Questions

Summing up, physical activity and exercise have preventive and therapeutic potential in mental health. This effect is mediated by a multitude of neurobiological and psychological mechanisms, involving various neurotransmitter systems, affective changes, and alterations in neuroplasticity, reward processing, and stress. The aims of this dissertation are

(i) *to provide a systematic review on the therapeutic effects of exercise interventions in different mental disorders, especially those which are underrepresented in previous reviews, e.g. substance use disorders*

(ii) *to investigate neural and psychoneuroendocrine mechanisms that may underlie the effects of exercise in humans, especially the reward system, and the neural and psychoneuroendocrine systems involved in stress reactivity.*

Therefore, four articles are assembled to form this dissertation thesis:

Article I systematically reviews studies that applied exercise interventions in different mental disorders. The scope of this paper is to elucidate whether evidence is sufficient to consider exercise as a general treatment strategy in mental disorders, as is often implicated in narrative reviews and in the popular media.

More specifically, **Article II** addresses this question for substance use disorders (SUD). These not only constitute a particularly high burden of disease, but are associated with neurobiological pathologies in reward processing. Since exercise has been shown to have a strong impact on the processing of reward (see section

2.2.4.), it can be hypothesized that it represents a promising approach for patients with SUD. Nevertheless, all previous reviews and meta-analyses focused on nicotine and smoking cessation (Ussher, Taylor & Faulkner, 2008), and none has so far summarized studies on exercise effects in alcohol or drug dependence.

For **Article III**, an fMRI study was conducted in order to investigate alterations of neural reward processing associated with chronic and acute exercise, which have rarely been investigated in humans. Healthy young participants who were either highly trained or untrained performed 30 minutes of moderate aerobic exercise (AER) vs. placebo exercise (PLAC) prior to an fMRI task. By this, I aimed at investigating the modulating effects of exercise on the neural processing of non-substance-related (monetary) reward. This design allowed to analyze both long-term and acute effects of aerobic exercise, and their potential interactions.

Finally, **Article IV** focused on (di)stress as a central component of many models of mental disorders which appears to be modifiable by physical activity (see section 2.2.5). With the same design as in Article III, I applied the Montreal Imaging Stress Task (MIST) to highly trained and untrained young men after AER or PLAC, investigating how exercise modifies the neural processing of, and the subjective and neuroendocrine reaction to psychosocial stress.

3. Article I: Exercise Interventions in Mental Disorders

A slightly adapted version of this chapter has been published as:

Zschucke E., Gaudlitz K. & Ströhle A. (2013). Exercise and Physical Activity in Mental Disorders: Clinical and Experimental Evidence. *Journal of Preventive Medicine and Public Health,46*, S12-S21; doi: 10.3961/jpmph.2013.46.S.S12.

http://dx.doi.org/10.3961/jpmph.2013.46.S.S12

3.1. Abstract

Several epidemiological studies have shown that exercise and physical activity can prevent or delay the onset of different mental disorders, and have therapeutic benefits when used as sole or adjunct treatment in mental disorders. This review summarizes studies that used exercise interventions in patients with anxiety-, affective-, eating-, substance use disorders, schizophrenia, and dementia/mild cognitive impairment. Despite several decades of clinical evidence with exercise interventions, controlled studies are sparse in most disorder groups. Preliminary evidence suggests that exercise can induce improvements in physical, subjective and disorder-specific clinical outcomes. Potential mechanisms of action are discussed, as well as implications for psychiatric research and practice.

3.2. Introduction

Mental disorders constitute a huge social and economic burden for the health care systems worldwide (Wittchen et al., 2011), raising the question of effective and lasting treatments. Physical activity is constantly gaining attention of practitioners

and researchers with regard to prevention and treatment of different psychopathological abnormalities.

3.2.1. Epidemiology / Correlational Studies

In the general population, several epidemiological studies found significant cross-sectional correlations between mental health and levels of physical activity. In an adult US population regular physical activity is associated with a significantly decreased prevalence of current major depression, panic disorder, agoraphobia, social phobia, and specific phobia (Goodwin, 2003). A study from Norway (Harvey, Hotopf, Overland & Mykletun, 2010) confirmed this negative cross-sectional association between depression and leisure-time physical activity of any intensity (not work-related physical activity), and pointed out that social factors such as social support play an important role, rather than biological markers. Recently, a Dutch study replicated this finding, reporting lower rates of any affective, anxiety, or substance use disorder in subjects who exercised at least 1h/week, without finding a linear dose-response relationship (ten Have, de Graaf & Monshouwer, 2011).

Prospectively, the overall incidence of mental disorders and co-morbid mental disorders decreases by physical activity, as well as the incidence of anxiety, somatoform and dysthymic disorder (Ströhle et al., 2007). Furthermore, a four-year prospective study revealed that physical activity decreases the incidence rates of depressive and anxiety disorders in older adults (Pasco et al., 2011). Finally, ten Have and colleagues reported in their epidemiological study that patients engaging in regular physical activity were more likely to recover from their mental illness at a three-years follow-up (ten Have et al., 2011).

3.2.2. Mechanisms of Action

In psychiatric patients, different mechanisms of action for physical activity and exercise have been discussed:

On a neurochemical and physiological level, a number of acute changes occur during and following bouts of exercise, and several long-term adaptations are related to regular exercise training. For instance, exercise has been found to normalize reduced levels of brain-derived neurotrophic factor (BDNF) and therefore has neuroprotective or even neurotrophic effects (Seifert et al., 2010; Ströhle et al., 2010; Sylvia, Ametrano & Nierenberg, 2010). Animal studies found exercise-induced changes in different neurotransmitters such as serotonin and endorphins (Fumoto et al., 2010; Meeusen, Piacentini & de Meirleir, 2001), which relate to mood, and positive effects of exercise on stress reactivity, e.g. the hypothalamus-pituitary-adrenal (HPA) axis (Rejeski, Thompson, Brubaker & Miller, 1992; Rimmele et al., 2007). Finally, anxiolytic effects of exercise mediated by atrial natriuretic peptide (ANP) have been reported (Ströhle et al., 2005).

Potential psychological mechanisms of action include learning and extinction, changes in body scheme and health attitudes / behaviors, social reinforcement, experience of mastery, shift of external to more internal locus of control, improved coping strategies, or simple distraction (Read & Brown, 2003; Stathopoulou, Powers, Berry, Smits & Otto, 2006).

3.2.3. Physical Comorbidity

Patients with mental disorders display a high comorbidity of physical conditions such as respiratory, metabolic, cardio-vascular and neurological diseases (Lin,

Zhang, Leung & Clark, 2011; Scott & Happell, 2011). Many of the conditions named above are linked to overweight, smoking, and unhealthy lifestyle (Scott & Happell, 2011), therefore lifestyle interventions based on nutrition and exercise are promising approaches to reduce physical comorbidity (Chacon, Mora, Gervas-Rios & Gilaberte, 2011). Furthermore, psychiatric patients who regularly exercised reported higher health-related quality of life in a cross-sectional study (Schmitz et al., 2004).

3.3. Methods

For the present article, the search engines PubMed, Medline and Web of Science were comprehensively searched for original research articles or reviews in English, German, or French published between 1970 and 2012. The following search terms were used: [exercise OR physical activity] AND [mental disorder OR affective disorder OR depression OR mania OR bipolar disorder OR anxiety OR panic disorder OR agoraphobia OR social phobia OR generalized anxiety disorder OR posttraumatic stress disorder OR obsessive-compulsive disorder OR eating disorder OR anorexia nervosa OR bulimia nervosa OR binge eating disorder OR substance use disorder OR alcohol OR nicotine OR illicit drug OR cannabis OR cocaine OR heroine OR amphetamine OR schizophrenia OR psychosis OR dementia OR mild cognitive impairment OR cognitive decline OR Alzheimer's disease]. The bibliographies of all retrieved articles were searched for additional references.

Only intervention studies using exercise and physical activity as a sole or combined treatment and reviews/ meta-analyses focusing on intervention studies were included.

The level of evidence is heterogeneous amongst different mental disorders (see Table 1). In the following sections, evidence for exercise/physical activity interventions is summarized for anxiety disorders, obsessive-compulsive disorder, affective disorders, eating disorders, substance use disorders, schizophrenia / psychosis, and dementia / mild cognitive impairment.

Table 3.1. Level of evidence for the therapeutic activity of exercise in different groups of mental disorders according to the Agency of Heath Care Policy and Research

Classification	**Source of Evidence**	**Disorder**
1A	Meta-analysis of Randomized Controlled Trials	Major depressive disorder Nicotine dependency
1B	Randomized Controlled Trials	Social phobia Panic disorder Post-traumatic stress disorder Generalised anxiety disorder Binge eating disorder Bulimia nervosa Schizophrenia Alzheimer's dementia Mild cognitive impairment
2	Non-randomized controlled trials (quasi experiment)	Alcohol and drug dependence Anorexia nervosa
3	Observational studies with controls	--
4	Observational studies without controls	Bipolar disorder Obsessive compulsive disorder

3.4. Results: Exercise Interventions in Mental Disorders

3.4.1. Anxiety Disorders

In anxiety disorders, one possible mechanism of action is the exercise-induced reduction in anxiety sensitivity, a personality trait related to the development and course of anxiety disorders (Smits et al., 2008). Subjects with high anxiety sensitivity also report lower levels of physical activity, higher perceived barriers, and lower benefits of physical activity, compared to subjects with low anxiety sensitivity (Sabourin, Hilchey, Lefaivre, Watt & Stewart, 2011).

Two meta-analyses concluded that acute and chronic interventions result in decreases in state- and trait anxiety and psycho-physiological correlates of anxiety in different clinical and non-clinical samples (Petruzzello et al., 1991; Wipfli et al., 2008). Specifically, aerobic and anaerobic exercise were found to be similarly effective as cognitive/behavioral therapy, and more effective than most other anxiety-reducing activities (Wipfli et al., 2008). Additionally, a recent study in adults with intellectual disabilities found that an exercise intervention decreased trait and state anxiety in this population (Carraro & Gobbi, 2012).

3.4.1.1. Panic Disorder (PD)

One of the first studies compared a jogging and a walking intervention in patients with PD, finding similar symptom reductions in both groups after eight weeks, and negative correlations between fitness increase and anxiety scores (Sexton, Maere & Dahl, 1989). Comparing endurance training with clomipramine and placebo revealed that both active treatments were significantly different from placebo after ten weeks, although the effects of clomipramine occurred significantly faster, and

dropout rates were higher in the exercise group (Broocks et al., 1998). Another study (Wedekind et al., 2010) that compared paroxetine with placebo, each combined with either relaxation or running respectively, reported significant effects for paroxetine compared to placebo, but mostly no differences between exercise and relaxation. A recently-published RCT compared exercise to a standardized cognitive-behavioral therapy (CBT) and found CBT to be superior to exercise in reducing panic and agoraphobic symptoms up to 12 months post-treatment (Hovland et al., 2012). However, a significant symptom reduction relative to the baseline was seen in the exercise group as well.

Three studies focusing on the acute exercise found a protective effect of exercise against the subsequent induction of panic attacks via CO_2 and CCK-4 (Esquivel et al., 2011; Esquivel et al., 2008; Ströhle et al., 2009).

3.4.1.2. Post-Traumatic Stress Disorder (PTSD)

Evidence is sparse for PTSD. In three pilot studies, positive effects of aerobic exercise (Manger & Motta, 2005; Newman & Motta, 2007) and moderate walking (Diaz & Motta, 2008) on PTSD symptom severity and associated depressive and anxious symptoms in children (Newman & Motta, 2007), adolescents (Diaz & Motta, 2008), and adults (Manger & Motta, 2005) have been reported. However, all of these studies have severe methodological limitations such as very small sample sizes, inclusion of participants without a clinical diagnosis of PTSD, and lacking control groups.

A RCT focusing on pain in traumatized refugees showed that exercise further improved therapy outcomes of biofeedback-based CBT (Liedl et al., 2011). More

RCT with sufficient sample size are needed to determine positive effects and possible risks or adverse events when using exercise as adjunct treatment in this clinical population.

3.4.1.3. Generalized Anxiety Disorder (GAD)

In a recent RCT, a six-week program of resistance exercise or aerobic exercise (two weekly sessions) was applied in sedentary female patients with GAD. Compared to a wait list control, reductions of anxiety-tension and irritability were found in the resistance exercise group after six weeks (Herring, Jacob, Suveg & O'Connor, 2011), as well as moderately lower worry symptoms in the combined exercise groups (Herring, Jacob, Suveg, Dishman & O'Connor, 2012).

3.4.1.4. Social Phobia

Only one study targeted exercise interventions for social phobia so far, comparing exercise to mindfulness-based stress reduction (Jazaieri, Goldin, Werner, Ziv & Gross, 2012). Both interventions were associated with diminished social anxiety and depression and increased subjective well-being post-intervention and after three months.

3.4.1.5. Other Anxiety Disorders/ Mixed Samples

Two clinical trials (Merom et al., 2008; Oeland, Laessoe, Olesen & Munk-Jorgensen, 2010) found that patients suffering from different anxiety disorders achieved higher levels of physical activity and functional capacity through exercise training (Oeland et al., 2010), and that anxiety, depression, and perceived stress

declined significantly stronger in a combined CBT+exercise treatment, compared to CBT alone (Merom et al., 2008). Patients with social phobia were more likely to benefit from the exercise enhancement, compared to patients suffering from other anxiety disorders.

3.4.2. Obsessive-Compulsive Disorder (OCD)

Preliminary evidence for beneficial effects of exercise on obsessive-compulsive and concurrent anxious and depressive symptoms comes from two pilot studies. In patients stably medicated with selective serotonin-reuptake-inhibitors (SSRIs), reductions in self-reported OCD symptoms and depression after six weeks of walking intervention and at one-month-follow-up were found, as well as temporarily reduced anxiety scores (Lancer, Motta & Lancer, 2007). Combining behavioral therapy or pharmacotherapy with a 12-week moderate aerobic exercise program, the second study reported reduced OCD symptom severity at the end of the treatment, and up to 6 months later (Brown et al., 2007). After each 20-40 minutes training session, patients reported significantly lower anxiety, negative mood, and OCD symptoms relative to the beginning of the session (Abrantes et al., 2009). This effect was particularly dominant at the beginning of the 12-week intervention and diminished as baseline levels decreased.

However, because of lacking control groups and very small sample sizes, the above-listed results need to be replicated in larger controlled studies.

3.4.3. Affective Disorders

3.4.3.1. Major Depressive Disorder (MDD)

A large number of clinical studies investigated exercise-induced decreases in depressive symptoms, negative affect, and sleep disturbances, and these findings where summarized in several reviews (e.g. Dinas, Koutedakis & Flouris, 2011). In a recent Cochrane review (Rimer et al., 2012), meta-analyses were conducted over 30 RCT which either compared an exercise intervention with no treatment (waitlist, placebo, no-treatment), or with any other type of intervention (psychotherapy, pharmacotherapy, alternative therapies), or exercise-augmented treatment vs. treatment alone. Overall, a moderate clinical effect was found, when exercise was compared to no-treatment or a control treatment. Contrasting exercise interventions to cognitive therapy (six trials) or antidepressants (three trials), no significant differences in the reduction of depressive symptoms were found at the end of treatment, indicating that exercise was as effective as these standard treatments. Considering only studies with adequate allocation concealment, intention-to-treat analysis and blinded outcome assessment, only a small effect in favour of exercise was found. Follow-up data from seven trials also indicated a small long-term benefit of exercise interventions. Mixed and resistance exercise showed larger effect sizes (but also larger confidence intervals) than aerobic exercise.

In contrast to studies on dementia and mild cognitive impairment (MCI; see 3.4.7.), exercise failed to improve neurocognitive functions in depressed middle-aged and older adults, compared to sertraline and placebo (Hoffman et al., 2008). Some

studies, however, reported normalized BDNF levels after acute exercise in remitted MDD patients (Laske et al., 2010).

3.4.3.2. Bipolar Disorder (BD)

Bipolar patients experience faster exhaustion during moderate aerobic exercise than healthy controls (Shah et al., 2007). Two studies investigated the effects of regular aerobic exercise training (Edenfield, 2007; Ng, Dodd & Berk, 2007), indicating that exercise interventions (both elective and prescribed) are feasible for BD patients, and decrease stress, depressive and anxious symptoms (Wright, Everson-Hock & Taylor, 2009). All cited studies lacked power and adequate experimental control strategies, therefore further research will need to determine potential benefits, but also limitations and risks of physical activity in this population (for detailed suggestions see Wright et al., 2009). Using semi-structured interviews, Wright and colleagues carved out subjective benefits, potential harms and barriers to exercise in BD patients, concluding that exercise is perceived to be helpful in managing mood fluctuations on the one hand, but on the other hand to inhere a certain risk of intensifying manic symptoms (Wright, Armstrong, Taylor & Dean, 2011).

Other reviews discussed exercise-induced changes in neurotransmission in BD (Alsuwaidan, Kucyi, Law & McIntyre, 2009), exercise as a possible treatment for neurocognitive dysfunction in BD (Kucyi, Alsuwaidan, Liauw & McIntyre, 2010), and reductions of allostatic load by exercise (Sylvia et al., 2010).

3.4.4. Eating Disorders (ED)

As in BD, the role of physical activity and exercise in ED is ambivalent, displaying positive aspects such as weight loss in patients with binge eating disorder (BED), or prevention of bone mass loss in anorexia nervosa (AN), and negative aspects like excessive physical activity with compulsive features, deteriorating therapy outcomes (Bratland-Sanda et al., 2010).

3.4.4.1. Binge Eating Disorder (BED)

In BED, the promotion of exercise is essential, given that most patients tend to not exercise at all (Hrabosky, White, Masheb & Grilo, 2007). Of the two studies addressing therapeutic effects of exercise in BED, one found moderately reduced weight and depression scores after six months of moderate exercise intervention (walking) compared to a control group (Levine, Marcus & Moulton, 1996), and the other one reported significantly larger reductions in body mass index (BMI), depression scores, and binge episodes up to 12 months of combined CBT+exercise treatment (Pendleton, Goodrick, Poston, Reeves & Foreyt, 2002). Interestingly, the second study revealed positive effects despite sub-optimal exercise compliance, with patients' activity levels returning to baseline immediately after the end of treatment. This observation is in line with findings suggesting that the perceived effects of being active may be more relevant than actual fitness gains (Plante, 1999).

3.4.4.2. Bulimia Nervosa (BN)

The only study published for BN compared exercise to CBT treatment and found that exercise was as effective as CBT in reducing the “Bulimia” & “Body dissatisfaction” subscales of the Eating Disorder Inventory (EDI), and outreached CBT in terms of “Drive for thinness” and bulimic behavior up to 18 months after discharge (Sundgot-Borgen, Rosenvinge, Bahr & Schneider, 2002).

3.4.4.3. Anorexia Nervosa (AN)

Reviewing six studies on the effects of exercise in AN, Zuncker and colleagues concluded that exercise programs with light to moderate intensity seem to have the potential to reduce obligatory attitudes and beliefs towards exercise, reduce emotional stress, protect bone mass, and enhance weight gain (Zunker, Mitchell & Wonderlich, 2010). One additional recent study found neither beneficial nor detrimental effects of a 12-week resistance training program in teenage anorectic patients (del Valle et al., 2010). Since none of the studies did satisfy RCT-criteria (lacking randomization (one trial), quasi-experimental design (one trial)) or had insufficient sample sizes (four trials), further research is needed in this patient group.

3.4.5. Substance Use Disorders (SUD)

3.4.5.1. Nicotine Dependence

For nicotine dependence, there is evidence from a large number of RCT that exercise, combined with CBT and/or nicotine replacement therapy, has a complementary benefit on therapy outcomes in smoking cessation (see Ussher et

al., 2008; Zschucke, Heinz & Ströhle, 2012). This effect mainly relies on acute relief of cigarette craving, which helps to prevent relapse. In order to successfully support patients, exercise programs should begin prior to smoking cessation, have rather high intensities, a minimum duration of approximately ten weeks, and promote exercise as a coping strategy for acute mood-regulation and craving-reduction (Ussher et al., 2008).

3.4.5.2. Alcohol and Drug Dependence

In contrast, evidence is much weaker for the efficacy of exercise in alcohol and drug rehabilitation (see review by Zschucke et al., 2012). Most published studies did not employ adequate control groups, had too small sample sizes, non-generalizable populations like homeless veterans, heavy-drinking college students without clinical diagnosis, or mandatorily treated patients, or no intention-to-treat-analyses to correct for the high number of dropouts.

However, there is preliminary evidence for additional benefits of exercise in terms of abstinence, concurrent depression and anxiety symptoms, supported by a large number of preclinical studies (Smith & Lynch, 2011). Future RCT with sufficient sample sizes and controlled designs are necessary to confirm or disprove these findings. Besides effects specific for exercise, different mechanisms of action (structured social events, general lifestyle modifications, a non-substance use related social environment) have been discussed in the literature (Read & Brown, 2003) and should be investigated in the context of SUD.

3.4.6. Schizophrenia and Psychosis

Compared to standard care, stronger (yet non-significant) reductions in body fat, BMI, and positive and negative symptoms were found after 16 weeks of treadmill training in one study (Beebe et al., 2005). Another study combined 12 weeks of aerobic and strength training, finding significant improvements in the total *Mental Health Inventory* score in the exercise group compared to standard care, which were correlated with increased functional capacity (Marzolini, Jensen & Melvielle, 2009). One additional quasi-experimental study found significant reductions in positive and negative symptoms after ten weeks of moderate aerobic exercise compared to standard therapy (Acil, Dogan & Dogan, 2008). A recent study demonstrated that one possible mechanism of action in schizophrenia is exercise-induced neuroprotection/neurogenesis (Pajonk et al., 2010). This study not only found exercise-induced decreases in positive and negative symptoms, but also increases in hippocampal volumes after three months of aerobis exercise. Those increases also were positively correlated with fitness increases (Pajonk et al., 2010).

Recently, a couple of studies investigated the effects of yoga on positive and negative symptoms in schizophrenia, and a review of three RCT (Vancampfort et al., 2012) concluded that yoga was more effective than exercise with regard to symptom reduction. Acutely, 30 min of exercise or yoga were found to reduce state anxiety and distress (Vancampfort et al., 2011).

3.4.7. Dementia and Mild Cognitive Impairment (MCI)

Several prospective studies found that high levels of physical activity seem to delay the onset of dementia (see Hamer & Chida, 2009 for a review). Since improvements in strength and endurance after training were found in cognitively impaired patients as well as healthy controls (Heyn, Johnson & Kramer, 2008), physical activity interventions are generally feasible in this population.

3.4.7.1. Mild Cognitive Impairment (MCI)

Several studies investigated the impact of physical activity interventions in elderly individuals with MCI, reporting heterogeneous results. A recent review concluded that exercise interventions of all types are beneficial to slow down cognitive decline, and that the best effects can be found with moderate intensity exercise (e.g. brisk walking) for at least 30 min on five days per week (Denkinger, Nikolaus, Denkinger & Lukas, 2012). Interventions with different types of physical activity and a group setting seem to be particularly helpful in this population. In one study, it became evident that partial improvements in memory and attention occurred only in subjects with greater exercise adherence (van Uffelen, Chin, Hopman-Rock & van Mechelen, 2007).

3.4.7.2. Alzheimer's Disease (AD)

For AD, preliminary evidence suggests that exercise interventions may improve communication performance (Friedman & Tappen, 1991), Mini Mental State Examination (MMSE) scores and verbal fluency (van de Winckel, Feys, de Weerdt & Dom, 2004), and disruptive behavior (Holliman, Orgassa & Forney, 2001). Four

RCT (Kemoun et al., 2010; Rolland et al., 2007; Santana-Sosa, Barriopedro, Lopez-Mojares, Perez & Lucia, 2008; Stevens & Killeen, 2006) found that physical activity slowed down and partially reversed the decline in activities of daily living performance and progression of the cognitive symptoms related to dementia, in contrasts to one older study which did not find improvements in functional ability (Francese, Sorrell & Butler, 1997).

Potential neurophysiological mechanisms and target transmitter systems of exercise interventions in cognitive decline and AD are summarized in a recent review (Foster, Rosenblatt & Kuljis, 2011).

3.5. Conclusions and Future Directions

Although a number of studies yield positive results for the effectiveness of exercise as an adjunct treatment, evidence is limited for most psychiatric disorders. Generally, studies using equal contact control groups revealed smaller effects than studies comparing physical activity with no intervention. This leads to the assumption that unspecific effects such as therapeutic contact, social support, and distraction may drive some of the effects of lower intensity exercise in particular, which is in line with epidemiological findings (Harvey et al., 2010). Cost-efficacy cannot be estimated for any group of disorders yet. Future studies should consider risks and adverse effects, as well as benefits of exercise. Precise description of conditions, standardized interventions, validated assessment strategies, adequate randomization and control conditions, and power estimations are essential to obtain meaningful results and to allow for the calculation of effect sizes in meta-analyses.

However, some conclusions can be drawn concerning frame conditions which can make exercise a promising intervention for mental disorders: Studies that followed public health recommendations (Pate et al., 1995) concerning the intensity and duration of their exercise intervention are more likely to find significant clinical improvements. Patients' compliance during the exercise program and continuation after program termination were found to be more relevant for treatment outcomes than actual fitness gains (Murphy, Pagano & Marlatt, 1986; Plante, 1999). Social support seems to be crucial for exercise adherence and positive effects of exercise (Harvey et al., 2010; Moore, Moore & Murphy, 2011), as may be time structure, therapeutic contact, and positive reinforcement (Read & Brown, 2003). There is evidence that indoor/outdoor activity may have differential effects on mood states (Coon et al., 2011). Professional supervision and training management should be provided, especially in the beginning, and physical activity and exercise should be integrated into psychotherapy (e.g. using training and mood diaries). Recent studies indicate that training effects and mood improvements can also be achieved using internet- or telecommunication-based support (Mailey et al., 2010; Sparrow, Gottlieb, DeMolles & Fielding, 2011). Caregivers providing exercise should be aware of differential acute effects depending on training history and actual fitness: trained subjects usually experience greater improvements in vigor, positive affect, and fatigue, than non-trained subjects (e.g. Hoffman & Hoffman, 2008; Petruzzello, Jones & Tate, 1997). Besides physical exercise, "mindful exercise interventions", such as yoga, are constantly gaining attention as adjunct treatment, e.g. in depression and anxiety (Saeed, Antonacci & Bloch, 2010), schizophrenia (see 2.4.6.), eating disorders (Carei, Fyfe-Johnson, Breuner & Brown, 2010), and

smoking cessation (Bock et al., 2012; Elibero, Janse Van Rensburg & Drobes, 2011). Also, martial arts were found to have favorable acute effects in depressed patients (Bodin & Martinsen, 2004).

3.5.1. Implications for Future Research

In exercise research, blinding of the patients is a general problem: the patients know that exercise is supposed to make them feel better, resulting in a potential bias (Rosenthal effect), which points out the need for adequate and credible control interventions. The dose-response relationship remains unclear for most mental disorders (except for MDD and some aspects of anxiety), as well as the most effective type of exercise for each disorder group. Costs, efficacy, risks, adverse events, and contraindications of exercise interventions need to be specified. Finally, strategies are needed to enhance motivation of patients during the program and after program termination (see Ekkekakis et al., 2011).

4. Article II: Exercise in the Therapy of Substance Use Disorders

A slightly adapted version of this chapter has been published as:

Zschucke E., Heinz A., Ströhle A. (2012). Exercise and physical activity in the therapy of substance use disorders. *The Scientific World Journal* , 901741; doi: 10.1100/2012/901741.

4.1. Abstract

Exercise and physical activity are constantly gaining attention as adjuvant treatment for substance use disorders, supplementing classical pharmacological and psychotherapeutic approaches. The present work reviews studies addressing the therapeutic effects of exercise in alcohol abuse and dependence, nicotine abuse and dependence, as well as illicit drug abuse and dependence. In the field of smoking cessation, evidence is strong for exercise as an effective adjuvant treatment, whereas no generalizable and methodologically strong studies have been published for alcohol and drug treatment so far, allowing only preliminary conclusions about the effectiveness of exercise in these disorders. A couple of potential mechanisms are discussed, by which exercise may act as an effective treatment, as well as future directions for studies investigating exercise as a treatment strategy for substance use disorders.

4.2. Introduction

Substance use disorders (SUD), both abuse and dependence, are a common mental health problem with 12-month-prevalences ranging from 3.8 - 5.6%

(Wittchen et al., 2011), causing immense social and economic costs due to physical, psychological and social comorbidities and consequences (rank 5 of disability adjusted life years (DALY) in the European Union, see Wittchen et al., 2011).

Despite increasingly effective psychopharmacologic and psychotherapeutic intervention strategies, relapse rates are commonly high, resulting in a need for adjuvant therapies that help maintaining abstinence and target physical conditions related to the SUD.

4.2.1. Exercise as Preventive and Therapeutic Intervention

In several cross-sectional studies, levels of exercise and physical activity were found to be negatively associated with different mental disorders (e.g. Goodwin, 2003), and higher levels of physical activity were longitudinally associated with lower onsets of mental disorders (Ströhle et al., 2007). SUD (alcohol dependence, nicotine dependence, and any SUD) were shown to be less prevalent in physically active subjects (Ströhle et al., 2007), and one longitudinal study reported a preventive action of regular physical activity with regard to alcohol intoxications, alcohol-related problems and drug use (Korhonen, Kujala, Rose & Kaprio, 2009).

Additionally, many studies have demonstrated therapeutic effects of exercise interventions in other mental disorders, especially depression and anxiety disorders (Broocks et al., 1998; Mead et al., 2009; Merom et al., 2008; Wipfli et al., 2008). physical activity and exercise may also help to reduce chronic physical

conditions which are frequent in patients with mental disorders, especially SUD (Chacon et al., 2011; Lin, Zhang, Leung & Clark, 2011).

This systematic review aims at subsuming empirical evidence for therapeutic effects of physical activity and exercise in SUD, and arriving at conclusions concerning further research and clinical practice.

4.3. Methods

The databases PubMed, Medline and Web of Science were searched for studies in English or German published between 1970 and 2011 which had investigated any form of exercise as therapeutic intervention strategy. Search terms included “exercise”, “physical activity”, “substance use disorder”, “dependence”, “abuse”, “illicit drugs”, “alcohol”, “nicotine”, “cannabis”, “opiate”, “stimulant”, and “cocaine”, in the respective languages.

The bibliographies of all retrieved articles were searched for additional references.

Studies exclusively focusing on exercise as a prevention strategy were excluded.

For nicotine abuse and dependence, only randomized-controlled trials (RCTs) were included into this review. Since the literature was very limited concerning RCTs on alcohol abuse and dependence as well as illicit drug abuse and dependence, studies with inadequate control strategies and small samples were also included into this review.

4.4. Results

In the following sections, studies will be reviewed separately for different SUD, due to the heterogeneity concerning study designs, methods and results.

4.4.1. Nicotine Abuse and Dependence

Smoking is very prevalent both in the general population and as a comorbid mental disorder (Schroeder & Morris, 2010). Unassisted smoking cessation attempts are mostly unsuccessful, with success rates ranging from 3-5% in the 6-12 months follow-up (Hughes, Keely & Naud, 2004). Success rates can be increased by behavioral therapy, nicotine replacement therapy (NRT) and medication (e.g. buproprion, varenicline (Batra, 2011).

Since a large number of studies investigated the effects of exercise during and after smoking cessation, only RCTs are listed in table 2 (see end of section 4.4.1.).

Seventeen RCTs were identified. Fourteen of these trials studied otherwise healthy subjects (Bock, Marcus, King, Borrelli & Roberts, 1999; Chaney & Sheriff, 2008; Hill, 1985; Hill, Rigdon & Johnson, 1993; Kinnunen et al., 2008; Marcus et al., 1999; Marcus, Albrecht, Niaura, Abrams & Thompson, 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007; Prochaska et al., 2008; Russell, Epstein, Johnston, Block & Blair, 1988; Ussher, West, McEwen, Taylor & Steptoe, 2003; Williams et al., 2010), one included patients after acute myocardial infarction (Taylor, Houston-Miller, Haskell & Debusk, 1988), another one studied depressed patients (Vickers et al., 2009), and one trial investigated smoking cessation in abstinent alcohol-dependent subjects (Martin et al., 1997).

Purely female samples were studied in 11 trials (Bock et al., 1999; Chaney & Sheriff, 2008; Kinnunen et al., 2008; Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007; Russell et al., 1988; Vickers et al., 2009; Williams et al., 2010), purely male samples in one trial (Taylor et al., 1988), and mixed samples in five trials (Hill, 1985; Hill et al., 1993; Martin et al., 1997; Prochaska et al., 2008; Ussher et al., 2003). The durations of exercise interventions ranged from 5-26 weeks, and four studies used exercise counseling instead of exercise interventions (Martin et al., 1997; Prochaska et al., 2008; Ussher et al., 2003; Vickers et al., 2009).

Exercise interventions were either compared to a standard intervention without exercise component (Chaney & Sheriff, 2008; Hill, 1985; Marcus et al., 1991; Taylor et al., 1988), to CBT (Prapavessis et al., 2007), to medication and/or NRT (Hill et al., 1993; Martin et al., 1997; Prochaska et al., 2008), or to a contact control intervention (Bock et al., 1999; Kinnunen et al., 2008; Marcus et al., 1999; Marcus et al., 1995; Marcus et al., 2005; Russell et al., 1988; Ussher et al., 2003; Vickers et al., 2009; Williams et al., 2010). All studies reported smoking-related outcomes such as cigarette craving, withdrawal symptoms, and abstinence and relapse rates, respectively. Compared to a standard intervention, exercise was found to improve one or multiple smoking-related outcomes in all four studies. When compared to CBT, exercise was found to be as effective concerning abstinence rates (and especially effective when combined with NRT). Two studies reported similar effects for exercise and medication / NRT (Hill et al., 1993; Prochaska et al., 2008), whereas one study (Martin et al., 1997) found exercise-augmentation of CBT to be

superior to NRT-augmentation at post-treatment and similarly effective at 1-year follow-up. Comparing exercise to a control intervention, three studies did not find positive effects of exercise on smoking-related outcomes (Marcus et al., 2005; Russell et al., 1988; Vickers et al., 2009), three studies reported a trend towards positive exercise effects (Kinnunen et al., 2008; Marcus et al., 1995; Williams et al., 2010), and two found positive exercise effects (Marcus et al., 1995; Ussher et al., 2003).

Evidence is also mixed for secondary outcomes like depression, tension, stress, anxiety, etc. on the one hand, and weight gain on the other hand. Concerning emotional changes, two studies reported positive acute or long-term changes (Bock et al., 1999; Ussher et al., 2003), two studies did not find exercise-induced improvements (Vickers et al., 2009; Williams et al., 2010), and one study found even higher tension and anxiety in the exercise group at one follow-up time-point (Russell, Epstein, Johnston, Block & Blair, 1988). Smoking cessation-related weight gain was lower in the exercise condition of three studies (Chaney & Sheriff, 2008; Marcus et al., 1999; Prapavessis et al., 2007) and higher in one study (Vickers et al., 2009), while three studies (Marcus et al., 2005; Ussher et al., 2003; Williams et al., 2010) reported similar weight gain in exercise and control conditions.

Taken together, evidence is mixed, but some preliminary conclusions can be drawn concerning favorable effects of exercise intervention in smoking cessation. First, exercise intervention show the clearest effects when compared to standard treatment, which become more unequivocal, when exercise is compared to control

groups which offer a similar amount of social support, therapeutic contact, and preoccupation with health-related topics. Second, by the majority studies have shown that exercise interventions are as effective as other standard interventions for smoking cessation, such as CBT or NRT / medication. The intensity and frequency of training may be a key point: Studies using ≥ 3 training sessions per week (e.g. Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Marcus et al., 2005; Prapavessis et al., 2007) were likely to find fitness gains in the exercise group, whereas 1-2 times per week seem not to be sufficient to achieve fitness gains (Kinnunen et al., 2008). Although objective assessment of fitness changes were not performed in all studies, five studies that reported fitness gains also reported favorable smoking outcomes (Hill, 1985; Marcus et al., 1999; Marcus et al., 1991; Marcus et al., 1995; Taylor et al., 1988) compared to three which did not (Marcus et al., 2005; Prapavessis et al., 2007; Prochaska et al., 2008), one study reported positive smoking outcomes despite identical increases of fitness in all groups (Kinnunen et al., 2008), and two studies found neither fitness increases nor favorable smoking outcomes (Russell et al., 1988; Vickers et al., 2009).

Importantly, four studies concluded that exercise adherence rather than the admission to an exercise intervention per se predicted smoking abstinence (Hill et al., 1993; Marcus et al., 2005; Prochaska et al., 2008; Williams et al., 2010), suggesting an important role of motivation, individual resources, and self-efficacy.

One crucial aspect lies in the moment of implementation of the exercise program: one study demonstrated that patients may be overstrained and react with negative affect, when smoking cessation and the exercise intervention are realized simultaneously (Batra, 2011). The implementation of exercise a couple of weeks

prior to the quit date may be advisable for another reason: exercise can serve as a skill to acutely reduce withdrawal and craving symptoms.

A couple of studies addressed this issue (see reviews by Taylor, Ussher & Faulkner, 2007; Ussher et al., 2008). In most cases, temporarily abstinent smokers were compared after a short bout of exercise vs. a control condition (e.g. passive waiting or video). Compared to the control conditions, exercise was found to

- reduce the desire to smoke (effect sizes 0.53 - 2.2 during and after exercise, and 0.14 - 0.74 at the latest follow-up time point)
- reduce withdrawal symptoms (stress, anxiety, tension, irritability, restlessness) and negative mood
- reduce the anticipation of smoking being rewarding and pleasurable
- increase the latency period until the next cigarette (effect size 0.85-1.20)

The acute exercise interventions ranged from 5 min of isotonic muscle contraction to a brisk one-mile walk. Effects generally appeared very quickly (faster than with oral NRT), lasted between 5 and 50 min, and were not solely explained by distraction, as controlled by different control conditions.

Table 4.1. Randomized-Controlled Trials Investigating Exercise as an Intervention in Nicotine Dependence

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Hill (1985)	N=36 untrained smokers (f, m) >10 cig/day ethnicity not reported	Duration: 5 weeks Group counselling smoking cessation program (10 sessions)	Duration: 5 weeks 2 times / week 30 min of supervised training + instruction to be as physically active as possible, esp. in case of craving Aerobic EX (type and intensity not reported)	Standard therapy	Trend towards lower number of smoked cigarettes and higher percentage of abstinent patients (not significant) Higher PA (self report) at the end of treatment and after 1, 3, 6 months	- Small N - Lack of equal contact time control - Lack of objective measurement of training effects - EX duration too short to improve fitness - no effect size reported
Russell et al. (1988)	N=42 heavy smokers (f) 23±7 cig/day ethnicity not reported	Duration: 1+9 weeks behavioral smoking cessation program (4x1h during first week) + 9 weeks of maintenance	Duration: 9 weeks 3 times / week (once supervised, twice alone) 20-30 min of walking/ jogging at 70-80% of max HR	A: One 30-min educational meeting per week B: One 30-min contact control meeting per week	Abstinence rates comparable in all groups at end of treatment and after 3, 6, 18 months No increase in fitness in EX group Higher tension/anxiety in EX group after 6 months	- Small N - Purely female sample - EX compliance only assessed by self-report - no effect size reported
Taylor et al. (1988)	N=160 in-patients (m), 10-14 days after acute myocardial infarction (N= 68 smokers) ethnicity not reported	treadmill EX testing	Duration: 3-26 weeks A: home EX training B: medically-supervised group EX Type, frequency, duration and intensity not reported	Standard therapy	No group differences concerning abstinence and relapse rates, but lower number of smoked cigarettes after 26 weeks in groups A and B significant fitness increases in groups A and B	- Lack of clarity concerning type and intensity of EX intervention - Nonuniform training durations - No smoking cessation intervention - Special sample and high dropout rate due to cardiac events - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Marcus et al. (1991)	Pilot study N=20 untrained smokers (f) >10 cig/day ethnicity not reported	Duration: 4 weeks 8 sessions of behavioral out-patient smoking cessation treatment	Duration: 15 weeks 3 times / week supervised training 30-45 min aerobic training (walking, rowing, or cycle ergometry) at 70-85% max HR Beginning 3 weeks prior to smoking cessation program	Standard therapy	Significantly higher abstinence rates after 1, 3 and 12 months significant increases in fitness	- Very small N - Purely female sample - Lack of equal contact time control - no effect size reported
Hill et al. (1993)	N=82 heavy smokers (f, m) ≥ 30 y of smoking, 28±14 cig/day ethnicity not reported	Duration: 12 weeks 12 sessions of behavioral training	Duration: 12 weeks Weeks 1-4: 3 times / week Weeks 5-8: 2 times / week Weeks 9-12: once a week + instruction for individual training 45 min walking at 60-70% of HR-R A: EX + behavioral training B: EX alone	C: Standard therapy D: Standard therapy + NRT	Significantly higher abstinence rates in groups with behavioral training (A, C, D) Trend towards higher abstinence in regular vs. non-regular walkers within group B	- Low compliance concerning EX program - Lack of objective measurement of training effects - Lack of blinding: therapists = investigator in each group - no effect size reported
Marcus et al. (1995)	N=20 untrained smokers (f) 8-40 cig/day ethnicity not reported	Duration: 12 weeks 12 sessions of behavioral smoking cessation program	*(as in [15])* Duration: 15 weeks 3 times / week supervised training 30-45 min aerobic training (walking, rowing, or cycle ergometry) at 70-85% max HR Beginning 3 weeks prior to smoking cessation program	One 30-min educational meeting per week (12 sessions, same contact time)	Descriptively increased 7-day-abstinence at end of therapy and at 1&3 months follow-up Significant fitness gains at end of treatment	- Very small N - Purely female sample - No statistical data analysis - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

Article II

Author, Year	Sample charac-teristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Martin et al. (1997)	N=205 smokers of > 10 cig/day (f, m) with history of alcohol dependence (≥ 3 months of alcohol abstinence) > 90% caucasian	Duration: 8 weeks CBT smoking cessation program or standard ALA-intervention + „Nicotine Anonymous“ meetings	CBT counseling + EX ACSM-based EX prescriptions given during last week of CBT: engaging in 3 times of 15-45 min walking per week and using the laboratory EX equipment	A: CBT counseling + NRT (2-12 mg / day) B: Standard ALA-intervention + „Nicotine Anonymous“ meetings	Significantly higher validated abstinence rates post-treatment (not maintained at 6- or 12-month follow-up) Relapse rates for alcohol/drugs not significantly different between groups	- Late implementation of EX program - EX training not supervised - Lack of objective measurement of training effects - no effect size reported
Marcus et al. (1999)	N=281 untrained smokers (f) 23±10 cig/day ethnicity not reported	Duration: 12 weeks 12 sessions of behavioral smoking cessation program	Duration: 12 weeks 3 times / week supervised training 30-45 min aerobic training (walking, rowing, or cycle ergometry) at 60-85% HR-R Beginning 3 weeks prior to smoking cessation program	One 30-min educational meeting per week (12 sessions, same contact time)	Higher abstinence rates at all post-quit time points (8, 20, 60 weeks) Lower weight-gain at end of treatment (not maintained at follow-up) Significant fitness gains	- Purely female sample - Significant group differences in initial body weight (EX > Control) - no effect size reported
Bock et al. (1999)	Two sub-samples of N=62 untrained smokers (f) > 90% White	as in Marcus et al. (1999)	as in Marcus et al. (1999)	as in Marcus et al. (1999)	Significant positive acute effects of EX on mood, craving, and withdrawal symptoms (comparison pre-post EX sessions) No significant long-term effects of EX on mood	- Purely female sample - Unequal group sizes (44:18) - Only comparisons at baseline and 12 weeks, no time course reported - no between-group comparison reported, but paired t-tests within groups - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition (s)	Outcome variables & findings Exercise > control condition	Comments
Ussher et al. (2003)	N=299 untrained smokers (f, m) 22±9 cig/day predominantly white sample (88%)	Duration: 6 weeks NRT (15 mg/ day) + one weekly CBT group session	EX counseling: Prescription of 5-30 min of EX on ≥ 5 days per week EX recommended as self-control strategy	Health education advice (same contact time)	Significantly higher abstinence rates after 1 + 2 weeks (no difference after 3,4,6 weeks) Reductions in tension, stress, irritability, restlessness 1 week after end of treatment (partly maintained throughout follow-up) Significantly higher self-reported PA at 1,4,6 weeks post-quit No differences concerning weight gain	- No objective measurement of EX adherence or training effects - no effect size reported
Marcus et al. (2005)	N=217 untrained smokers (f) 21±9 cig/day predominantly white sample (82.5%)	Duration: 8 weeks CBT smoking cessation program (8 sessions) + NRT as necessary	Duration: 8 weeks once per week: supervised training + prescription to individually train 4 times / week 30-45 min aerobic training at 50-69% max HR (resulting in 165 min / week of moderate intensity training) Beginning 1 week prior to quit day	Health education advice (same contact time)	No differences in continuous abstinence or 7-day point prevalence of smoking at post-treatment, and 6 or 12 months follow-up, except for 7-day point prevalence of smoking at 6-month follow-up(EX>Control), BUT Amount of EX = significant predictor for abstinence Significant fitness gains No differences concerning weight gain	- Inclusion of light smokers (≥ 5 Zig/Tag) - Extremely low abstinence rates in whole sample (<1% after 12 months) - no effect size reported
Prapavessis et al. (2007)	N=142 untrained smokers (f) >10 cig/day ethnicity not reported	Duration: 12 weeks Comparison of CBT and EX, each with and without NRT	Duration: 12 weeks 3 times / week supervised training 45 min aerobic training (walking, rowing, or cycle ergometry) at 60-75% HR-R Beginning 6 weeks prior to quit day A: with NRT B: without NRT	C: CBT with NRT D: CBT without NRT	No significant differences in abstinence rates after 3 and 12 months Short-term improvement of abstinence up to 6 weeks by nicotine replacement (both in EX and CBT) Significant fitness gains after 12 weeks (back to baseline at 12-month follow-up) Delayed weight gain in EX conditions at end of treatment	- Relatively low abstinence rates in all groups after 3 and 12 months - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition (s)	Variables & findings Exercise > control condition	Comments
Chaney et al. (2008)	N=101 smokers (f) (amount of smoking not reported) ethnicity not reported	Duration: 8 weeks 1h / week of behavioral counseling + social support + NRT	Duration: 8 Wo ≥ 3 times / week 30 min of circuit training (mixed aerobic / anaerobic) in women's gym	Standard therapy	Significantly higher abstinence rates at end of treatment Significantly lower weight gain	- High dropout rate - No validation of self-reported smoking - No objective measurement of training effects - No follow-up data reported - no effect size reported
Procha-ska et al. (2008)	N=407 smokers (f, m) 19±8 cig/day mixed sample (71% Caucasian)	Identical treatment for 12 weeks: NRT + bupropion (2x150mg/ day) + 5 group-based smoking cessation sessions	Weeks 14-16: Baseline PA measurement (pedometer) Week 16-52: Relapse prevention program including two counseling sessions (at week 16 and 20) to increase steps 10% biweekly towards 10.000 steps / day A: Standard therapy + 40 weeks EX B: Standard therapy + 40 weeks EX + another 40 weeks of bupropion C: Standard therapy + 40 weeks EX + 40 weeks of placebo	D: Standard therapy without further intervention E: Standard therapy + another 40 weeks of bupropion F: Standard therapy + 40 weeks of placebo	Increase in PA predicted abstinence in week 24 Significant increase in PA in groups A-C compared to groups D-F	- Group differences in terms of abstinence not reported - Relapse prevention program was no pure EX intervention (included motivational aspects, social support, mood and weight regulation) → no adequate control group - PA increases partly due to group differences in baseline PA (D-F > A-C) - Pedometer data available from only 15% of subjects - No intention-to-treat analysis - No objective measurement of fitness gains - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

Article II

Author, Year	Sample charac-teristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Kinnu-nen et al. (2008)	N=182 untrained smokers (f) 19±8 cig/day predominantly white sample (81.5%)	Duration: 19 weeks 8 brief (10 min) weekly CBT counseling sessions + NRT	Duration: 19 weeks week 1-5: twice a week week 6-19: once a week 30 min of supervised aerobic training (tread-mill) at 60-80% max HR Beginning 3 weeks prior to quit day	A: Standard therapy (CBT counseling) B: Standard therapy (CBT counseling) + health education (same contact time)	Trend towards higher abstinence rates in EX and control group A at end of treatment and 12 month follow-up Advantage of EX and control group A in preventing early relapse (at 1 week) Significant fitness increases in all groups	- High dropout rate (only 55/182 completed treatment - High relapse rates - No selective training effect in EX group - no effect size reported
Willi-ams et al. (2010)	Pilot study: N=60 untrained smokers (f) >5 cig/day 85% non-hispanic white	Duration: 8 weeks Smoking cessation program with brief (15-20 min) counseling sessions + NRT	Duration: 8 weeks 3 times / week 50 min of aerobic training (treadmill) up to 70% of max HR minimal interaction with groups members and staff	Wellness videos (3 times / week 30 min) minimal interaction with groups members and staff	Trend towards higher prolonged abstinence and lower 7-day point prevalence at post-treatment No significant group differences with regard to withdrawal symptoms, affect, and weight gain Correlation of abstinence rates and attended EX sessions Subjects with high self-efficacy more likely to benefit from EX	- Small N, but high compliance - Changes in fitness not reported - EX behavior was not maintained after end of treatment - no effect size reported
Vickers et al. (2009)	N=60 untrained smokers (f) with current depression 21±8 cig/day (almost purely white sample)	Duration: 10 weeks Behavioral counselling for smoking cessation (10 min/ week) + NRT (21 mg/ day)	Duration: 10 weeks 30 min of CBT-based EX counseling once per week, aiming at increasing PA to 30 min/day on ≥ 5 days / week and using EX to overcome acute craving	30 min of general health counseling once per week (same contact time)	No group differences with regard to abstinence, mood and depression More PA reported in EX group, but no changes in fitness measures Significant weight gain only in EX group (!)	- Concurrent treatment with different medication and psychotherapy for depression - No direct group comparisons reported (just within pre-post differences) - no effect size reported

Abbreviations: ALA = American Lung Association, CBT = cognitive-behavioral therapy, cig = cigarettes, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, NRT = nicotine replacement therapy, PA = physical activity

4.4.2. Alcohol Abuse and Dependence

For the post-acute alcohol treatment following detoxication, several psychotherapeutic interventions have proven effectiveness, e.g. brief interventions which include psychoeducation, motivational interviewing, and counseling, as well as cognitive-behavioral interventions including cue exposure, self-management strategies, and coping skills (Haber, Lintzeris, Proude & Lopatko, 2009).

Furthermore, psychopharmacological treatment with acamprosate or naltrexone significantly increases abstinence rates in the long run (Kienast & Heinz, 2005). However, the rates of relapse and physical and mental comorbidities are rather high, pointing out the need for adjuvant therapies and long-term life-style modifications.

Compared to smoking, evidence is more limited in alcohol abuse and dependence, and RCTs are extremely rare. Nine studies were identified that investigated the effects of exercise programs on abstinence, relapse rates, and/or different associated somatic, emotional, and psychological outcomes (see table 3 at the end of section 4.4.2.).

In these studies, treatment duration ranged from four weeks (Gary & Guthrie, 1972; Palmer, Vacc & Epstein, 1988) to four months (Weber, 1984), with training frequencies ranging from three to five times a week. exercise interventions were mostly aerobic (Abrantes et al., 2009; Donaghy, 1997; Frankel & Murphy, 1974; Gary & Guthrie, 1972; Murphy, Pagano & Marlatt, 1986; Palmer et al., 1988; Sinyor, Brown, Rostant & Seraganian, 1982; Weber, 1984), but one study used a

holistic “Body-Mind” intervention which impedes conclusions about exercise alone (Ermalinski, Hanson, Lubin, Thornby & Nahormek, 1997).

Six studies reported drinking episodes, craving, or days of abstinence as substance-related outcomes (Brown et al., 2009; Donaghy, 1997; Ermalinski et al., 1997; Gary & Guthrie, 1972; Murphy et al., 1986; Sinyor et al., 1982), and four of these studies found significantly stronger improvements in the exercise group (Brown et al., 2009; Ermalinski et al., 1997; Murphy et al., 1986; Sinyor et al., 1982), whereas two studies did not find any group differences (Donaghy, 1997; Gary & Guthrie, 1972). Secondary psychological outcomes like depression, anxiety, stress, self-concept, locus of control, and sleep quality, which increased at least in one of the exercise conditions, were reported in four studies (Frankel & Murphy, 1974; Gary & Guthrie, 1972; Palmer et al., 1988; Weber, 1984). In contrast, two studies did not find group differences concerning the reduction of depression (Donaghy, 1997; Ermalinski et al., 1997) and anxiety (Donaghy, 1997).

Significant increases in fitness were reported in eight studies (Brown et al., 2009; Donaghy, 1997; Ermalinski et al., 1997; Frankel & Murphy, 1974; Gary & Guthrie, 1972; Murphy et al., 1986; Sinyor et al., 1982; Weber, 1984), which were preserved at 5-month follow-up in one study (Donaghy, 1997), whereas one other study (Palmer, Vacc & Epstein, 1988) did not find significant changes in fitness.

Only one study fulfilled criteria for a RCT (Donaghy, 1997), whereas the other studies had several methodological limitations. Seven studies included control groups (Donaghy, 1997; Ermalinski et al., 1997; Gary & Guthrie, 1972; Murphy et al., 1986; Palmer et al., 1988; Sinyor et al., 1982; Weber, 1984), whereas one study was a one-group pre-post comparison (Frankel & Murphy, 1974), and one

study (Brown et al., 2009) did not employ control conditions at all. Random assignment of study participants to a treatment condition was performed in four studies (Donaghy, 1997; Gary & Guthrie, 1972; Murphy et al., 1986; Weber, 1984), whereas one study used a time-staggered control group (Palmer et al., 1988), another study compared samples from different centers (Sinyor, Brown, Rostant & Seraganian, 1982), and one study did not state their assignment strategy (Ermalinski et al., 1997).

Sample sizes were small in five studies (Brown et al., 2009; Gary & Guthrie, 1972; Murphy et al., 1986; Palmer et al., 1988; Weber, 1984), and none of the studies performed intention-to-treat analyses to control for the high number of dropouts. Four studies did not specify the patients' diagnoses (Donaghy, 1997; Palmer et al., 1988; Sinyor et al., 1982) or included subjects without a clinical diagnosis of alcohol abuse or dependence (Murphy et al., 1986).

In summary, so far there is only limited evidence for the efficacy of exercise interventions in alcohol rehabilitation. Most cited studies must be interpreted cautiously due to methodological limitations. However, it can be stated that three (Donaghy, 1997) or four (Palmer et al., 1988) weeks of supervised exercise may not be sufficient to induce significant additional changes in anxiety, depression, and abstinence rates, and that fitness gains are neither necessary nor sufficient to account for the behavioral and emotional changes reported in most studies.

One possible mechanism of action which is often hypothesized regarding the effects of exercise is craving reduction. One study (Ussher, Sampuran, Doshi, West & Drummond, 2004) investigated the acute effects of exercise in detoxified

patients, using a cross-over design with 10 min of either moderate or light aerobic exercise on a bicycle ergometer. During moderate exercise, significant reductions of craving were observed. However, this effect did not continue after the end of the intervention, and there was a trend towards higher baseline levels of craving in the moderate exercise condition. Therefore, the craving-reducing activity of exercise remain subject to further studies.

An additional study gives information about exercise attitudes and behaviors in a sample of day-clinic patients (Read et al., 2001). Generally, 75% of patients were interested in exercise programs, and almost half of the patients stated to exercise regularly (preferably walking, weight lifting, and cycling). exercise was appreciated for providing tension relief, stress reduction, and a more positive attitude. Barriers named by the patients included high costs, lack of motivation, time, knowledge, and confidence, and physical disability.

Hence, adequately powered RCTs are necessary to confirm or disprove beneficial effects of exercise interventions in alcohol use disorders, and to disentangle potential mechanisms of action.

Table 4.2. Studies Investigating Exercise in the Therapy of Alcohol Abuse and Dependence

Author, Year	Sample charac-teristics	Study design, standard therapy	Exercise intervention (EX)	Control condition (s)	Outcome variables & findings Exercise > control condition	Comments
Gary & Guthrie (1972)	N = 20 Alcohol-dependent patients (m) ethnicity not reported	In-patient alcohol rehab treatment Group therapy, recreation programs Duration and type of therapy not reported Random assignment to EX or Control	Duration: 4 weeks 5 times / week Incremental running program (1 mile / training day)	Standard care (Group therapy, recreation programs)	No effects with regard to drinking episodes notices by staff (no other alcohol-related outcomes reported) significant gains in cardiovascular fitness and self-cathexis scale, significantly reduced sleep disturbances	- Small N - Lack of equal contact time control - Duration and type of therapy not reported - No direct alcohol-related outcomes reported - No follow-up data reported - no effect sizes - no measures of physical health
Frankel & Murphy (1974)	N = 214 alcohol-dependent patients (m) ethnicity not reported	In-patient alcohol rehab treatment Group psycho-therapy, physical fitness program, work assignment, education, family counseling, individual therapy Duration: 12 weeks	Duration: 12 weeks 5 times / week, 1 h each Warm-up, individual strengthening activi-ties, 20 m in of cardio-vascular training (group walk or run)	none	No alcohol-related outcomes reported significant gains in cardiovascular fitness, reductions in self-reported depression and paranoia	- One-sample pre-post comparison - Lack of control condition to control for general treatment/ recovery effects - No alcohol-related outcomes reported - No follow-up data reported - no effect sizes - no measures of physical health
Sinyor et al. (1982)	N = 58 patients (m,f) (diagnoses not reported) ethnicity not reported	In-patient alcohol rehab treatment Daily group therapy led by abstinent alcoholics Type of therapy not reported Duration: 6 weeks	Duration: 6 weeks 5 times / week, 1 h each Stretching, calisthenics, muscle-strengthening EX, running or cross-country-skiing	Control group with standard care in different therapy center	At 3-month follow-up significantly higher abstinence rates (self-report, validated by family members or colleagues) Significant fitness gains	- Comparison of patients from different study centers (effects of patient or treatment characteristics interfering with effects of EX)) - Lack of randomization - no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

Author, Year	Sample charac-teristics	Study design, standard therapy	Exercise intervention (EX)	Control condition (s)	Outcome variables & findings Exercise > control condition	Comments
Weber (1984)	N = 46 alcohol-depen-dent patients (m) ethnicity not reported	In-patient alcohol rehab treatment Type of therapy not reported Duration: 4 months Randomized assignment to treatment group	Duration: 4 months 3 times / week Running with increasing intensity and duration (individually adjusted)	Standard therapy (type not reported)	No alcohol-related outcomes reported Significant training effects: almost all patients were able to run ≥ 1h at the end of treatment Significantly stronger reductions of Stress (self-developed scale),non- significant improvements regarding state- anxiety (STAI), depression, psychosomatic symptoms, coping, well-being	- Small N - Lack of equal contact time control - No alcohol-related outcomes reported - Lack of intention-to-treat analysis to correct for high dropout rate (only 26/46 patients included in analyses) - No follow-up data reported - no effect sizes - no measures of physical health
Murphy et al. (1986)	N = 48 students (m) classified as „heavy social drinkers“ ethnicity not reported	Daily Journals recording 15 different variables Duration: 16 weeks:2 weeks baseline, 8 weeks Intervention, 6 weeks follow-up Randomized assignment to condition	Duration: 8 weeks 3 times / week (+ instruction to train at least once / week on their own) 30 min of running at individual intensity	Control 1: standard intervention (daily journals) Control 2: 3 times / week supervised meditation	Significantly stronger reduction in alcohol consumption during treatment phase (also trendwise during follow-up) Only alcohol consumption on weekdays affected, not on week-ends Significant fitness gains	- Small N - Subjects without clinical diagnosis of alcohol abuse/dependence - Only self-report of drinking behavior - Drinking behavior uncorrelated with fitness gains → general lifestyle modification? - Subjects with high treatment compliance from Control 2 improved as much as subjects in EX group - no effect sizes - no measures of physical health
Palmer et al. (1988)	N = 27 „alcoholic patients“ (m,f) (diagno-ses not reported), 92% white	In-patient alcohol rehab treatment (influenced by AA-philosophy) Duration: 4 weeks	Duration: 4 weeks 3 times / week 20-30 min walking/ run-ning at 60-80% maximum HR	standard care without EX (time-staggered)	No alcohol-related outcomes reported No fitness gains in EX group Significantly lower anxiety and depression in EX group at the end of treatment	- Small N - Lack of equal contact time control - EX duration too short to improve fitness - No alcohol-related outcomes reported - No follow-up data reported - no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

Article II

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition (s)	Outcome variables & findings Exercise > control condition	Comments
Donaghy (1997)	N = 165 „alcoholic patients“ (m,f) (diagnoses not reported) ethnicity not reported	Multi-center study: in-patient and out-patient treatment programs of different kinds and durations	Duration: 3 weeks supervised EX, followed by 12 weeks home-based EX 3 times / week 30 min of aerobic and muscle-strengthening training following ACSM-guidelines	Duration: 3 weeks of supervised gentle stretching and breathing exercises, followed by 12 weeks home-based EX 3 times / week, 30 min each	No significant differences in abstinence rates significant higher improvement in power, fitness, body self-perception and self-esteem after 15 weeks Power and fitness gains maintained at 5-month follow-up Anxiety and Depression equally reduced in both groups	- Diagnoses and type of therapy not reported - Lack of intention-to-treat analysis to correct for high number of dropouts at follow-up - no effect sizes
Ermalinski et al. (1997)	N = 90 veterans (m) ethnicity not reported	In-patient alcohol rehab treatment daily group psychotherapy, didactic sessions, incentive therapy Duration: 6 weeks	Duration: 6 weeks “Body-Mind-Component” 5 times / week, 1.5h each Fitness component including Yoga, incremental jogging in place up to 20 min; other components: motivational aspects, responsibility for health elements	standard care without “Body-Mind-Component”	Significantly reduced craving in “Body-Mind-Component” group Only partial fitness gains No impact of “Body-Mind-Component” on depression, body satisfaction Significant increase of internal locus of control and responsibility for health	- No pure EX program: unclear which part of the “Body-Mind-Component” is related to reported changes - Non-generalizable sample (veterans) - no effect sizes - no measures of physical health
Brown et al. (2009)	N = 19 alcohol-dependent patients (m,f) after detoxification (mean 19 days) ethnicity not reported	pilot study, out-patient alcohol treatment program (no details reported)	Duration: 12 weeks Once per week supervised, including CBT-based EX counseling, 2-3 times / week alone 20-40 min (gradually increasing) of aerobic training (treadmill, ergo-meter) at 50-69% max HR	none	Significantly higher rate of abstinent days at end of treatment and 3-month follow-up Significantly increased fitness at end of treatment (no difference at 3-month follow-up)	- Very small N - Lack of control group, therefore effects not explained by EX alone - no effect sizes - BMI decreased, fitness increased

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

4.4.3. Illegal Substance Abuse and Dependence

Besides substitution therapy, established therapies for illicit drug abuse/ dependence include medication for relapse prevention (e.g. naltrexone), as well as different psychotherapeutic approaches (Motivational Interviewing, CBT, psychodynamic and systemic approaches, psychoeducation, and social therapy). So far, no studies satisfying RCT-criteria have been published for this specific population. However, eight studies were identified which investigated therapeutic effects of exercise in drug-dependent patients (see table 4 at the end of section 3.4.3.).

In these studies, treatment duration ranges from to two weeks (Buchowski et al., 2011) to six months (Roessler, 2010), with training frequencies ranging from several times a day (Li, Chen & Mo, 2002) to twice a week (Williams, 2000).

Six studies reported substance-related outcomes like craving, percentage of abstinent subjects, or continuous days of abstinence (Brown et al., 2010; Buchowski et al., 2011; Burling, Seidner, Robbins-Sisco, Krinsky & Hanser, 1992; Collingwood, Reynolds, Kohl, Smith & Sloan, 1991; Li et al., 2002; Roessler, 2010), which improved with treatment in all six studies. Secondary psychological and social outcomes like depression, anxiety, tension, self-concept, locus of control, employment and dwelling were reported in five studies (Burling et al., 1992; Collingwood et al., 1991; Li et al., 2002; Palmer, Palmer, Michiels & Thigpen, 1995; Roessler, 2010), which generally increased at least in one of the exercise conditions.

Fitness increases were reported in three studies (Brown et al., 2010; Collingwood et al., 1991; Roessler, 2010), whereas the other studies did either not report or find significant changes in fitness.

All studies suffer from severe methodological limitations which constrain possible conclusions. Only two studies included control groups (Burling et al., 1992; Li et al., 2002), two studies performed post-hoc classifications between improvers and non-improvers (Collingwood et al., 1991; Williams, 2000), and four studies did not employ control conditions at all (Brown et al., 2010; Buchowski et al., 2011; Palmer et al., 1995; Roessler, 2010).

Sample sizes were very small (Brown et al., 2010; Buchowski et al., 2011; Palmer et al., 1995; Roessler, 2010; Williams, 2000) or contained unequal group sizes (Burling, Seidner, Robbins-Sisco, Krinsky & Hanser, 1992) in six studies, and most studies did not perform intention-to-treat analyses to correct for the high number of dropouts.

The study participants were mostly in the post-acute phase after detoxification, except for the study by Li et al. (2002). Three studies did not specify the patients' diagnoses (Palmer et al., 1995; Williams, 2000) or included sub-clinical participants (Collingwood, Reynolds, Kohl, Smith & Sloan, 1991). Furthermore, two studies included culture-specific interventions that were no pure exercise interventions (Burling et al., 1992; Li et al., 2002) which hampers generalizability. In three studies (Collingwood et al., 1991; Li et al., 2002; Palmer et al., 1995), group differences concerning specific outcome variables were found already at the beginning of the study, partly explaining group differences at the end of treatment. Finally, self-

reported substance use was not chemically validated in three studies (Buchowski et al., 2011; Collingwood et al., 1991; Roessler, 2010).

In summary, evidence is very weak concerning the efficacy of exercise as an adjunct therapy in the treatment of illicit drug abuse and dependence. The studies published so far are not methodologically sound and generalizable. Therefore, only a few preliminary conclusions can be drawn pointing towards unspecific benefits of exercise, given a certain duration and training intensity of the exercise intervention. Well-designed studies using adequate sample sizes and control groups are needed to determine if exercise programs are effective for treating SUD, and if so, under which conditions.

Table 4.3. Studies investigating Exercise in the Therapy of Illicit Drug Abuse and Dependence

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Colling-wood et al. (1991)	N=74 teenagers (mean 16.8 y) at-risk of drug abuse OR abusing drugs OR drug-dependent (m,f) ethnicity not reported	N=54 secondary school at-risk classes drug prevention program N=11 community-based substance abuse counseling agency program durationN=6 weeks N=9 in-patient chemical dependency unit treatment Duration: 8 weeks	Duration: 9 Weeks 1-2 times / week supervised group EX, 2 individual weekly training sessions 60-90 min, stretching, strength development, individual aerobic EX	none statistical comparison between subjects with (N=38) vs. without (N=36) significantly increased fitness (“improvers” vs. “non-improvers”)	“Improvers”: Significantly fewer multiple drug users and alcohol uses per week, and higher abstinence rate (but no differences concerning the use of individual substances) Significantly higher flexibility and strength, and lower body fat Stronger decrease of depression and anxiety, more positive self-concept	- No experimental design - Post-hoc classification possibly confounded with other variables (EX adherence and abstinence may depend on the same external factors; causality is not given) - Heterogeneity of diagnoses and institutions - Significant differences between groups concerning initial fitness levels, self-concept, abstinence rates, depression, and anxiety - Drug use only assessed by self-report - no effect sizes - no measures of physical health
Burling et al. (1992)	N=218 veterans with drug and/or alcohol abuse or dependence (m) 50% black, 41% white, 9% other	In-patient rehabilitation program for homeless substance-dependent veterans Group-based CBT skills training Duration ≥ 30 days	Duration ≥ 30 days (optional continuation as out-patient) Softball team (N=34): 2 trainings, one game (men’s city league), one team meeting / week	Two control cohorts: A: N=102, patients treated at the same time who chose not to participate in EX B: N=82, patients treated 1 year prior to EX cohort	Significantly higher abstinence rate in softball cohort at 3-month follow-up Trend for higher employment and dwelling Significantly higher treatment duration and - completion	- Unequal group sizes (32 : 102 : 82) - Self-selection of participants, no randomization - Lack of pure EX intervention, includes social interaction, team-building, time structuring etc. - Lack of equal contact time control group controlling for these factors ***- Cultural specificity of softball (lack of generalizability)*** - no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

Author, Year	Sample charac-teristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Palmer et al. (1995)	N=45 patients with „problems with alcohol, cocaine or other drugs“ (m,f) (diagnoses not specified) 60% black, 40% white	In-patient rehabilitation program Duration: 28-45 days Random assignment to one of three EX conditions	Duration: 4 weeks 3 times / week, 30-40 min supervised EX A: Step-Aerobic program at 60% max HR (aerobic training) B: Bodybuilding program (anaerobic strength training) C: Circuit training (mixed aerobic and anaerobic training)	none	No drug-related outcomes reported No fitness gains in either group after 4 weeks Significantly reduced depression scores in group B (bodybuilding), no changes in groups A and C	- Small N - Heterogeneity and lack of clarity concerning the diagnoses - Initial differences between groups concerning depression scores → significant reductions in group B possibly explained by higher initial scores - Training in group B in teams of 2-3, in A and C alone → social confounds - EX duration too short to improve fitness - Lack of Intention-to treat analysis to correct for high number of dropouts - No follow-up data reported - no effect sizes - no changes in blood pressure or pulse
Williams (2000)	N=20 „asymptomatic offenders“ (m,f) consuming metamphetamine, alcohol, cannabis or other drugs (diagnoses not specified) 70% Cauca-sian, 20% Hispanic, 5% Afro-American, 5% Native-American	Out-patient community-based treatment program with 2 weekly sessions for relapse prevention Duration: 12 weeks	Duration: 12 weeks Daily Journals recording PA and optional 2 times / week of supervised muscle strengthening training	none post-hoc comparison between program “completers” and “non-completers”	No drug-related outcomes reported „Completers“ more involved into EX behavior even before the treatment Subjects agreed that EX was effective in preventing them from relapse	- Very small N (9 dropouts), no meaningful statistic - No group assignment, no control group - Post-hoc classification possibly confounded with other variables (EX adherence and abstinence may depend on the same external factors; causality is not given) - Self-selection of participants - no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Li et al. (2002)	N=86 heroin-dependent patients (m) ethnicity not reported	Mandatory in-patient treatment (detoxofication) Duration: 1-3 months	Duration: 10 days 4-5 times / day 25-30 min Pan Gu Qigong	A: 10 days of medi-cation with lofexidin-HCl B: detoxification without special treatment except for PRN medication against severe withdrawal symptoms	Fewer withdrawal symptoms and earlier negative morphine test in Qigong group Fewer symptoms of anxiety in Qigong group compared to control groups A and B	- Ethical problems (mandatory treatment) - Lack of specific EX intervention (multi-faceted intervention) ***- Cultural specificity of Pan Gu Qigong (lack of generalizability)*** - no effect sizes - no measures of physical health - Initial group differences on day 1 concerning withdrawal symptoms → faster reductions possibly explained by lower initial scores - No follow-up data for post-acute phase reported
Roess-ler (2010)	pilot study N=38 patients dependent of cannabis, opiate, medication, heroine, cocaine, and/or amphetamine (m,f) ethnicity not reported	Day clinic for substance dependent patients, (type of treatment not reported) Duration: 2 and 6 months, respectively	Duration: 2 and 6 months, respectively 3 times / week 2h of endurance training, strengthening EX, and team sports (badmin-ton, volleyball)	none	Improvements in subjective control, craving, role oft he substance Significantly improved fitness at end of treatment subjective reports: increased fitness reduces withdrawal symptoms and improves body perception, vigor, sleep quality and self-confidence	- Very small N, very high dropout rates (N=17 for pre-post comparison) - Sample selected by clinic staff based on physical condition, compliance etc. - Lack of control group → changes can not be attributed to EX - No validation of self-reported substance use - no statistics at all, no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

Author, Year	Sample characteristics	Study design, standard therapy	Exercise intervention (EX)	Control condition(s)	Outcome variables & findings Exercise > control condition	Comments
Brown et al. (2010)	pilot study N=16 untrained patients dependent of alcohol, cannabis, cocaine, opiates, and/or sedatives (m,f) 81% Caucasian, 13% Afro-American, 6% hispanic	different concurrent treatments for substance use (in-patient, out-patient, day-clinic, individual sessions with psychiatrists Duration: not standardized	Duration: 12 weeks 1 supervised and 2-3 individual training sessions per week, progressively 20-40 min of moderate aerobic training (55-69% max HR) 1 brief weekly CBT intervention to increase motivation for PA incentive component for EX adherence	none	At end of treatment 66% of patients abstinent, with significantly lower relapse rates in patients who had attended at least 75% of EX sessions Significantly increased fitness after 12 weeks	- Very small N, high dropout rate - Lack of control group → changes can not be attributed to EX alone - EX adherence and abstinence may depend on the same external factors (causality not given) - no effect sizes - BMI, body composition
Buchowski et al. (2011)	pilot study N=12 untrained cannabis-dependent patients NOT seeking treatment for their cannabis dependence ethnicity not reported	none	Duration: 2 weeks 5 times / week supervised training session (total of 10) 30 min moderate treadmill walking/ running	none	Cannabis consumption significantly reduced compared to baseline during intervention and at 2-week follow-up Significantly reduced craving after each training session	- Very small N - Lack of control group, no substance-related intervention - EX duration too short to improve fitness - Only self-report of cannabis consumption - Motivation of patients unclear: ostensibly no desire for change concerning cannabis consumption, but very high adherence rates - no effect sizes - no measures of physical health

Abbreviations: AA = Alcoholics Anonymous, ACSM = American College of Sports Medicine, CBT = cognitive-behavioral therapy, EX = exercise, f = female, h = hour(s), HR = heart rate, HR-R = heart rate reserve, m = male, max HR = maximum heart rate, min = minutes, N = sample size, PA = physical activity

4.5. Conclusions and Future Directions

The above cited studies, especially in the field of nicotine abuse and dependence, provide some evidence for positive treatment effects that can be achieved using exercise interventions.

Nevertheless, it becomes obvious that evidence is very sparse with regard to alcohol and illicit drugs. Given the self-evident presence of exercise programs as an integral part of almost every rehabilitation facility, it has to be pointed out that so far, no methodologically firm studies are present to verify the long-term benefits of exercise interventions with regard to craving, abstinence, relapse, and other psychological variables. Although beneficial effects induced by exercise are theoretically plausible, clinically admitted, and highly intuitive, well-designed studies need to be conducted to empirically corroborate these assumptions. Future studies should report effect sizes in order to make exercise effects comparable to other active treatments, such as pharmacological or psychotherapeutic interventions.

Generally, patients with poor physical condition are often excluded from studies or drop out early. In the future, more emphasis should be put on the question on a) how patients with poor physical health can be included into exercise programs, and b) how physical health changes moderate SUD-related therapy outcomes. In the field of medication abuse, amphetamines and synthetic drugs, no studies have been published so far.

Some further questions are of particular interest:

- Which mechanisms of action are particularly important in SUD patients?
- Is there a linear (or curvilinear) dose-response relationship of exercise and therapy outcome?
- What is the minimal duration and intensity of an efficient exercise program?
- Which types of exercise are the most effective, and how is the type of effective exercise related to the patients' characteristics and cultural background?
- Which roles do factors like indoors vs. outdoors, individual vs. group exercise, supervised vs. non-supervised training play?
- Does an effective exercise intervention necessarily require fitness increases?
- How can patients be motivated to adhere and continue exercise programs?

5. Article III: Exercise and Reward Processing

This is a non-final version of the article “Acute Exercise Influences Reward Processing in Highly Trained and Untrained Men” published in a final form in *Medicine and Science in Sports and Exercise 2013; 45(3)*, 583–591.

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5.1. Abstract

Introduction: Physical activity activates brain regions and transmitter systems that represent the reward system (i.e., the ventral striatum (VS) and dopamine). To date, the effect of training status and acute exercise on reward processing have not been investigated systematically in humans. To address this issue, we examined highly trained (HT) and sedentary (SED) men with a monetary incentive delay (MID) paradigm.

Methods: We used functional magnetic resonance imaging (fMRI) to investigate the neural correlates of monetary incentive processing after acute exercise. HT and SED subjects were randomized into two groups. One group run on a treadmill (AER) for 30 min at 60-70 % of their maximal oxygen uptake, whereas the other group performed placebo exercise (PLAC). Approximately one hour after exercise, the MID task was conducted. Mood was assessed using the Positive and Negative Affect Schedule prior to and after the exercise intervention.

Results: The psychological assessment showed that exercise significantly increased mood in HT and SED. During gain anticipation and gain feedback of the MID task, the VS was significantly stronger activated in the PLAC group than in the

AER group. No effect of training status, and no interactions between training status and acute exercise were found.

Discussion: Acute exercise diminishes sensitivity to monetary rewards in humans. This finding is discussed with regard to interactions between tonic and phasic dopamine in the VS.

5.2. Introduction

Physical exercise activates the brain reward system and might interact with the processing of other rewarding stimuli, like food or drugs.

Several rodent studies demonstrated that e.g. wheel running has reinforcing properties, for which rats are willing to “work”, and show conditioned place preference (CPP; Belke & Wagner, 2005; Brené et al., 2007). In this context, one relevant neurotransmitter is dopamine (DA), which is involved in both motor action and reward. Several micro-dialysis studies in rats demonstrated acute increases in extracellular DA levels not only in nigro-striatal (motor associated) areas, but also in mesolimbic (affective) areas induced by 20-60 min of treadmill or wheel running at moderate intensities (Hattori, Naoi & Nishino, 1994; Meeusen et al., 1997; Wilson & Marsden, 1995). In these studies, DA levels remained elevated for up to two hours (Meeusen et al., 1997) after the exercise treatment.

When exercise is frequently performed over a longer period, several long-term adaptations of the dopaminergic reward system seem to occur. Here, results from animal studies are contradictory regarding the direction of findings: basal striatal DA levels were either found to be reduced (Meeusen et al., 1997) or increased (Marques et al., 2008) in trained rats.

In humans, even if a high proportion of athletes reports withdrawal-like symptoms when deprived from their habitual level of physical activity (Aidman & Woollard, 2003), evidence is sparse on a neurophysiological level. In a PET study by Wang and colleagues (2000) investigating DA neurotransmission with [11C]raclopride, nine out of twelve subjects displayed a moderately reduced binding of [11C]raclopride, indicating an increased release and binding of endogenous DA, whereas three displayed an increased antagonist binding (Wang et al., 2000). In another PET study focusing on opioidergic mechanisms, Boecker and colleagues (2008) reported reductions in frontolimbic opioid receptor availability after 2 hours of endurance running, also indicating an increase of endogenous opioids, which was correlated with euphoria (Boecker et al., 2008). This phenomenon, also known as the “runner’s high”, has been described along with other positive acute and chronic effects of exercise such as mood improvement, or reduced tension and anxiety (Reed & Ones, 2006; Wipfli et al., 2008; Yeung, 1996).

Besides the rewarding properties of physical activity and the according activation of the brain reward circuits described above, acute and chronic exercise have been shown to alter the processing of other rewarding stimuli.

For example, several studies reported that long-term aerobic exercise (across several weeks) decreased the reinforcing effects of different psychotropic drugs (cocaine and 3,4-methylenedioxymethamphetamine) and reduced CPP for drugs (Smith, Schmidt, Iordanou & Mustroph, 2008; Thanos et al., 2010). Chronic exercise also impaired the acquisition of cocaine self-administration (Smith & Pitts, 2011) and cue-induced and cocaine-primed reinstatement (Zlebnik, Anker, Gliddon

& Carroll, 2010). Acutely, concurrent access to a running wheel reduced cocaine-seeking behavior and self-administration in female rats (Zlebnik et al., 2010).
In humans, cigarette craving has been shown to be reduced after acute bouts of exercise (Taylor, Ussher & Faulkner, 2007). Studies investigating the influence of physical activity on non-drug-related reward effects in humans found that exercise decreased self-reported chocolate craving and consumption (Oh & Taylor, 2012). A recent fMRI study found that after exercise, the subjective rating of hunger was diminished. This behavioral finding was supported by significant reduced limbic and reward associated brain response to high-energy food (Evero, Hackett, Clark, Phelan & Hagobian, 2012).

In the current study, we investigated the effects of acute exercise on the reward system of trained and untrained subjects. In order to examine the interaction between chronic and acute exercise, we used a well-established, non-drug related monetary incentive delay (MID) task (Knutson, Fong, Bennett, Adams & Hommer, 2003) which has been shown to evoke reliable activation of the mesolimbic reward system, especially the ventral striatum (VS; Knutson, Adams, Fong & Hommer, 2001).
We hypothesized that (I) acute exercise would alter the subsequent anticipation and processing of monetary reward and punishment, (II) highly trained (HT) and sedentary (SED) men would differ in the anticipation and processing of monetary reward on a neural level, and (III) there would be an interaction between training status and acute exercise.

5.3. Materials and Methods

5.3.1. Participants

The recruitment of HT and SED men took place from August 2009 to August 2010 at Berlin Universities, the institute of sport sciences and the elite sport training centre in Berlin-Hohenschönhausen.

Inclusion criteria were solid German language skills, 20 - 32 years of age, non-smokers, no abuse of any drugs or medicaments in the past year, BMI 19-26 kg/m^2. Subjects only were included if they exercised less than once a week (SED) or if they performed endurance exercise (e.g. running, cycling, swimming, rowing or triathlon) on a competition level and with at least three training units per week (HT). Subjects with an intermediate level of physical activity were excluded. Eligible candidates gave written informed consent to participate, in accordance with the Declaration of Helsinki. The study was approved by the local ethics committee.
Forty-three healthy right-handed male volunteers without psychiatric or neurological history were eligible to participate in the present study (nineteen HT: mean age 25.11 ± 3.73 years; and twenty-four SED: mean age 24.46 ± 2.81 years).

On a separate examination at the sports medicine prior to the actual testing session, subjects´ VO_2max values were assessed using a modified Bruce protocol, starting with 3 km/h without elevation and increasing the speed in 1-km/h steps every 3 minutes up to 6 km/h. Thereafter, the treadmill elevation was increased by 3% every three minutes. Maximal heart rate and maximal oxygen uptake

(VO_2max, in ml/kg/minute) were assessed, as well as subjective exertion using the Borg Rating of Perceived Exertion Scale (Borg & Linderho.H, 1970).

Half of each subgroup was randomly assigned to one of two treatments. One group performed aerobic exercise on a treadmill (AER) for 30 min at 60-70 % of their individual maximal oxygen uptake (VO_2max), whereas the other group performed placebo exercise (PLAC, exercises that did not induce significant changes in cardiovascular activation). The PLAC condition (as described in Knubben et al., 2007) consisted of light stretching exercises for the calves, thighs, lateral trunk, neck/shoulders, fingers, and pectoral muscles, and light gymnastic exercises such as arm circling. Each muscle group was stretched 3-5 times for 20 s each, followed by a 40 s resting interval. Unlike the intervention intensity, the training location, the investigators and the duration of interactions with the investigators (every 5 min) did not differ between treatment groups.

The German version of the Positive and Negative Affect Schedule (PANAS) was administered immediately before and after the exercise treatment to assess mood changes (Watson, Clark & Tellegen, 1988).

During data analysis, five subjects had to be excluded due to artefacts in the functional scans (N=2), lacking understanding of the paradigm (N=1), interruption of the training schedule in the HT group (N=1) and because of an abnormal VO_2max -value (N=1). Finally, the subgroups included into the analyses consisted of 11 SED_AER, 13 SED_PLAC, 9 HT_AER and 10 HT_PLAC subjects.

As listed in Table 5.1, the four groups did not significantly differ with regard to age, body mass index (BMI), Beck Depression Inventory (BDI) score and education,

whereas VO_2max values and training units per week differed significantly ($p < .001$) between HT and the SED (but not between treatment groups).

Table 5.1.: Sample Characteristics

	HT		SED		Comparison
	AER n = 9	**PLAC n = 10**	**AER n = 11**	**PLAC n = 13**	
Age [years]	24.00 (± 3.97)	26.10 (± 3.38)	25.09 (± 2.95)	23.92 (± 2.69)	n.s.[a]
BMI [kg/m^2]	22.79 (± 2.01)	22.98 (± 1.92)	22.43 (± 1.45)	21.59 (± 1.49)	n.s.[a]
BDI	2.22 (± 2.39)	2.90 (± 5.49)	3.45 (± 3.30)	3.00 (± 2.77)	n.s.[a]
VO_2max [ml/min/kg]	56.00 (± 5.17)	55.10 (± 6.19)	48.36 (± 6.76)	50.15 (± 2.91)	ME GROUP: $p < .01$[a] HT vs. SED: $p < .001$[b]
Training [units/week]	4.61 (± 1.58)	5.35 (± 1.45)	< 1	< 1	ME GROUP: $p < .001$[a] HT vs. SED: $p < 0.001$[b]
Education	A-level (median)	A-level (median)	A-level (median)	A-level (median)	n.s.[c]

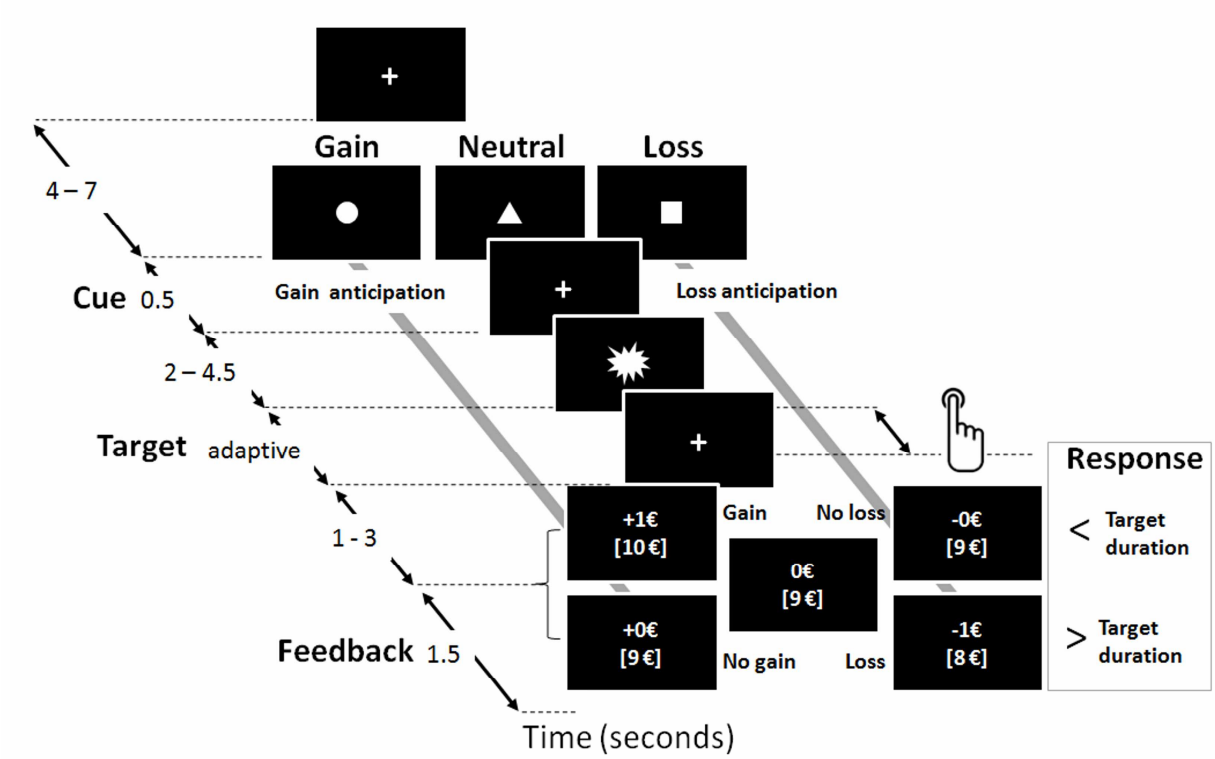
Abbreviations: HT = highly trained men; SED = sedentary men; AER = aerobic exercise; PLAC = placebo exercise; BDI = Beck Depression Inventory; BMI = Body Mass Index; VO_2max = maximal oxygen uptake; n.s. = nonsignificant; ME = main effect
Test statistics: [a] General Linear Model (Univariate ANOVA); [b] T-Test for Independent Samples; [c] Chi-Square Test

5.3.2. Monetary Incentive Delay (MID) Task

Participants accomplished a modified version of the adaptive MID task (Knutson et al., 2003). On average, the MID task started 63.38 min (SD 11.01 min) after the end of the exercise treatment. Each experimental trial consisted of a cue, a target stimulus, and a feedback phase. The cue (500 ms) indicated either a potential gain of 1 € (circle), a potential loss of 1 € (square) or a neutral outcome (triangle), inducing gain or loss anticipation. After a jittered delay of 2 – 4.5 s, a target stimulus flashed. Participants were instructed to quickly press a button at the appearance of the target, irrespective of the cue type shown before. If the button press was fast enough, the subjects either won 1 € (gain condition) or prevented to lose 1 € (loss condition).

This design resulted in five possible outcomes: gain after gain anticipation (gain), no gain after gain anticipation (no gain), neutral outcome after no anticipation, loss after loss anticipation (loss), or no loss after loss anticipation (no loss). After 1-3 seconds, a feedback screen was displayed for 1.5 s reporting the outcome of the last trail and the actual amount of money gained (credits). The inter-trial interval was between 4 and 7 seconds (see Figure 5.1.).

Figure 5.1. Monetary Incentive Delay (MID) Task. Reward paradigm consisting of three cues (gain, neutral, loss) and five possible outcomes (gain, no gain, neutral, loss, no loss)



The experiment consisted of 75 trials, 25 of each condition (gain, neutral, loss), which were presented in pseudo-randomized order with jittered inter-stimulus intervals. Each trail lasted between 8.5 and 16 s, resulting in a total duration of 12 min. Before entering the scanner, participants were provided with written instructions and a brief demonstration trial. In the MR scanner and prior to the actual experiment, all participants accomplished a training consisting of 15 trials. Based on behavioural data from this training session, an initial estimate for the first target duration was computed. In order to obtain an overall success rate of about 67.5% across all participants, an adaptive algorithm estimated the duration of each

target separately. To this end, the reaction time distribution of the 15 previous gain/loss trials was analysed online by the stimulation program.

The MID task was programmed with PRESENTATION (version 0.71, http://www.neurobs.com/). The reaction time (RT), the rate of button press within target duration (hit rate in %) and the total amount of money won during the task (final credits) were recorded and used as dependent variables in an Analysis of Variance (ANOVA) to investigate differences between groups with regard to these variables.

5.3.3. Image Acquisition

MR data were collected using a 1.5-T Siemens Magnetom Sonata MRI scanner (SIEMENS Medical Systems, Erlangen, Germany) and a standard circularly polarized head coil (CP-Headcoil). For fMRI, thirty-five axial slices covering the entire brain were acquired in an odd-even interleaved ascending order (gradient-echo echo-planar imaging - GE-EPI; repetition time (TR)= 2000 ms; echo time (TE)= 40 ms; flip angle= 90°; matrix= 64 × 64; field of view= 224 mm; slice thickness= 3.0 mm; inter-slice gap= 0.45 mm; voxel size= 3.5 mm × 3.5 mm × 3.45 mm). Functional images were acquired continuously, resulting in 355 scans per run. Prior to the fMRI session, the B_0 field was mapped using a gradient-echo pulse sequence with a spatial orientation and resolution as used in fMRI (TR= 536 ms; TE(1)= 5.19 ms; TE(2)= 9.95 ms; flip angle= 60°).

In addition, a high resolution structural T1-weighted inversion recovery 3D-magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence was recorded (TR= 2280 ms, inversion time (TI)= 1100 ms; TE= 3.93 ms, flip angle=

15°, matrix= 256 × 256; field of view= 256 mm; slice thickness= 1.0 mm; voxel size= 1 mm × 1 mm × 1 mm). Head movements were minimized by a lateral fixation.

5.3.4. Image Processing and Analysis

Functional MRI data were processed and analysed using the software package Statistical Parametric Mapping (SPM8; Wellcome Department for Cognitive Neuroscience, University College London, UK).

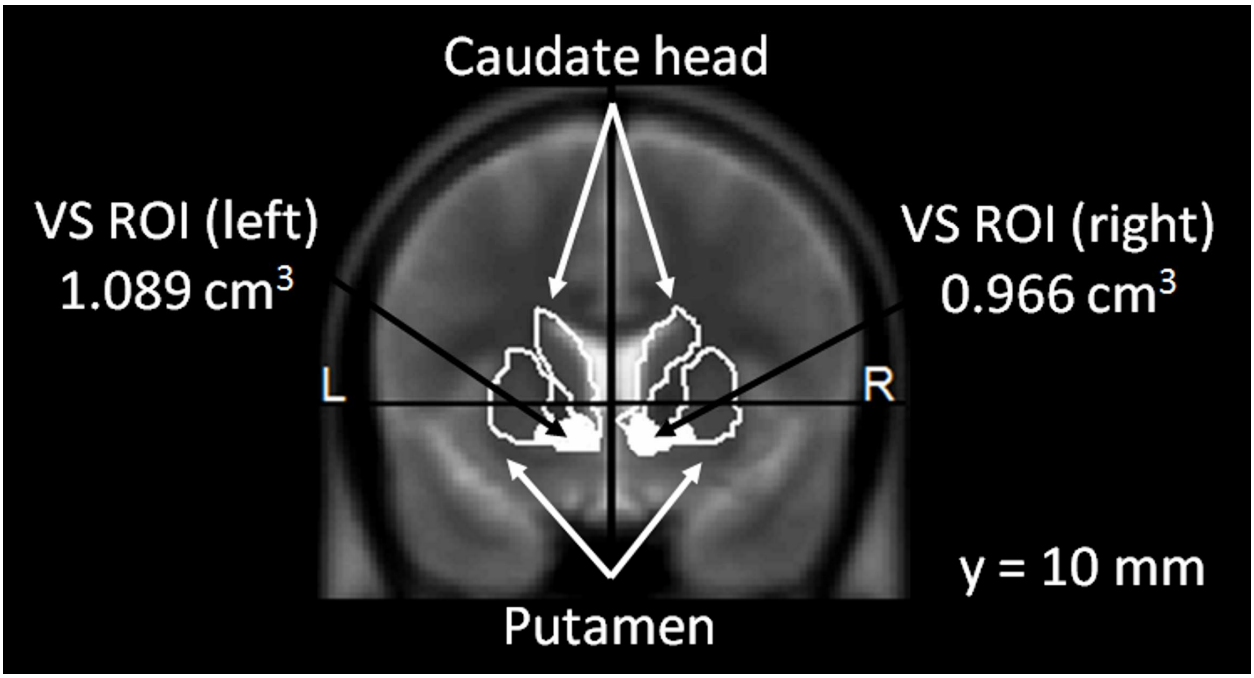
To allow for steady state magnetization, the first three scans were discarded. Prior to the pre-processing, the image origin was set to the anterior commissure. Individual voxel displacement maps (VDMs) were calculated from the B_0 - Fieldmaps to correct for distortion caused by magnetic field inhomogeneity. EPIs were corrected for acquisition delay and motion artifacts as well as unwarped using the VDMs. The anatomical reference image was co-registered to the mean unwarped EPI, transformed into the standard space as provided by the International Consortium for Brain Mapping (ICBM) and segmented using the unified segmentation approach as implemented in SPM8 . Functional images were normalized applying the linear and non-linear transformations estimated by this procedure. Spatial smoothing was accomplished with a Gaussian kernel to even the signal and improve the signal-to-noise-ratio (full-width-half-maximum, FWHM = 7 mm). A high pass filter with a cut off frequency of 1/128 Hz was applied to the data. Finally, images were visually inspected to ensure quality.

Statistical analyses were performed in a two-stage Mixed Effects model. In the first stage, neural activity was modeled by a delta function at stimulus onset. The BOLD response was modeled convolving these delta functions with the canonical hemodynamic response function (HRF) as implemented in SPM. The resulting time courses were downsampled for each scan to form the explanatory variables of a general linear model (GLM; Friston et al., 1995). The resulting GLM comprised 16 regressors for the conditions of interest: cues gain, neutral and loss; feedback gain, no gain, neutral, loss and no loss, as well as the cue and feedback regressors parametrically modulated by the current amount of credits. To control for nuisance variance, 9 additional regressors of no interest were included in the GLM: target responses for each cue type and the six rigid-body movement parameters determined from motion correction (to account for signal fluctuations caused by head movements – movement by susceptibility interaction). Finally, a single constant represented the mean over scans. Weighting parameters for the GLM were estimated by restricted maximum likelihood (ReML) fit. Linear contrast images were computed for the following effects of interest: gain anticipation [cue(gain) > cue(neutral)], loss anticipation [cue(loss) > cue(neutral)], gain feedback [(gain + gain*credits) > (no gain + no gain*credits)] , and loss feedback [(loss + loss*credits) > (no loss + no loss*credits)]. In the feedback contrasts, the amount of credits gained until the actual trial was included as a parametric modulator.

For these contrast images, second level random effects analyses were conducted. First, one-sample t-tests (whole sample) for all above-mentioned contrasts were computed to allow comparisons between the activation patterns found in our

sample and previous studies using the MID task. Secondly, two 2 x 2 ANOVAs were computed separately for anticipation and feedback, using the between subject factors GROUP (HT vs. SED) and TREATMENT (AER vs. PLAC). Thirdly, a-priori probabilistic literature-based Regions of Interest (ROIs) for small volume alpha error adjustment were created for the left and right VS combining anatomical hypotheses with functional findings as reported in the literature for comparable experimental designs (see Figure 5.2. and Appendix A1 for detailed information about computation of literature-based probabilistic ROIs).

Figure 5.2. A-priori Probabilistic Literature-Based ROIs. ROI for right and left Ventral Striatum overlaid on a mean normalized brain of the whole sample.



Abbreviations: VS = Ventral Striatum; ROI = Region of Interest

The significance level for all voxel-wise comparisons was set to a liberal whole brain threshold of p<.01 uncorrected for multiple comparisons and p<.05 family

wise error (FWE) corrected within ROI, with a minimal cluster size of 10 adjacent voxels. Only effects surviving the alpha error adjustment within the a-priori ROIs (Small Volume Correction – SVC – as implemented in SPM) are discussed (whole brain results are illustrated in Figure 5.3. and listed in Supplementary Tables A2-A5). All spatial information is given in MNI coordinates. For display purposes, results are shown overlaid on a mean anatomical image of the whole sample.

5.3.5. Behavioural Data Analysis

We used IBM SPSS Statistics 19 to evaluate the psychological assessment, the MID task performance and the demographical group characteristics. All metrical variables (age, BMI, BDI, VO_2max, task performance) were analysed using a two-way ANOVA with the between subject factors GROUP (HT / SED) and TREATMENT (AER/ PLAC). The PANAS scores were analysed using a three-way ANOVA for repeated measures with the within subject factor TIME (Pre / Post TREATMENT) and the between subject factors GROUP (HT / SED) and TREATMENT (AER / PLAC). All analyses were preceded by test of homogeneity of variance, and results were Greenhouse-Geisser-corrected where appropriate. The direction of significant main effects was analyzed post-hoc using t-tests for independent samples or paired t-tests, respectively. Education level was analyzed with the Chi-square test.

5.4. Results

5.4.1. Behavioural Data

Psychological assessment - PANAS: The three-factorial repeated measures ANOVA for the positive PANAS subscale revealed a significant main effect of TIME ($F_{(1,39)}$= 5.90, p= .020) and a significant TIME x TREATMENT interaction ($F_{(1,39)}$= 11.70, p= .001). Positive affect increased significantly over time across the whole sample ($T_{(42)}$= 2.12, p= .040). This increase was significantly greater for the AER group ($T_{(26.3)}$= 3.24, p= .003). No further main effects or interactions could be found.

A second ANOVA revealed a main effect of TIME for negative affect ($F_{(1,39)}$= 6.96, p= .012), with a decrease over time across the whole sample ($T_{(42)}$= -2.801, p= .008). No further main effects or interactions were found.

MID task performance- reaction time (RT), hit rate and final credits: Only the repeated-measures three factorial ANOVA for RT revealed a significant main effect of CUE ($F_{(1.5,\ 61.9)}$= 31.78, p< .001). Post-hoc paired t-test showed that RT were significant lower in the gain and loss conditions than in the neutral condition (gain>neutral: $T_{(42)}$= -7.40 , p< .001; loss>neural: $T_{(42)}$= -5.62 , p< .001), without main effects for GROUP or TREATMENT, or interactions.

5.4.2. Brain Response

Anticipation and feedback of gain (whole sample): One sample t-tests for the linear contrast “gain anticipation” and “gain feedback” revealed the well-known activation in striatal regions for gain anticipation and frontal regions including anterior cingulate and medial prefrontal area for gain feedback as described elsewhere

(Breiter, Aharon, Kahneman, Dale & Shizgal, 2001; Knutson et al., 2001; Knutson et al., 2003; see Figure 5.3. and Supplementary Tables A2 and A3 for details which show the activation patterns during gain anticipation and feedback for the whole sample).

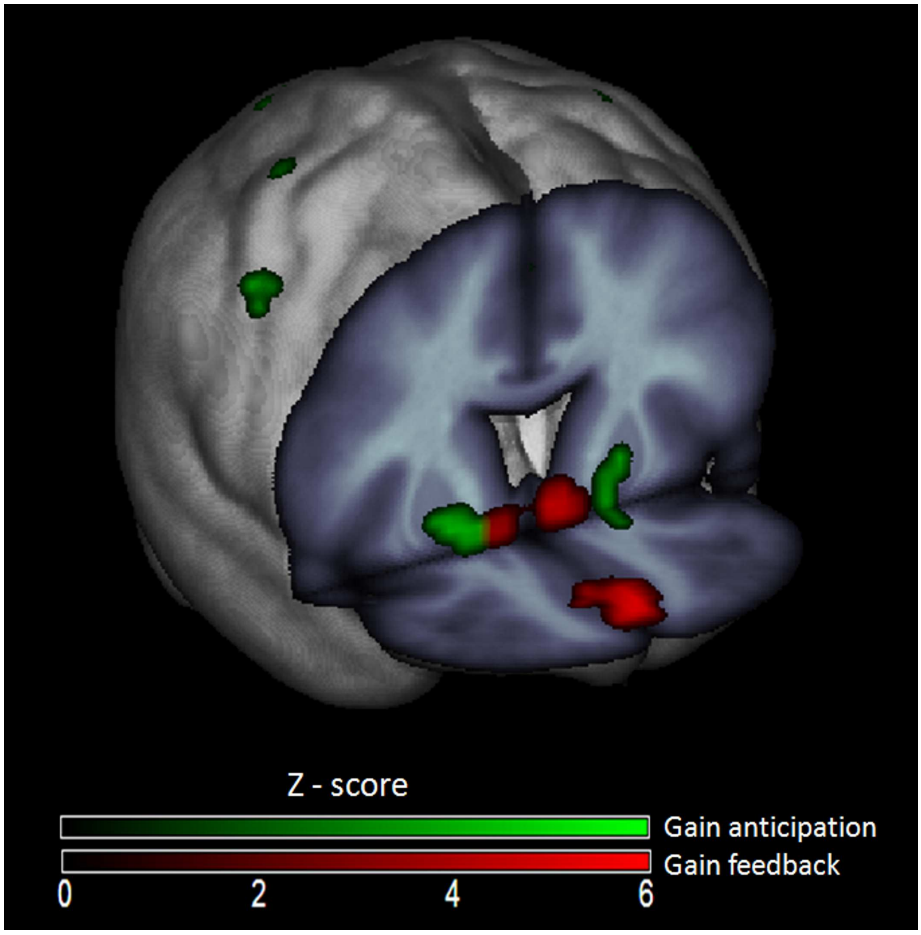
Effects of chronic and acute exercise: 2 x 2 ANOVAs for anticipation and feedback processing revealed main effects only for TREATMENT, both for gain anticipation and gain feedback. No further main effects or interactions were found for these linear contrasts. Moreover, no effects at all were found for loss anticipation and loss feedback.

Whole brain results – Processing of gain anticipation: The anticipation of monetary gain evoked more pronounced neural activity in the PLAC versus AER group in mesolimbic and mesocortical dopaminergic regions like the VS, hippocampus (Hipp) and subgenual anterior cingulate cortex (sgACC). Additionally, several brain structures potentially associated with motor preparation (primary and supplementary motor areas) as well as structures belonging to the ventral (lingual gyrus) and dorsal (cuneus, precuneus) visual pathway showed stronger BOLD responses to gain anticipation in the PLAC group compared with the AER group (see Figure 5.4. (left panel) and Supplementary Table A4 for details about whole brain results).

ROI-based alpha error adjustment (p<.05 FWE corr.) – Gain anticipation: The effects in the left VS (x/y/z= -5 / 7 / -8 ; z= 3.01 ; p= .029) remained significant after a-priori ROI based small volume correction. Status of habitual training (HT / SED)

did not reveal significant differences, and no interactions between training status and acute exercise were found.

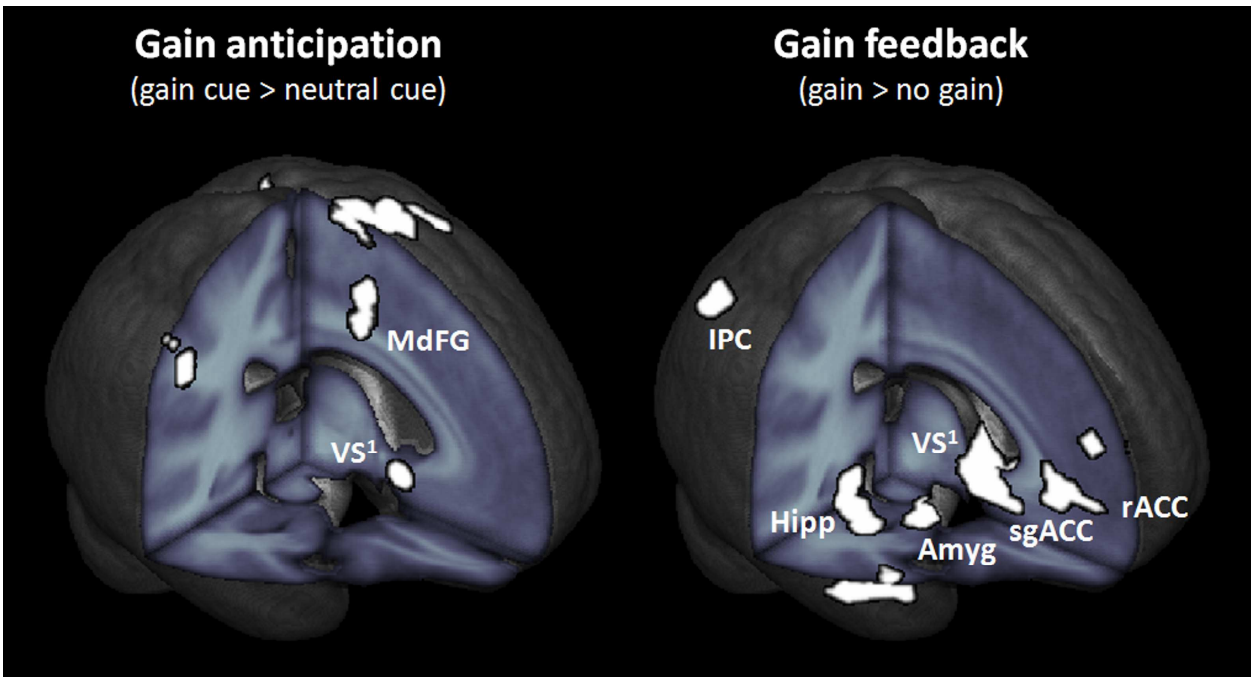
Figure 5.3. Brain responses to gain anticipation and feedback of gain (whole sample). Results overlaid on a mean normalized and rendered brain of the whole sample (one-sample t-tests for the whole sample, p = .001 (uncorr.), minimal cluster size = 10 voxels (all results listed are also listed in Supplementary TablesA2 and A3).



Whole brain results – Processing of gain feedback: For feedback processing of monetary gains, BOLD responses were also more pronounced in the PLAC group than in the AER group. Moreover, these differences were stronger and spatially more distributed than during gain anticipation. In this analysis as well, effects were found in mesolimbic and mesocortical dopaminergic structures like the VS, caudate

nucleus, sgACC, rostral anterior cingulate cortex (rACC), Hipp and amygdala (Amyg), and in parts of the ventral (fusiform gyrus) and dorsal (precuneus) visual pathway (see Figure 5.4. (right panel) and Supplementary Table A5 for details about the whole brain results).

Figure 5.4. Brain regions showing increased BOLD-response in MID task after placebo > treadmill exercise.
Left panel: gain anticipation. Right panel: gain feedback processing. Results of post-hoc t-tests overlaid on a mean normalized and rendered brain of the whole sample.



Abbreviations: MdFG = Medial Frontal Gyrus; VS = Ventral Striatum; IPC = Inferior Parietal Cortex; Amyg = Amygdala; Hipp = Hippocampus; sgACC = Subgenual Anterior Cingular Cortex; rACC = Rostral Anterior Cingular Cortex; [1]Findings significant at FWE p < .05 corrected for ROI volume; ANOVA = Analysis of Variance

ROI based alpha error adjustment (p.05 FWE corr.) – Processing of gain feedback:

After alpha error adjustment for a-priori ROIs, the effects in right VS (x/y/z= 6 / 7 / -5 ; z= 2.95 ; p= .025) remained significant. Status of habitual training (HT / SED)

did not reveal significant differences, and no interactions between training status and acute exercise were found.

5.5. Discussion

Our study revealed two major findings.

First, after PLAC exercise, the VS as the core of the dopaminergic reward system showed significantly stronger activation during gain anticipation (left VS) and gain feedback (right VS), compared to the AER group.

Secondly, neither the participants' habitual training status had an effect on reward anticipation or processing, nor were there interactions between training status and acute exercise.

The first finding is not unexpected, because animal and human studies have shown exercise-induced reductions in sensitivity for high-caloric food (Evero et al., 2012; Oh & Taylor, 2012) and drugs (Smith & Pitts, 2011; Smith et al., 2008; Thanos et al., 2010; Zlebnik et al., 2010). Exercise could therefore also lead to a comparable phenomenon during monetary reward processing.

Our results are in line with the tonic/phasic DA hypothesis (Grace, 1995) stating an interaction between tonic and phasic DA release in the VS (Hernandez & Shizgal, 2009; Wightman & Robinson, 2002). Experimental evidence for this assumption comes from several animal studies (Hattori, Hashitani, Matsui & Nishino, 1996; Hattori et al., 1994; Meeusen et al., 1997). It was shown that DA is elevated by acute exercise and stays significantly above baseline in the striatum and NAcc up to 1-2h after running in both trained and untrained animals (Hattori et al., 1996; Hattori et al., 1994; Meeusen et al., 1997; Wilson & Marsden, 1995). This

extracellular DA outside of the synaptic cleft, which is assessed by micro-dialysis, is often referred to as “tonic” DA (Hernandez & Shizgal, 2009; Wightman & Robinson, 2002). Although the elevation of tonic DA level during and after exercise were not yet replicated in humans (Wang et al., 2000), one can assume that exercise induces higher tonic levels of extracellular DA in humans as well. Tonic DA per se is not directly linked to reward, but rather controls the responsiveness to phasic activation (Grace, 2000; Hernandez & Shizgal, 2009).

Phasic DA, in contrast, which is released into the synaptic cleft and rapidly removed by reuptake, has been shown to be released during reward anticipation or unexpected reward (Schultz, 1998). Although ventral striatal activation in an fMRI task is not identical with DA release, PET-studies demonstrated that BOLD signal increase in the VS correlates with phasic DA transmission during monetary reward tasks (Schott et al., 2008; Zald et al., 2004).

Animal experiments suggest also that an exercise-induced tonic DA turnover mainly interacts with D_2-type-DA-receptors in their high affinity state (Floresco, West, Ash, Moore & Grace, 2003; Schultz, 1998). According to the tonic-phasic DA hypothesis, and because extracellular DA is known to downregulate DA terminals in the NAcc via stimulation of presynaptic autoreceptors, higher levels of tonic extracellular DA following acute exercise could directly inhibit the magnitude of phasic DA-release (Floresco et al., 2003; Grace, 1995). This mechanism might explain why the BOLD response to the MID task was significantly reduced in the VS after exercising.

This interpretation is in line with results reported by Knutson and colleagues (Knutson et al., 2004). In this study, a treatment with dextroamphetamine or

placebo preceded the MID task. In the dextroamphetamine-treated group, the mesolimbic reward system showed significantly less activation during gain anticipation (gain vs. nongain anticipation) than the placebo-treated group. The authors discuss these results in terms of an augmented tonic VS activity by dextroamphetamine which blunts activations observed in the MID task. Several animal studies reported similar effects (Zlebnik et al., 2010).

Alternative explanations such as lacking concentration or motivation after exercise can be excluded, since reaction times, hit rate and final credits did not differ between groups. Furthermore, one-sample-t-tests revealed activations comparable to the original studies of Knutson and colleagues, indicating that the paradigm indeed evoked reward anticipation and processing (Breiter et al., 2001; Knutson et al., 2001; Knutson et al., 2003).

In contrast to gain anticipation and feedback, there were no effects of exercise on anticipation of loss or loss feedback processing. In this regard, it has to be mentioned that the contrast we used for loss feedback (loss > no-loss) differed from the contrast (no-loss > loss) used by Knutson and colleagues (2003), because we aimed at depicting monetary loss after loss anticipation vs. no-loss after loss anticipation. Therefore, our results in the loss conditions are hardly comparable to contrasts reported by other authors. Nevertheless, this result supports our suggestion that the effects in gain anticipation and feedback may be DA-mediated because DA is known to affect processing of positive outcome more than effects of negative outcome (Schultz, 1998).

On a behavioural level, exercise-induced changes of positive affect are in line with earlier findings (Reed & Ones, 2006; Yeung, 1996), although we did not find

differential effects of AER and PLAC exercise on negative affect, which some studies found to be reduced after exercise (Bixby, Spalding & Hatfield, 2001). The increase in positive affect did not depend on the subjects' training status, which contrasts other studies that reported larger mood changes after acute exercise in trained than in untrained individuals (Hoffman & Hoffman, 2008). This finding may be explained by the fact that the exercise intervention of the present study was adjusted to the participants' individual fitness level, which was determined beforehand, resulting in a moderate strenuousness for both groups. Since changes in tonic DA seem not to be directly related to mood or sensations of reward (Hernandez & Shizgal, 2009; Liggins, Pihl, Benkelfat & Leyton, 2012), the reported mood-enhancing effects as assessed with the PANAS in the current study may rely on other mechanisms, such as the opioidergic or endocannabinoid system (Boecker et al., 2008; Dietrich & McDaniel, 2004).

The lack of differences in reward processing between HT and SED men reflects contradictory findings from the animal and human literature regarding long-term adaptations after chronic exercise. Although dorsal striatal volumes were found to be higher in highly-active compared to non-active children (Chaddock et al., 2010), basal dopamine levels were either found to be higher or lower in trained rodents (Marques et al., 2008; Meeusen et al., 1997). Since the exercise protocol was individually adapted to the participant's VO_2max, the running speed and distances were systematically different between groups, with higher running speed and longer distances covered by the HT group.

Adjustment to individual training level was necessary to prevent excessive or too low demands. It is possible that HT men would have needed a more strenuous and

longer training protocol as for example used in the study by Boecker and colleagues (2008) to show a significant effect in fMRI compared to SED men. To date, the complex adaptations of the dopaminergic system following long-term exercise (e.g. changes in basal DA levels, receptor density and sensitivity, dopamine synthesis capacity) are poorly understood.

Finally, applying an adequate control condition in exercise studies is tricky and has been solved in different ways, e.g., using table football (Pajonk et al., 2010), relaxation techniques (Crocker & Grozelle, 1991), passive sitting (Hillman et al., 2009; Ströhle et al., 2009), or watching videos (Ussher, Nunziata, Cropley & West, 2001). Because in our study, testing sessions were performed individually, we aimed at choosing an intervention that was somehow compatible with the exercise intervention, yet did not induce cardiovascular and/or emotional arousal (such as table football), and did not actively influence mental state (such as relaxation).

In two [11C]raclopride PET studies (de la Fuente-Fernandez et al., 2001; Scott et al., 2008), an increase in striatal dopaminergic activity was found after placebo interventions. Thus, similar effects may have occurred in our study. If DA was released not only in the AER group (similar to animal studies that found significant DA increases in the VS after exercise, see above) but also in the PLAC group, this placebo-induced DA release may also have occurred in a prolonged manner. This would have diminished phasic DA release during MID task by interference with presynaptic D2 receptors in the PLAC group as well. In this case, differences in the BOLD signal between the two groups would have been reduced or even abolished. It is therefore possible that differences in the BOLD signal would have been even more pronounced without a placebo exercise intervention in the control group.

5.6. Limitations

Because of technical limitations (MR scanner replacement), the acquisition of a greater sample was not possible. The resulting decrease in statistical power might increase the amount of undetected effects (e.g., in loss anticipation). Further studies including more participants should investigate these possibly additive effects.

5.7. Conclusions

Altogether, our results show that acute aerobic exercise increases mood more than placebo exercise, in the MID task however, subjects showed a significantly stronger activation after placebo exercise. This suggests that acute exercise influences the function of dopaminergic brain structures, which presumably leads to a modulation of phasic dopaminergic response during the processing of gain anticipation and gain feedback. Nevertheless, DA is just one of several players modulating the complex exercise induced neurophysiology and details remains to be explored in following studies.

6. Article IV: Exercise and Stress Reactivity

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6.1. Abstract

According to the Cross-Stressor Adaptation Hypothesis, physically trained individuals show lower physiological and psychological responses to stressors other than exercise, e.g. psychosocial stress. A reduced stress reactivity may consitute a mechanism of action for the beneficial effects of exercise in maintaining mental health. With regard to neural and psychoneuroendocrine stress responses, the acute stress-buffering effects of exercise have not been investigated yet.

A sample of highly trained (HT) and sedentary (SED) young men was randomized to either exercise on a treadmill at moderate intensity (60-70% VO_2max) for 30 minutes, or to perform 30 minutes of “placebo” exercise (PLAC). 90 minutes later, an fMRI experiment was conducted using an adapted version of the Montreal Imaging Stress Task (MIST). The subjective and psychoneuroendocrine (cortisol and α-amylase changes induced by the exercise intervention and the MIST were assessed, as well as neural activations during the MIST. Finally, associations between the different stress responses were analyzed.

Participants of the AER group showed a significantly reduced cortisol response to the MIST, which was inversely related to the previous exercise-induced α-amylase and cortisol fluctuations. With regard to the sustained BOLD signal, we found higher bilateral hippocampus (Hipp) activity and lower anterior cingulate cortex (ACC) activity in the AER group. Participants with a higher aerobic fitness showed lower cortisol responses to the MIST.

Since the Hipp and ACC are brain structures prominently involved in the regulation of the hypothalamus-pituitary-adrenal (HPA) axis, these findings indicate that the acute stress-buffering effect of exercise relies on negative feedback mechanisms. Positive affective changes after exercise appear as an important moderator largely accounting for the effects related to physical fitness.

6.2. Introduction

In a large number of longitudinal epidemiological studies, exercise and more generally, physical activity were found to improve physical and mental health (Ströhle et al., 2007; WHO, 2010). Besides mental disorders like post-traumatic stress disorder and depression, several cardiovascular, immunological and metabolic diseases are nowadays recognized as “distress-related”, implying that chronic stress and/or dysregulations of the stress response are involved in the pathogenesis and progress of these disorders. Therefore, several authors suggested that reducing reactivity to stress may be one key mechanism which mediates the beneficial effects of physical activity on health (e.g. Gerber, 2008; Iwasaki, Zuzanek & Mannell, 2001).

Interestingly, exercise shares several characteristics of an acute stressor, requiring hemodynamic, endocrine, and metabolic adaptations to restore homeostasis (Hackney, 2006; Sothmann et al., 1996). Amongst others, the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) system are activated in an intensity- and duration-dependent manner (Deuster et al., 1989; Hackney, 2006; Rohleder & Nater, 2009). While the sympathetic nervous system (SNS) is already activated by low exercise intensities, the HPA axis requires a minimum of 50-60% VO_2max to elicit a distinct response (Deuster et al., 1989; Hackney, 2006; Hill et al., 2008). On a subjective level however, voluntary exercise is rarely described as a stressor. Instead, several authors ascribe rewarding, anxiolytic and mood-enhancing properties to acute bouts of exercise (Brené et al., 2007; Reed & Ones, 2006; Stranahan, Lee & Mattson, 2008; Wipfli et al., 2008). Moreover, regular exercise can buffer the deleterious effects of chronic stress (see Tsatsoulis & Fountoulakis, 2006b for a review). In the context of animal studies, voluntary aerobic exercise has been labelled a “harmless threat to homeostasis” (Stranahan et al., 2008) due to the absence of features characterizing harmful stressors, like force, uncontrollability, and threat.

On this background, the relationship between exercise as a “positive stressor” and other forms of stressors has been investigated. The “cross-stressor adaptation hypothesis” postulates *“[...] that exercise training promotes cross-stressor tolerance by adaptation of the physiological stress response systems [...]*” (Sothmann et al., 1996). According to this hypothesis, the repeated physiological challenge of exercise should result in adaptations which lead to a reduced sensitivity to subsequent stressors. This hypothesis has since been tested in several studies not

only for homotypic (subsequent exercise), but even for heterotypic stressors (other than exercise). In trained persons, catecholaminergic and HPA responses to absolute (but not relative and maximal) exercise workload are reduced and recovery happened faster, indicating an adaptation to the homotypic stressor (Gerber, 2008; Hackney, 2006).

Regarding heterotypic stressors, evidence is more heterogeneous. Acute exercise was found to reduce self-reported distress and anxiety in response to stressful situations (Rejeski et al., 1992; Taylor, 2000). Additionally, a meta-analysis on 15 randomized-controlled trials concluded that blood pressure responses to a laboratory stressor are attenuated when the stress test was preceded by a moderate-to-high-intensity bout of aerobic exercise (Hamer et al., 2006). For the HPA axis, the acute stress-buffering effect of exercise has not been investigated yet.

Regarding long-term adaptations following regular exercise, a recent meta-analysis did not replicate earlier findings of lower cardiovascular stress reactivity in aerobically fit subjects, but instead reported slightly higher cardiovascular reactivity, but faster recovery in physically fit subjects (Jackson & Dishman, 2006). Other recent studies however found not only attenuated SNS stress markers, but also lower cortisol responses to a psychosocial stress test in trained subjects and subjects with high levels of physical activity, respectively (Martikainen et al.; Rimmele et al., 2009), indicating a lower stress response on the level of the HPA axis in humans. In rodents, both amplification and attenuation of HPA responses were reported, depending on the nature of the heterotypic stressor (see Stranahan et al., 2008).

Neurobiological mechanisms underlying the observed adaptation of the HPA axis are likely related to the glucocorticoid feedback mechanisms of the HPA axis. In a healthy organism, elevated cortisol levels inhibit further HPA axis activity. Several brain regions with a high density of mineralocorticoid (MR) and glucocorticoid (GR) receptors are involved in HPA axis regulation. The paraventricular nucleus (PVN) of the hypothalamus, which initiates the neuroendocrine signalling cascade of the HPA axis via the secretion of corticotrophin-releasing hormone (CRH) into the pituitary, receives mostly inhibitory input from the hippocampus (HC), the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC). The amygdala (AG) in contrast exerts mostly excitatory input on the PVN (see Herman, Ostrander, Mueller & Figueiredo, 2005). Animal studies found stronger amygdala activation after 8 weeks of voluntary wheel running in rats, which may contribute to higher basal HPA axis activity in trained animals (Burghardt, Pasumarthi, Wilson & Fadel, 2006).

Beside functional effects, exercise likely affects also brain structures at a neurophysiological level. Thus, running was also found to reduce hippocampal MR affinity to corticosterone, without changing the total number of MR and GR receptors (Droste et al., 2003). Furthermore, exercise seems to protect hippocampal neurons against cell damage usually caused by high level glucocorticoid exposition (Stranahan, Khalil & Gould, 2007).

Unlike animal studies which use foot shocks, restraint or forced swimming as laboratory stressors, human studies mostly focus on psychosocial stress as a model of potentially harmful stress with robust SNS and HPA axis activations. Among standardized stress tests, the Trier Social Stress Test (TSST; Kirschbaum,

Pirke & Hellhammer, 1993) and the Montreal Imaging Stress Task (MIST; Dedovic et al., 2005) are well established in stress research. Both stress tests combine a cognitive task (mental arithmetics) with socio-evaluative threat components.

Neuroimaging studies using the MIST reported mostly a decrease in brain response in the hippocampus, amygdala, ventral striatum, hypothalamus, dorsal and ventral PFC, orbitofrontal cortices, temporal poles and anterior and posterior cingulate cortices (ACC/PCC; Dedovic et al., 2009; Pruessner et al., 2008). This was interpreted as a stress-related deactivation of the limbic system by the authors. Moreover brain responses in hippocampus and amygdala were found to be negatively correlated with the stress-induced cortisol increase (Lederbogen et al., 2011; Pruessner et al., 2008). However, beside this pattern of reduced brain responses, other authors reported higher stress-related brain activity in the right temporo-parietal junction, anterior and posterior cingulate cortices, the bilateral insula and hypothalamus (Lederbogen et al., 2011), pointing to the complexity of the investigated processes and the associated methodical challenges in this kind of experiments.

The aim of the present study was to investigate the neural mechanisms underlying the acute and long-term stress-buffering effect of aerobic exercise according to the cross-stressor adaptation hypothesis, as well as potential interactions of habitual and acute exercise in humans.

For this purpose, we applied the MIST subsequently to 30 minutes of either moderate aerobic exercise (AER) or “placebo” exercise (PLAC) in highly trained (HT) and sedentary (SED) men.

6.3. Materials and Methods

6.3.1. Participants

Two groups of participants were recruited via announcements at different Berlin universities and an elite sport training centre: sedentary (SED) men who did not exercise at all (< once a week), and highly trained (HT) men who intensively trained an endurance sport at least three times a week (e.g. running, cycling, swimming, rowing or triathlon). Participants with a medium level of PA were excluded. The participants had to be non-smokers, aged 20-30, right-handed, normal-weighted (BMI 19-25 kg/m^2), free of medication, and without a history of neurological or mental illness (assessed with the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

The enrolled sample consisted of N=20 HT and N=20 SED men. Data from four subjects had to be excluded during data analysis due to scanner failure (N=2) or intolerable head movements during the fMRI data acquisition (N=2). The remaining sample consisted of 19 HT and 17 SED men, who did not differ in terms of age, education, or body mass index (BMI). However, HT men were significantly more experienced with MR examinations, and had a higher aerobic capacity. Furthermore, they described themselves as less open to experiences and more conscientious than SED men, and had a higher physical self-esteem, which resulted in a higher global self-esteem as well (see Table 6.1).

Table 6.1: Sample characteristics. Descriptive statistics and results of a two-way analysis of variance (ANOVA) for the between subject factors TRAINING STATUS and TREATMENT.

Variable	Treat-ment	Sedentary men (SED)	Trained men (HT)	Statistics
Age (years)	**AER**	24.63 (3.11)	24.40 (3.95)	n.s.[a]
	PLAC	24.11 (3.02)	26.11 (3.59)	
Education	**AER**	A-level[d]	A-level[d]	n.s.[b]
	PLAC	A-level[d]	A-level[d]	
Body Mass Index (kg/m^2)	**AER**	22.84 (1.46)	22.67 (1.93)	n.s.[a]
	PLAC	21.98 (1.43)	22.99 (2.03)	
VO_2max (l/min/kg)	**AER**	47.50 (7.65)	55.80 (4.92)	**ME TRAINING STATUS[a]**
	PLAC	49.78 (3.23)	55.00 (6.56)	**HT > SED[c]: $T_{(34)}$=-3.57, p=.001**
previous MRI ex-perience y/n (%)	**AER**	2/6 (25%)	4/6 (40%)	**ME TRAINING STATUS[a]**
	PLAC	1/8 (11%)	6/3 (67%)	**HT > SED[b]: chi$^2_{(1)}$=4.760, p=.029**
Depression (BDI-II)	**AER**	3.00 (2.98)	2.30 (2.26)	n.s.
	PLAC	4.11 (2.62)	3.11 (5.76)	
Neuroticism (NEO-FFI)	**AER**	16.00 (9.38)	14.80 (7.39)	n.s.
	PLAC	14.67 (4.95)	10.89 (5.88)	
Extraversion (NEO-FFI)	**AER**	31.00 (4.72)	26.70 (7.60)	n.s.
	PLAC	29.22 (5.54)	31.67 (5.81)	
Openness (NEO-FFI)	**AER**	35.75 (6.04)	26.90 (6.17)	**ME TRAINING STATUS[a]**
	PLAC	31.78 (5.40)	29.00 (6.56)	**SED > HT[c]: $T_{(33.91)}$=2.84, p=.008**
Agreeableness (NEO-FFI)	**AER**	33.00 (7.11)	29.50 (6.64)	n.s.
	PLAC	30.33 (6.69)	28.33 (5.79)	
Conscientiousness (NEO-FFI)	**AER**	28.50 (7.84)	35.50 (5.02)	**ME TRAINING STATUS[a]**
	PLAC	31.67 (4.64)	33.22 (6.76)	**HT > SED[c]: $T_{(34)}$=-2.09, p=.044**
General self-esteem (MSWS)	**AER**	117.25 (20.54)	124.10 (17.42)	n.s.
	PLAC	116.00 (9.06)	127.67 (16.19)	
Physical self-esteem (MSWS)	**AER**	49.50 (7.86)	58.20 (6.11)	**ME TRAINING STATUS[a]**
	PLAC	47.89 (8.94)	56.22 (3.15)	**HT > SED[c]: $T_{(25.52)}$=-3.87, p=.001**
Self-concept skills internality (FKK)	**AER**	67.00 (8.99)	73.10 (8.58)	n.s.
	PLAC	68.11 (3.89)	71.11 (7.66)	
Fatalistic / social externality (FKK)	**AER**	43.13 (8.90)	41.50 (8.50)	n.s.
	PLAC	47.22 (5.04)	41.89 (6.49)	

Abbreviations: SED = sedentary men, HT = highly trained men, AER = aerobic exercise intervention, PLAC = placebo intervention, ME = main effect, n.s. = not significant VO_2max = maximal aerobic capacity (oxygen uptake in l/min/kg), MRI = magnetic resonance imaging, y = yes, n = no
Statistics: a = 2x2 Analysis of Variance, b = Chi Square Test, c = post-hoc t-test, d= median

6.3.2. Experimental Procedure

Potentially interested candidates were informed about the experimental procedures and screened for inclusion and exclusion criteria. If the subjects were eligible to participate, they gave written informed consent and underwent an examination at the institute of sports medicine to assess their aerobic fitness level. Besides a physical examination to rule out medial contraindications for moderate exercise, the subjects' VO_2max values were assessed using a modified Bruce protocol (see Bothe et al., 2013 for description).

In a second testing session, each participant was randomly assigned to one of two treatment groups after having completed a number of trait and state questionnaires (see below). The AER group walked/ran on a treadmill for 30 min at 60-70 % of their individual VO_2max, the PLAC group performed 30 minutes of placebo exercise. This treatment (as described in Knubben et al., 2007) did not induce significant cardiovascular activation and consisted of light stretching exercises for different muscle groups and light gymnastic exercises such as rotation of an ankle. The training location, the investigators and the frequency and duration of interactions with the investigators (every 5 min) did not differ between treatment groups.

After the treatment, participants completed the same state questionnaires again and underwent then three fMRI paradigms: (1) an emotion processing paradigm, (2) a monetary incentive delay task (Bothe et al., 2013; Knutson, Westdorp, Kaiser & Hommer, 2000) and finally a modified version of the Montreal Imaging Stress Task (MIST). The interval between the end of the treatment and the

beginning of the MIST was 92.75 (±10.73) min. Afterwards, the same state questionnaires were administered again.

In order to assess treatment- and stress-related fluctuations in SNS and HPA activation, cortisol and α-amylase levels were obtained from saliva samples taken throughout the testing session: upon arrival of the participant at the testing room (baseline 1), after the completion of questionnaires (baseline 2; pre-exercise), after the exercise treatment (post-exercise), before entering the MR scanner (pre-MRI), after the first (emotion processing) paradigm (MRI +20), after the second (MID) paradigm (MRI +35 min), after the structural MRI scan which was taken right before the MIST (pre-MIST), directly after the MIST (+1), and after the subject left the MR scanner (MIST +10, +20, +30, +45 min).

The study was approved by ethical board of the Charité – Universitätsmedizin Berlin and conducted in accordance with the Declaration of Helsinki.

6.3.3. Questionnaires

In order to assess mood changes related to the exercise treatment and the MIST, three state questionnaires were administered before and after the treatment and after the MIST. These state questionnaires were the German version of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), the German State Trait Anxiety Inventory (STAI; Laux, Glanzmann, Schaffner & Spielberger, 1981), and a numerical analogous scale (NAS) to evaluate how stressed the participants felt.

In order to elucidate whether training status was associated with different personality traits, we assessed self-perceived emotional stability (neuroticism), extraversion, openness to experience, conscientiousness, and agreeableness using the German NEO-Five Factor Inventory (NEO-FFI; Borkenau & Ostendorf, 1993). For the subjective locus of control, we administered the questionnaire for competence and control beliefs (FKK; Krampen, 1991), and the multidimensional self-esteem scale (MSWS; Schütz & Sellin, 2006) for general and body-related self-esteem. Finally, subjects rated their depressive symptoms using the German Beck's Depression Inventory (BDI-II; Beck et al., 2006).

6.3.4. Montreal Imaging Stress Task (MIST) – modified

To activate stress-associated neural and endocrinological processes we used an adapted version of the MIST (Dedovic et al., 2005). The stressor characteristics (mental arithmetic's combined with social evaluation), the adaptive algorithm for performance control and the layout did not differ from the original. Keeping in mind the temporal dynamics of cortisol secretion and related non-genomic feedback mechanisms, we refrained from using a traditional block design with repeated runs of control and stress conditions. Instead, a fixed sequence of 1) a no-stress condition, 2) a moderate stress condition, and 3) a high-stress condition was used in order to avoid baseline shifts due to increasing stress systems activation.

During the no-stress phase, which was announced as a non-recorded training phase and conceptually equals the control condition of the MIST, the participants were allowed a sufficiently large time interval of 20 sec to solve the arithmetic

problems. The average performance was above 90%, and timeouts virtually did not occur.

After 40 trials, the fMRI experimenter announced that trials were now recorded and that the participant's performance was now monitored by the two experimenters. During this moderate stress condition, the algorithm allowed the participant 25% less than their average reaction time from the no-stress condition, resulting in more timeouts and incorrect responses (approximately 75% correct answers). Additionally, an indicator for the faked average performance of all former participants was displayed on the feedback screen, which was consistently above the participant's performance.

After another 40 trials, the experimenter gave the subject negative feedback on his/her performance, announcing a third and last run. During this high stress phase, the algorithm allowed even less response time, resulting in an average individual performance of 50%, which was significantly lower than the fake comparison group's performance. To ensure continuous engagement, response time and task difficulty were adapted in case the participant's performance was very low.

The MIST was operated by a second experimenter who acted in a reserved (and across the experiment in an increasingly strict) way, in contrast to the friendly and empathic experimenter who conducted the rest of the testing session. Participants were carefully debriefed after leaving the scanner.

6.3.5. Behavioural and Endocrine Data Analysis

Behavioural and hormonal data were analysed using IBM SPSS Statistics 19 (http://www-01.ibm.com/software/analytics/spss). Saliva samples were centrifuged and refrigerated at -20℃ immediately after the tes ting session. Cortisol and α-amylase concentrations were extracted from the saliva samples in a specialized laboratory (Institut für Biopsychologie, Technische Universität Dresden) using a chemiluminescence immunoassay (cortisol; IBL-International, Hamburg, Germany) and a quantitative enzyme kinetic method (α-amylase; see Rohleder, Nater, Wolf, Ehlert & Kirschbaum, 2004), respectively. Since Kolmogorov-Smirnoff tests revealed that α-amylase values were not normally distributed, the data were log-transformed.

For the state questionnaires, the sum scores for the respective scales were calculated according to the test manuals. To analyze treatment- and MIST-related changes in hormone concentrations and mood across time, factorial Analyses of Variance (ANOVAs) for repeated measures were conducted with the between subject factors TREATMENT (AER/PLAC) and TRAINING STATUS (HT/SED) and the within subject factor TIME (sampling time points).. Greenhouse-Geisser correction was applied when sphericity was violated. The direction of significant main effects was analyzed using post-hoc t-tests for independent samples or paired t-tests, respectively. Bivariate correlations were performed using Pearson's correlations.

6.3.6. Magnetic Resonance Image Acquisition

Brain images were acquired by means of a 1.5-T Siemens Magnetom Sonata MRI scanner (SIEMENS Medical Systems, Erlangen, Germany) equipped with a circularly polarized head coil. During the MIST, on average 460 BOLD sensitive whole brain images comprising thirty-five axial slices capturing were acquired in an odd-even interleaved ascending order using gradient-echo echo-planar imaging (GE-EPI) pulse sequence (time to repeat (TR)= 2000 ms, time to echo (TE)= 40 ms, flip angle= 90°, matrix= 64 × 64, field of view = 224 mm, slice thickness= 3.0 mm, inter-slice gap= 0.45 mm, voxel size= 3.5 mm × 3.5 mm × 3.45 mm). B_0 field characteristic was mapped using a GE pulse sequence with the same spatial orientation and resolution as for the fMRI data acquisition and subsequent used for the correction of non-linear image distortions in the EPI images (TR= 536 ms, TE[1]= 5.19 ms, TE[2]= 9.95 ms, and a flip angle of 60°). Prior to the MIST, a 3D high resolution structural T1-weighted image was recorded (magnetization prepared rapid acquisition gradient echo: MPRAGE, TR= 2280 ms, TE= 3.93 ms, flip angle= 15°, matrix= 256 × 256, field of view= 256 mm, slice thickness= 1.0 mm, voxel size= 1 mm × 1 mm × 1 mm).

6.3.7. Magnetic Resonance Image Processing

For the processing and statistical analyses of MRI data, Statistical Parametric Mapping software was used (SPM8; Wellcome Department for Cognitive Neuroscience, University College London, UK; www.fil.ion.ucl.ac.uk/spm). In order to allow for steady state magnetization, we discarded the first three scans of each run. Voxel displacement maps (VDMs) were calculated from the B_0 - Fieldmaps to

correct for distortion related to magnetic field inhomogeneity. EPIs were corrected for acquisition delay and motion artefacts, and unwarped using the VDMs created beforehand. The structural brain image was co-registered to the mean unwarped EPI, segmented using the unified segmentation approach as implemented in SPM8 (Ashburner & Friston, 2005) and transformed into the standard space provided by the International Consortium for Brain Mapping (ICBM, http://www.loni.ucla.edu/ICBM/). Structural and functional images were normalized applying linear and non-linear transformations as estimated in the step before. Finally, spatial low pass filtering was applied to the normalized EPI images using an isotropic Gaussian kernel (full-width-half-maximum, FWHM = 7 mm). The image and pre-processing quality was ensured by visual inspection. Participants with heavy head movements (> 3.5 mm and/or 1°), artefacts and/or pronounced signal extinctions due to susceptibility effects were excluded from further analyses.

6.3.8. Functional Magnetic Resonance Imaging Effect Modelling and Statistical Testing

Single subject analysis: As mentioned in the introduction, we were interested in the sustained brain responses associated with psychological stress. In other words, we aimed to capture the neural correlates of HPA axis activation as measured by cortisol increase. To this end, we used a somewhat unusual fMRI design. In contrast to the original MIST, we did not use alternating stimulation blocks with varying levels of stress, because we assumed low frequency (nearly sustained) neural effects associated with the slowly increasing cortisol level. To address this issue with an experimental design, mental arithmetic tasks and faked

social evaluation were only used to increase the stress level. The stress level itself in our opinion is best described by the constant of the general linear model (GLM), representing the mean signal within a experimental session or stress level period, respectively. Besides, the model contained regressors of no interest for the task and feedback screen, the motor response as well as the six motion parameters as obtained from the motion correction. Before fitting this model to the data, low frequency signal drifts were removed applying of a high-pass filter with a cut-off frequency of 1/256 Hz. Aliasing effects and serial correlations in the time series were modelled using an autoregressive model of 1st order (AR1). The parameters of the model were estimated by means of the restricted maximum likelihood (ReML) algorithm as implemented in SPM. Finally linear contrast images were computed for the sustained effects of the different stress levels.

Group analysis: These contrast images were analyzed by means of a three factorial Analysis of Covariance (ANCOVA) for repeated measures with the between subject factors TREATMENT (AER/PLAC) and TRAINING STATUS (HT/SED), the within subject factor STRESS LEVEL (no/moderate/high), and global normalization. Only results passing an statistical threshold of $p < .001$ (uncorrected for multiple comparisons) and with a minimum cluster size of ≥10 adjacent voxels were considered for report and discussion.

Exploratory correlation analyses: We conducted an exploratory correlation analysis between treatment-induced changes in BOLD response in brain structures have been shown to be particularly involved in HPA axis regulation (specifically the bilateral hippocampi and the ACC) and treatment-induced changes in cortisol levels, α-amylase levels, and positive mood. To this end, we extracted the BOLD

effect sizes within a sphere of 5 millimetres diameter around the voxel with the greatest difference in BOLD response between treatment groups in these brain structures.

6.4. Results

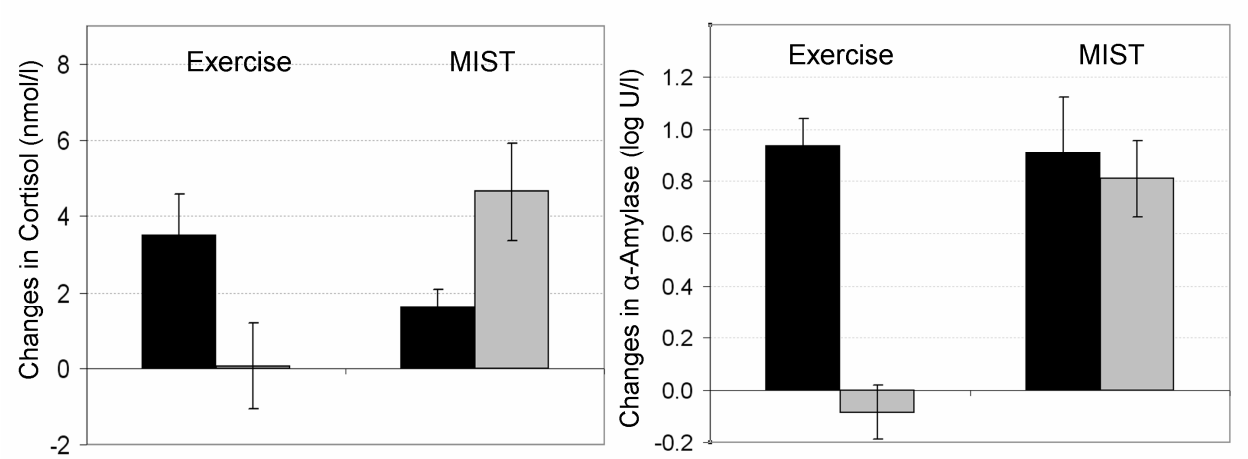
6.4.1. Cortisol and α-Amylase Responses to Treatment

Changes in α-amylase and cortisol levels over time significantly differed between TREATMENT groups (α-amylase: $F_{(1,32)}$ = 47.077, p<.001; cortisol: $F_{(1,32)}$=4.246, p=.048). We found larger α-amylase increases from pre- to post-treatment in the AER group compared to the PLAC group ($T_{(1,34)}$=6.933, p<.001). Cortisol levels decreased in the PLAC group, according to the diurnal slope, whereas they remained unchanged in the AER group ($T_{(1,34)}$=2.215, p=.034). Moreover, exercise-related changes in cortisol and α-amylase levels were positively correlated (r=.413, p=.012) and did not differ between HT and SED men (p>.1).

6.4.2. Effects of TREATMENT and TRAINING STATUS on Cortisol and α-Amylase Responses to the MIST

Cortisol responses to the MIST were significantly different between treatment groups (TIME*TREATMENT interaction $F_{(1.86,57.77)}$=3.512, p=.039), with larger MIST-induced cortisol increases in the PLAC compared to the AER group ($T_{(21.75)}$=-2.220, p=.037). A-amylase increases following the MIST did not differ between TREATMENT groups. Treatment-induced cortisol and α-amylase increases were inversely related to cortisol responses to the MIST (r=-.462, p=.005 for cortisol, and r= -.338, p=.044 for α -amylase).

Figure 6.1.: Cortisol (left panel) and α-amylase (right panel) responses to the exercise treatment and the MIST (mean and SEM).
Black bars represent the AER group, grey bars represent the PLAC group. Cortisol levels are adjusted for circadian slope.



With regard to TRAINING STATUS, we found no differences in baseline endocrine measures and exercise- or MIST-related changes in cortisol and α-amylase levels, nor interactions between TRAINING STATUS and TREATMENT. However, we found an interaction between the actually *measured* aerobic fitness (VO_2max) and cortisol responses to acute exercise and to the MIST, respectively: fitter males reacted with a higher cortisol increase to exercise (r=.312, p=.064, trend) and had a significantly lower cortisol response to the MIST (r=-.386, p=.020).

6.4.3. Mood changes after the TREATMENT

Across the whole sample, subjective stress ($T_{(35)}$= -2.727,p=.012) and negative affect ($T_{(35)}$= -2.260, p=.030) were significantly lower after the exercise intervention, and statistically a trend, positive affect was higher ($T_{(35)}$=1.961, p=.058). While stress and negative affect changes did not differ between AER and PLAC, there were larger increases in positive affect in the AER group ($T_{(34)}$=2.305,

p=.027), and fewer reduction in state anxiety ($T_{(34)}$= -1.783, p=.083 (trend)) than in PLAC. SED and HT did not differ in these mood changes, and TRAINING STATUS did not interact with TREATMENT group (all p > .1).

6.4.4. Effects of TRAINING STATUS and TREATMENT on MIST-related Mood Changes

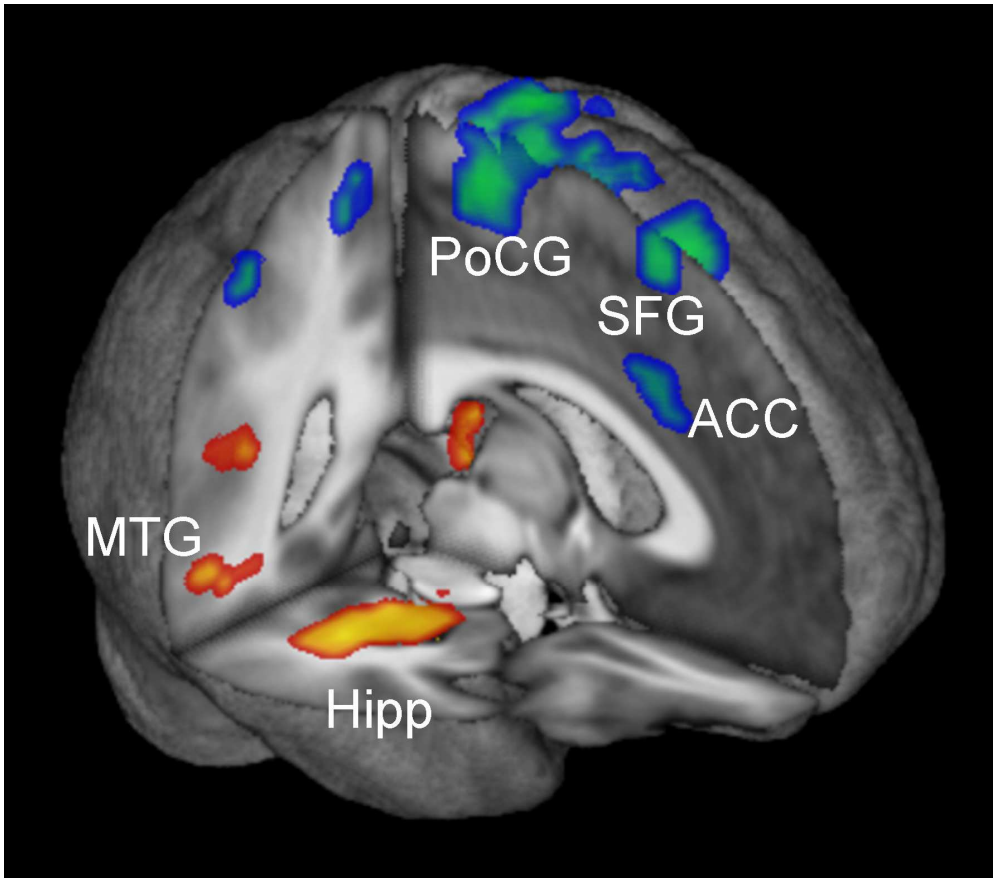
Across the whole sample, participants reported higher state anxiety ($T_{(35)}$= 6.435, p<.001), negative affect ($T_{(35)}$= 5.248, p<.001), subjective stress ($T_{(35)}$= 4.096, p<.001) and lower positive affect ($T_{(35)}$= -5.707, p<.001) after the MIST, compared to pre-MIST. No differences were found between AER and PLAC or SED and HT with regard to MIST-induced mood changes. Treatment- and MIST-related changes of state anxiety and positive affect were negatively correlated (state anxiety: r=-.604, p<.001, positive affect: r=-.428, p=.009).

6.4.5. Effects of TRAINING STATUS and TREATMENT on Brain Responses to the MIST

BOLD signal changes related to the STRESS LEVEL can be found in Supplementary Material B1 & B2. Across all stress levels, the AER group showed higher sustained BOLD signal in the bilateral hippocampus/parahippocampal gyrus and the bilateral middle temporal gyrus, compared to the PLAC group. In contrast, the PLAC group had a higher sustained BOLD signal in the bilateral paracentral lobule, the supplementary motor area (SMA), the pre-and postcentral gyri, the left anterior (ACC), the right middle cingulate cortex (MCC); the right middle and inferior frontal gyri and the right precuneus (see Figure 6.2; tables with whole-brain

activations are listed in Supplementary Material B3 & B4). These differences were independent of STRESSLEVEL. We found no significant interactions between TREATMENT and STRESSLEVEL.

Figure 6.2: TREATMENT-related differences in sustained brain responses to psychological stress.
Brain areas with a more pronounced BOLD response in the AER group are colour coded from red to yellow. Brain areas with a more pronounced BOLD response in the PLAC group are colour coded from blue to green.



Abbreviations: MTG = middle temporal gyrus, Hipp = hippocampus, PoCG = postcentral gyrus, SFG = superior frontal gyrus, ACC = anterior cingulate cortex.

6.4.6. Correlations between BOLD Signal and Behavioural Changes during Exercise

Moreover, the exercise treatment-induced changes in cortisol and alpha-amylase were positively correlated with the BOLD signal in the bilateral hippocampi, and negatively correlated with the BOLD signal in the left ACC.

Table 6.2: Correlation between treatment-induced behavioral and selected brain responses. Coordinates are given in MNI space (mm).

Brain structure	Treatment-induced changes in cortisol levels	Treatment-induced changes in α-amylase levels	Treatment-induced changes in positive affect
Hipp (left) (-26 -21 -19)	r= .215 p= .025	r= .308 p= .001*	n.s.
Hipp (right) (38 -25 -19)	r= .238 p= .013	r= .282 p= .003*	n.s.
ACC (left) (-1 21 31)	r= -.191 p= .048	r= -0.283 p= .003*	n.s.

Abbreviations: Hipp = Hippocampus, ACC = Anterior Cingulate Cortex
** Bonferroni corrected for multiple comparisons*

With regard to TRAINING STATUS, HT men had a (STRESSLEVEL-independent) higher BOLD signal in the left middle temporal gyrus and the left MCC, whereas SED men showed a higher sustained BOLD signal in the right temporal pole (see Table 6.3).

Table 6.3. TRAINING STATUS-related differences in brain response to MIST

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FDR)	p (FWE)	MNI coord. (mm) x	y	z
HT > SED									
Middle Temporal Gyrus TE 3 (10 %)	L	12	4.91	<.001	.011	.013	-64	-7	-15
Middle Cingulate Cortex SPL (5M) (30 %)	L	10	3.71	<.001	.252	.853	-1	-42	55
SED > HT									
Temporal Pole	R	13	4.59	<.001	.037	.063	59	14	-8
Temporal Pole	R		3.84	<.001	.174	.714	62	7	-5

Abbreviations: CP = cytoarchitectonic probability, H = hemisphere, vox = voxels, FDR = corrected for false discovery rate, FWE = corrected for family-wise error, MNI = Montreal Neurological Institute, HT = highly trained men, SED = sedentary men, l = left, r = right

6.5. Discussion

In our study, we found sustained effects of a 30-minutes aerobic exercise intervention on the cortisol and neural responses to the MIST, conducted more than 90 minutes later. Participants of the AER group showed lower cortisol responses to the MIST, and treatment-induced amylase- and cortisol level changes were inversely correlated to the cortisol stress response to the MIST. In the AER group, the sustained brain response was more pronounced in the bilateral hippocampi and middle temporal gyri, compared to the PLAC group. In contrast, we found a more sustained brain response in bilateral pre- and postcentral regions,

the anterior and middle cingulate cortices, and the right middle frontal gyrus in the PLAC group. Furthermore, changes in cortisol and alpha-amylase levels during the aerobic exercise were correlated with sustained brain responses to the MIST in the hippocampus and ACC.

As mentioned above, both the hippocampus and the ACC are closely involved in HPA axis negative feedback. Once cortisol circulates in the blood and binds to MR and GR receptors in the brain, the hippocampus exerts an inhibitory action on the PVN, reducing CRH secretion (Herman et al., 2005). In our study, the AER group showed higher sustained hippocampal activity, which was positively correlated with previous exercise-related cortisol increases, i.e. the sustained activity of the bilateral hippocampi was the higher, the more cortisol levels increased during exercise. Along with the negative correlations between treatment-induced and MIST-induced cortisol increases, this suggests that the negative feedback loops remain active for a sustained period, dampening further HPA responses. This is in line with earlier studies on the relationship between exercise-induced cortisol increases and subsequent “heterotypic stressors”. For example, the typical post-prandial cortisol increase was found to be diminished after previous exercise (Brandenberger & Follenius, 1975; Brandenberger, Follenius & Hietter, 1982), especially in untrained subjects (Duclos, Corcuff, Rashedi, Fougere & Manier, 1997). Our study additionally demonstrates that HPA axis activation (not even an increase, but simply a flatter circadian slope) inhibits the cortisol stress response 1 ½ hours later, when cortisol levels are comparable between treatment groups. For the SNS marker α-amylase, no such inhibitory effect was found, but

interestingly, a higher SNS activation during exercise was also negatively related to the subsequent cortisol stress reaction.

On the other hand, the ACC was more active in the PLAC > AER condition, and its activation was negatively correlated to the exercise-induced fluctuations in cortisol and alpha-amylase. This seems surprising, because similar to the hippocampus, the ACC is involved in HPA axis inhibition via the ventrolateral preoptic area, dorsomedial hypothalamus and peri-PVN region (Herman et al., 2005). The peak activity was found in the dorsal ACC which is considered as “cognitive” ACC. Thus, higher cognitive coping skills may have been required in PLAC subjects to solve the arithmetic tasks and cope with increasing negative feedback.

Other than the original MIST studies (Pruessner et al., 2008), we did not observe a general deactivation of the hippocampus and ACC during stress. Instead, we even found a stronger stress-related activation of the ACC. This may be related to the fact that we did not use a traditional fMRI block design (repeated baseline measures), but a design of increasing stress level. Other studies using the MIST or similar designs also reported increased ACC activation under stress (Lederbogen et al., 2011; Wang et al., 2005).

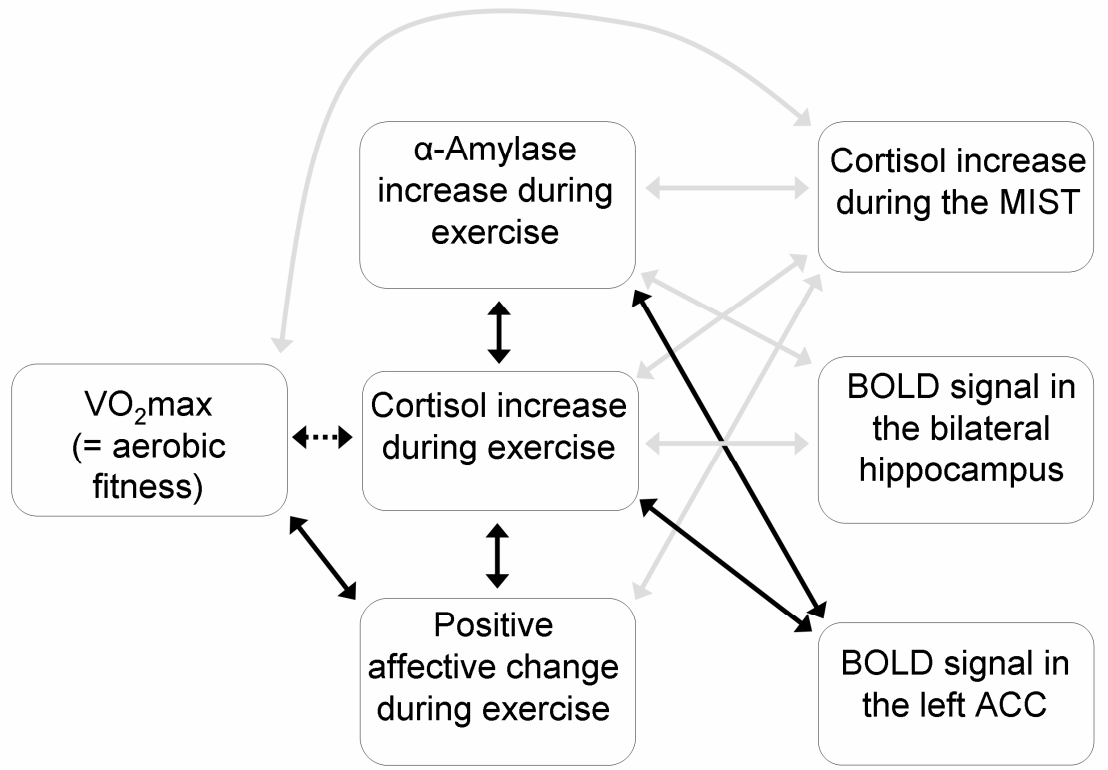
The exercise-induced hormonal and mood changes in the present study are mostly consistent with the literature. Like previously reported, even the very-light intensity PLAC condition was sufficient to reduce state anxiety, stress, and negative affect from pre- to post-treatment (Reed & Ones, 2006). In contrast, positive affect significantly increased during the treatment only in the AER group.

From previous studies, one may have expected larger positive increases in the HT sample (Hoffman & Hoffman, 2008), but the individually adapted intensity and self-paced speed (participants were free to walk or run, within the heart rate range that corresponded to 60-70% VO_2max) obviously allowed positive changes also in untrained subjects. Treatment-induced cortisol and positive mood change were positively correlated (r=.417, p=.011), which supports the suggestion that cortisol may exert a mood-buffering effect (Het, Schoofs, Rohleder & Wolf, 2011). In the present study however, the mood improvements induced by exercise did not buffer the self-reported mood decline following the MIST. In contrast, the MIST nullified any prior mood improvement reported by the participants, as reflected in the negative correlation between treatment- and MIST-induced positive affect and state anxiety.

Interestingly, the exercise-induced mood improvement turned out to be relevant at another level: increases in positive affect and decreases in negative affect during exercise were negatively correlated to MIST-related cortisol increases (positive affect: r= -.456, p=.005, negative affect: r=-.358, p=.032). Although few studies have directly investigated the stress-buffering effects of state positive and negative affect, this is in line with studies that found higher HPA axis reactivity after negative mood induction (Mendonca-De-Souza et al., 2007) and lower stress reactivity in subjects with higher (trait) positive affect (Dockray & Steptoe, 2010; Steptoe, Gibson, Hamer & Wardle, 2007). Since positive affect and cortisol changes after treatment were positively correlated (discussed above), this suggests interactions between affective changes and neuroendocrine mechanisms

with regard to the stress-buffering action of exercise. The interactions are illustrated in Figure 6.3.

Figure 6.3: Illustration of correlations between person characteristics, exercise-induced states and correlates of psychosocial stress.
Black lines represent positive correlations, grey lines represent negative correlations, solid lines represent statistical significance at p<.05, dotted lines represent a statistical trend (p<.1).



Abbreviations: VO_2max = maximal aerobic capacity, MIST = Montreal Imaging Stress Task, BOLD = blood oxygen level dependent, ACC = anterior cingulate cortex

In the context of a study like ours, there are several potentially stressful aspects depending on each subject's biography and personal characteristics, which interact with the experimental stressors of exercise and the MIST. For example, the mere fact of participation in a study comprising elements of physical

exercise or MRI examination may be experienced as stressful. Studies suggest that the MRI environment is a stressor *per se*, particularly for inexperienced subjects (Muehlhan, Lueken, Wittchen & Kirschbaum, 2010). Our results however found the opposite direction: HT men who had undergone MRI examinations significantly more often than SED men (see table 6.1), displayed trend-wise higher cortisol increases during the first 20 min inside the MRI scanner ($T_{(34)}$=-1.86, p=.071). One possible explanation is that HT men may be more prone to training-induced injuries requiring medical examinations. Therefore, they may know the scanner from an aversive, injury-related situation leading to an anticipatory HPA axis response. In any case, MRI-related cortisol fluctuations did not correlate with treatment- or MIST-induced cortisol changes, indicating that it did dot affect the exercise-related effects reported here.

Besides the acute effects of treatment discussed above, we also found some effects of training status (see Table 6.1). In line with the literature (Malinauskas, Dumciene, Mamkus & Venckunas, 2014; McAuley, Mihalko & Bane, 1997; Taylor & Fox, 2005), HT men reported higher levels of body-related self-esteem (resulting in a higher global self-esteem score) and conscientiousness. Unlike previous studies (de Moor, Beem, Stubbe, Boomsma & de Geus, 2006), our participants did not report higher extraversion and openness or lower neuroticism (Malinauskas et al., 2014; Rhodes & Smith, 2006).

These differences in personality traits may be related to the psychoneuroendocrine findings of our study. First, subjects with a higher self-esteem have been previously shown to show lower stress responses to laboratory psychosocial stress tasks

(Pruessner et al., 2005). As our results show, this effect may be related to aerobic fitness, which is associated with a higher physical (and as a result, a higher global) self-esteem. Second, the descriptive finding cortisol increases after entering the scanner environment may be related to lower openness and higher conscientiousness in HT men. One can speculate that these may have perceived a higher degree of performance pressure and evaluation prior to and during the beginning of the fMRI experiment, resulting in a small additional HPA axis activation.

Whereas α-amylase changes were not different in SED and HT men, the exercise treatment induced descriptively higher cortisol levels in HT men (statistical trend). This questions earlier reports on reduced HPA responses and faster recovery to absolute, but not to relative treatment workload in trained persons (Gerber, 2008; Hackney, 2006). Also, one may have expected higher psychological stress in unfitter men (feeling uncomfortable and evaluated during exercise). Unlike other studies (see Hackney 2006), we did also not observe baseline differences in cortisol levels between HT and SED men. The latter finding is likely related to the fact that an upcoming psychological study including exercise intervention and fMRI examination can hardly be compared to normal baseline levels on control days, as reflected in relatively high baseline cortisol levels across the whole sample.

In a correlational approach, fitter men had lower MIST cortisol responses, although in the ANOVA, SED and HT did not differ significantly. This limits the argument of higher self-esteem as a buffer for stress (see Pruessner et al., 2005)

in the present study, body-related self-esteem was indeed higher in the HT group, but we found no correlation between objectively measured aerobic fitness and self-esteem. Instead, the reported correlation may be related to an increase in positive affect during treatment, which was positively correlated with the VO_2max (r=.346, p=.038), i.e. fitter subjects archived greater mood improvements during acute exercise. As discussed above, this may substantially contribute to the stress-buffering effect during the MIST.

6.5.1. Limitations

There are a number of limitations with regard to our results. First, the MIST induced only small absolute increases in salivary cortisol. It is known from other studies using the MIST that it is a weaker stressor than e.g. the TSST, having a higher percentage of non-responders (Dedovic et al., 2009; Pruessner et al., 2008). This may be due to the lack of face-to-face social interaction with the experimenters, or the simple fact that the subject is in supine position, which has been shown to alter the neural processing of negative feedback (Harmon-Jones & Peterson, 2009). The stress-buffering effect of AER and the assumed HPA down-regulation should therefore be replicated in studies using more potent stressors, like the TSST.

Also, baseline cortisol levels were relatively high, which resulted in a cortisol decrease across the whole sample during exercise. In other studies, a longer rest interval was implemented at the beginning of the testing session, allowing the participants to recover to a lower baseline. Alternatively, exercise-induced increases in cortisol should be calculated relative to their circadian baseline (using

cortisol samples of a control day (see Thuma, Gilders, Verdun & Loucks, 1995) to avoid the risk of an underestimation of these increases when only a pre-exercise baseline is used.

The evidence presented here is limited to men. Since several studies pointed out gender differences regarding psychosocial stress and HPA axis feedback (Bangasser & Valentino, 2014), future studies should consider stress-specific effects and interactions.

Although our results seem to corroborate the cross-stressor adaptation hypothesis with regard to acute exercise, it remains speculative whether this effect is specific for exercise, or whether *any* pre-activation of the HPA axis will result in a blunted cortisol response and higher hippocampal activity. Studies using an inverse protocol (e.g. a psychosocial stressor subsequent to a bout of exercise or a rich meal) could clarify this issue.

Finally, our fMRI analysis approach is somewhat unusual and seems to ignore the relative character of fMRI data. However, previous studies reported long-lasting neural effects of stress and suggested other approaches than the BOLD contrast "*to study the neural substrates of psychological stress, because subjects could no longer return to a ''baseline'' state after stress tasks, as assumed in a conventional block design in BOLD fMRI*" (Wang et al., 2005). Therefore, our statistical model allows to capture tonic drifts of neural activity induced by increasing psychoneuroendocrine activation of the SNS and HPA axis.

Taken together, our results suggest that 30 minutes of aerobic exercise are related to a blunted cortisol response to a subsequent psychosocial stressor.

Mechanisms underlying this stress-buffering effect are the feedback inhibition of the HPA system and an exercise-induced increase in positive affect.

7. General Discussion

In the popular scientific media, exercise is widely proposed to be an effective treatment for mental disorders. Two systematic reviews (Articles I & II) aimed at elucidating whether scientific evidence is sufficient to recommend exercise as a treatment strategy for all groups of mental disorders. Article II focused on SUD, since no systematic review was published so far that looked beyond nicotine dependence. In an fMRI study, the neural correlates of two central mechanisms of action of exercise, namely reward processing (Article III) and stress reactivity (Article IV), were studied in healthy humans. The implications of the findings for research and practice are discussed in the following sections. The final part of this chapter will provide a discussion of study limitations and an outlook for future research directions.

7.1. Exercise as a Treatment for Mental Disorders

Despite articles abounding with certainty in the popular media (Hauschild, 2013; Heinhold, 2014) and optimistic reviews calling to support physical activity as a legitimate treatment for mental health problems (e.g., Callaghan, 2004), evidence is weaker for most groups of disorders than one may assume. The beneficial effects of exercise are highly attractive, intuitively plausible and widely supported by clinicians' experiences, yet there seems to be a mismatch between published scientific and perceived evidence. For depression and smoking, which are undisputedly two major public health problems, several meta-analyses support small, but clinically relevant effects of exercise interventions (Cooney et al., 2013; Ussher et al., 2008). In contrast, there are only single RCTs for anxiety disorders,

dementia, schizophrenia and eating disorders. For alcohol and drug dependence and bipolar disorder, there is only evidence from quasi-experimental or observational studies (by the time of publication of Articles I & II). Moreover, most of those have too small sample sizes or other methodological concerns limiting their informative value (see Articles I & II), not to mention conclusions about cost-efficacy or dose-response relationships. Two recent studies in alcohol dependent patients (Brown et al., 2014) and pathological gambling (Angelo, Tavares & Zilberman, 2013) yield promising results with regard to addictive behaviour and accompanying depressive or anxious sysmtoms, but lack an experimental design (self-selection of the participants to either exercise or control condition (Angelo et al., 2013) or use multi-faceted interventions (behavioural coaching+ exercise + incentives), therefore making it impossible to identify the pure exercise effect component (Brown et al., 2014).

This is even more astonishing considering that virtually *every* psychiatric and psychosomatic clinic (including university hospitals) offers exercise programs to their patients. It appears the effects of most of these innumerable exercise programs have either never been evaluated, or for some reason study results have not been published.

This highlights a number of problems related to research on exercise interventions in mentally ill:

First, the popularity of the assumption that exercise is beneficial for (mental) health may lead to a publication bias with negative results being less likely to get published. On the other hand, the published evidence is not concordantly positive

(contrary to selective citations in the popular media) with several studies reporting no significant effects of exercise interventions.

Second, exercise intervention studies seem less likely to receive funding. Although one would expect great interest in scientific evaluation and improvement of existing programs on the part of health and pension insurance companies, there is still no billion-dollar-lobby supporting this area of research.

Third, it is a huge challenge to involve patients with severe mental illness in exercise programs and sustain their compliance and adherence over several weeks or months. Attrition rates are generally a massive problem in exercise even in healthy, highly-functional individuals (see Woodard & Berry, 2001), which is even more true for patients with mental disorders (see Bezyak, Berven & Chan, 2011).

Studies show that people will only engage in regular exercise when the single bouts of exercise are acutely rewarding, pleasant and mood-enhancing to them (De Geus & De Moor, 2008; Kwan & Bryan, 2010). This depends not only on physical constitution and genetic factors influencing the responsivity of the brain reward system, but also on previous exercise experiences (Parschau et al., 2014) and a careful choice of exercise type, intensity and duration. In addition, patients require a particularly supporting, encouraging environment, feelings of success, and careful adjustment of task difficulty and feedback to their individual needs. This however interferes with the claim of standardization and quantifiability in RCTs.

In their qualitative study, Carless and colleagues point out that in severe mental illness not physicala activity *per se* is helpful, but the way in which exercise interventions are delivered (Carless & Douglas, 2012). This may explain

heterogeneous study results despite apparently similar exercise characteristics (duration, frequency, intensity). "*While prescription typically focuses on the technical or mechanistic aspects of provision, service user accounts often prioritise cultural and social aspects of provision such as (for example) social organisation, leadership style, or coaching approach. Given the challenges to physical activity initiation and maintenance among people with severe mental illness [...], it seems to us that the way physical activity is offered—aside from what is offered—may be critical in terms of participation* (Carless & Douglas, 2012). In line with this proposal, Harvey and colleagues (2010) suggest that social factors, compared to biological markers, may be more relevant in a realistic setting (Harvey et al., 2010). Recent studies highlight factors such as the exercise environment (Mitchell, 2012; Thompson Coon et al., 2011) or attitudes of the exercise providers and coaches (Lippke, Knauper & Fuchs, 2003) to be crucial for positive psychological exercise effects and adherence.

This questions, however, the specificity of the observed effects, and some authors even attribute a large portion of the observed (acute) changes to a placebo effect (Szabo, 2013). Indeed, it is hard to establish a suitable control condition in exercise studies, and effects are smaller, the better studies are controlled with regard to peer group interaction, or therapeutic contact time. Widely used control groups include educational sessions (Marcus et al., 1995; Ussher et al., 2003; Vickers et al., 2009), group discussion, meditation (e.g. Murphy et al., 1986), relaxation (e.g Wedekind et al., 2010.), or mindfulness-based exercise interventions such as yoga or qui-gong (Duraiswamy, Thirthalli, Nagendra & Gangadhar, 2007; Elibero et al.,

2011), which all have to be considered active treatments. This points towards psychological and social effects which are not exclusive to exercise and complement or superpose its physiological and neurobiological effects discussed in the introduction of this thesis.

In the context of SUD, a recent review also highlights the importance of timing (Lynch, Peterson, Sanchez, Abel & Smith, 2013). Depending on the stage of substance use (initiation of drug use, transition from use to addiction, withdrawal, and relapse), exercise may have a positive or negative impact and act via different neurochemical pathways and mechanisms (e.g. dopamine and glutamate signalling). To date, this “stage-dependent hypothesis” is mainly based on findings from animal studies, but will hopefully stimulate and systematize future research in humans.

Another topic underrepresented in the literature is the documentation of adverse exercise effects, which are most often reported in dementia (e.g. fall-related injury), eating disorders (compulsive exercise for weight reduction), and, in an anecdotic way, in bipolar disorder (triggering maniac episodes). In most other studies, adverse effects, especially of psychological nature, are not explicitly documented. Yet, one can assume that they are partly reflected in high dropout rates.

Besides the question of specificity in symptom reduction, a major and largely undisputed advantage of exercise interventions in the context of severe mental disorders is the reduction of physical comorbidity. People especially with chronic mental illness usually show poor physical health and health behaviour, and have a

higher risk for premature death from cardiovascular, metabolic respiratory or neoplastic diseases (see Bezyak et al., 2011; Chacon et al., 2011). Exercise interventions, along with coaching, may help patients giving some thought to generally modify lifestyle habits (Attux et al., 2011; Bezyak et al., 2011; Chacon et al., 2011).

With regard to clinical population, one needs to keep in mind that low exercise intensities, which are barely sufficient to induce any of the beneficial neurobiological or physical adaptations (fitness or strength increase) and are less promising in the long run (see Articles I & II), result in the greatest acute mood improvements (Reed & Ones, 2006). Maybe in very untrained subjects - and people with chronic severe mental illness usually are in a physically poor condition - (Chacon et al., 2011) training should consist of very light exercise to develop exercise-related self-efficacy and the positive expectation that exercise is a pleasant experience (and useful active coping strategy), instead of expecting measurable fitness increases within 10 weeks.

7.2. Acute Alterations in Reward Processing

In our fMRI study (Article III), we found that aerobic exercise diminished the neural response to the anticipation and feedback of monetary rewards in the ventral striatum. Anticipation and feedback of monetary losses were not affected by previous exercise, and the effects did not differ between highly trained and untrained men. We discussed our results with regard to the tonic-phasic dopamine hypothesis, assuming that acute aerobic exercise induced a tonic increase in

striatal dopamine levels which diminished the phasic responsiveness of dopaminergic neurons in the ventral striatum.

As mentioned in Article III, our findings corroborate the assumption that the neural activity elicited by non-drug rewards is reduced after acute exercise (Evero et al., 2012; Taylor & Oliver, 2009), which has behavioural consequences, e.g. lower ad-libitum chocolate consumption (Oh & Taylor, 2012) or craving for gambling (Angelo et al., 2013). Studies in smokers (Taylor et al., 2007; Ussher et al., 2004; Ussher et al., 2008) demonstrate that this conclusion can be extended to psychotropic substances, and thus, has a high clinical relevance. A recent study explicitly addressed the question of reward in this context (Kurti & Dallery, 2014). The authors found that acute aerobic exercise (best at moderate intensities) diminished the anticipated rewarding effects of smoking and increased the delay until the next cigarette. In contrast, exercise did not affect the subjects' expected relief from withdrawal symptoms, which is another component of craving.

Likewise, our fMRI study did not reveal an effect in the anticipation and processing of monetary losses, suggesting that exercise may selectively modulate appetitive/hedonic components of reward processing.

Linking this result to the clinical context of SUD (Article II), the reduction of anticipated rewarding properties may constitute one important mechanism of action in the long-term outcome of SUD by reducing the probability of relapse.

In our fMRI study, we found no difference between highly trained and sedentary men with regard to acute exercise-induced changes. As mentioned in Article III, the literature is controversial regarding long-term adaptations of the (dopaminergic) reward system to regular exercise. There is preliminary evidence that exercise can

positively influence SUD therapy outcomes in the long run (see Article II). It may be speculated that these positive long-term outcomes may be related to the accumulated acute effects of exercise. In a clinical context, it is encouraging that single bouts of exercise are able to induce craving reduction even in untrained subjects, rather than requiring several weeks of training before this effect can be observed. In this case, acute bouts of exercise could serve as an active coping strategy from the beginning of each SUD therapy.

Of course, one must be cautious to generalize our findings from healthy young volunteers to patients with mental disorders, especially SUD. Several neuro-imaging studies show that lower neural responses to reward are found in samples with pathological gambling (Reuter et al., 2005), depression (Pizzagalli et al., 2009), alcohol dependence (Beck et al., 2009), or eating disorders (Bohon & Stice, 2011). This hypoactivity of the reward system, probably related to a reward-deficiency-syndrome or a hypoactive behavioural activation system (BAS; see Ginty, 2013) needs to be carefully distinguished from the (supposedly) transient hypo-reactivity induced by exercise in healthy subjects.

The D_2 receptor, which probably mediates the acute effects of exercise described in Article III, was found to be downregulated in SUD (see Lynch 2013, Ginty 2013). Therefore, it is a thrilling question how exercise impacts on neural reward processing in clinical populations, and whether exercise can normalize disturbed reward processing. Animal studies and, to a lower extent human studies also suggest that the impact of exercise on reward processing may be particularly sensitive to the subject's stage of dependence (as reviewed by Lynch et al., 2013).

Thus, further research needs to be done to elucidate the effects and mechanisms in clinical populations.

7.3. Acute Alterations in Stress Reactivity

In our fMRI study on stress reactivity (Article IV), we found that the psychoneuroendocrine responses to a psychosocial stressor were inversely related to the previous affective and psychoneuroendocrine responses to acute exercise. We also found BOLD signal differences between the experimental and the control group, but the effects did not differ between highly trained and untrained men. These results were discussed in the light of HPA feedback mechanisms and positive affective changes as a moderator.

Our finding that acute exercise seems to produce sustained feedback loops in the HPA system which consequently impact on subsequent stressors appears trivial at first glance and has been hypothesized for several years (Sothmann, 2006). However, to our knowledge, no study has shown this inverse relationship in an experimental design so far. Additional to psychoneuroendocrinological measures, subjective and neuroimaging data yielded a comprehensive picture in our study.

A drawback of our study might be the possible influence of a couple of additional mild stressors which may have interfered with the experimental design that was set to investigate two heterotypic stressors, namely exercise and the MIST. The mere fact of participation in a scientific study (especially a study taking place in the psychiatric department of a university clinic) may have been a stressor for most subjects (reflected in the high baseline cortisol levels). Second, the subjective and

psychoneuroendocrinological responses to the exercise intervention were quite individual- for some participants placebo exercise seemed to be stressful enough, whereas others did not show any significant response to moderate treadmill exercise which, according to the literature, should have been sufficient to induce a HPA response (Deuster et al., 1989; Hill et al., 2008). Although experimenter contact was standardized and comparable in both conditions, some subjects may have felt more evaluated in one or the other exercise condition, based on previous experiences, personal preferences, and situational factors. Untrained subjects may have been generally more uncomfortable with the fact that they had to “exercise” under supervision for 30 minutes, which is a more common situation to highly trained athletes. Unfortunately, we did not assess subjective levels of stress during, or explicitly referring to the circumstances of exercise.

Additionally, as discussed in Article IV, the scanner environment obviously constituted another mild stressor to some of our participants, seen in increasing cortisol levels after entering the MR scanner especially in fitter subjects. Together with the fact that the overall psychoneuroendocrine responses to the actual psychosocial stress paradigm (the MIST) were small, this may limit the interpretation of our results. Yet one can argue that in real life, people are constantly facing different situations and encounters that are potentially stressful, and stress responses overlay and interact with each other all the time. The fact that we found a clear negative correlation between exercise-induced and MIST-induced stress markers despite intermediate stressors like the MR scanner environment indicates a relevant effect. Our study also indicates that the individual appraisal of a stressor is particularly relevant, as suggested by a pioneer of stress research,

Richard Lazarus (Folkman, Lazarus, Gruen & Delongis, 1986; Lazarus & Alfert, 1964). While in exercise, the activation of the SNS and HPA systems was associated with mood enhancement, similar changes were accompanied by significant mood worsening after the MIST. Thus, the suggestion of the "Cross-stressor adaptation hypothesis" (Sothmann et al., 1996) may in great parts rely on differential appraisal of the situation. Primary and secondary appraisal (and related variables like self-efficacy) are therefore worth being assessed during and after exercise and psychosocial stress in future studies, in order to find mechanisms which may modulate the cross-stressor buffering effect.

Future studies could also use structural equation modelling to confirm the associations we found in our exploratory correlation analyses between personal characteristics (aerobic fitness), exercise-induced changes (mood, cortisol, α-amylase) and psychobiological stress markers (cortisol, α-amylase, neural activity).

In the clinical studies reviewed for Articles I & II, several explicitly addressed subjective stress levels in different mental disorders, and most reported positive acute and long-term effects of exercise on subjective stress levels (e.g. Merom et al., 2008; Ng, Dodd & Berk, 2007; Vancampfort et al., 2011). The finding that an exercise intervention does not have to be strenuous to induce this effect (like yoga in Vancampfort et al., 2011) is in line with our result that subjective stress ceased likewise in the placebo and the exercise condition (Article IV). This indicates that other mechanisms than the ones related to pure physiological effects of aerobic exercise play a decisive role, e.g. distraction, being physically "active" in any way,

becoming comfortable with the previously unknown situation, and gaining confidence/self-efficacy that the task is manageable.

Since the MIST represents not only an apparently week stressor for the HPA axis, but also a highly artificial situation, our results should be replicated with stronger, and personally more relevant stressors. Unfortunately, this interferes with an fMRI testing environment, but mood, salivary stress markers, or psychophysiological parameters such as heart rate and electrodermal responses could be assessed in an ambulatory way.

As listed in detail in the introduction, HPA dyregulations and massive hyper- or hyporeactiviy to stress is common in mental disorders (e.g. Ströhle & Holsboer, 2003). Thus, a similar study like ours could be conducted in clinical populations to see how exercise affects stress reactions in a dysregulated system, and whether exercise (in the long run) can restore disturbed HPA and SNS functions, which would also be beneficial for diverse physical health outcomes.

7.4. Acute vs. Chronic Exercise Effects

In neither of the two fMRI studies, we found significant differences between sedentary (SED) and highly trained (HT) men regarding the neural processing of reward or stress, nor did acute exercise differentially impact the neural responses depending on training status (reflected in the lack of sample*treatment interactions). The greatest sample differences were found in the self-reported personality measures of openness, conscientious-ness and body-related self-esteem. Furthermore, objectively measured fitness was negatively correlated with

the cortisol stress response to the MIST, probably mediated by exercise-induced changes in positive affect.

While the finding of higher body-related self-esteem and higher conscientiousness are in line with previous literature (Malinauskas et al., 2014; McAuley et al., 1997), neuroticism, extraversion, and locus of control did not differ. Openness to experience was even lower in highly trained sample, contrary to large population-based studies (de Moor et al., 2006). Compared with young men of the general population (Körner et al., 2008), our sample was above-average extraverted and open to experience, and below-average neurotic. This may be related to the fact that they were well-educated men with strong academic interest (university students). Thus, in our study, extraversion, neuroticism and openness scores may have been subject to a ceiling/floor effect where training status had no further explanatory power.

In our two fMRI studies however, neither reward processing nor psychoneuroendocrine stress reactivity were different between SED and HT men. Regarding reward processing, this finding reflects the contradicting results regarding long-term adaptations of the dopaminergic system to exercise, which were contradictory in different studies (see Article III). Unlike previous stress studies (Rimmele et al., 2009; Rimmele et al., 2007; Traustadottir, Bosch & Matt, 2005), the sedentary subsample of our study was not more reactive to stress than the highly trained subsample (when using a factorial approach). There are different possible explanations for this lacking difference. First, the overall stress responses to the MIST were quite small (probably due to the fact that the subjects were lying in the scanner for almost an hour at the beginning of the stress phase, and the

technical and less social nature of the MIST, compared to the TSST. Second, although there was a significant fitness difference between SED and HT, even the SED sample had a remarkably high aerobic fitness. This may reflect a selection bias in our sample, or indicate that the subjects were not quite honest regarding their self-reported weekly amount of physical activity (in order to ensure their study participation). In line with this assumption, we found a negative correlation between objectively measured fitness and cortisol stress responses to the MIST, which probably mediated by differential changes in positive affect during exercise, depending on the aerobic fitness of the subject (see Article IV).

Another possible explanation is the difference between absolute and relative exercise workload as discussed in Article IV. The exercise intensity in the current studies was adjusted to the subject's individual fitness, resulting in comparable relative workloads. Regarding absolute workload, the HT men ran at a higher speed and covered a longer distance within the 30 minutes. Yet, this approach was chosen to ensure that all subjects exercised at a "moderate intensity", but may have masked differences between SED and HT men which certainly would have been found at the same absolute workloads. This also may explain the lacking interactions between training status and acute exercise.

As discussed above, the results of Articles III and IV, and some other studies (e.g. Abrantes et al., 2009; Angelo et al., 2013) suggest that positive long-term effects of exercise may in part rely on accumulated acute exercise after-effects. Given that acute bouts of exercise modify reward processing and physiological stress

reactivity, it is possible that psychopathological symptoms such as low affect, anxiety, or craving are decreased for a certain period after exercise, resulting in an overall higher well-being. The clinical studies reviewed in Articles I & II do not clearly confirm or deny this assumption. However, confounding factors are more likely to occur in the course of a 10-weeks exercise intervention than in a simple pre-post-exercise comparison. Although our fMRI studies in healthy subjects did not reveal sample effects or interactions, it is important to acknowledge that clinical studies found (preliminary) evidence for positive psychological long-term effects of exercise.

Whether relying on an accumulation of acute effects or true long-term alterations, patients should be supported to engage in regular physical exercise. If a person can turn the repeated experience of exercise to a pleasant, rewarding, mood-enhancing activity, this will probably enhance his/her self-efficacy, which in turn is crucial to maintain an exercise program over a longer period (Elavsky et al., 2005; Jerome & McAuley, 2013). Some researchers also points out the necessity of coaching in order to develop stable habits and transfer positive effects into other domains (see Biddle & Mutrie, 2008)

7.5. Limitations

For each of the four articles, as well as this thesis as a whole, there are some limitations.

The literature search for Article I & II did not include “grey literature” or unpublished data, which may have been particularly informative. Due to the popularity and intuitive plausibility of the “Exercise-is-good-for-(mental)-health” hypothesis, the file-drawer problem may be large in this research area. Also, both review articles neglected temporal dynamics in the course of disease, which may be crucial for the success of exercise interventions (see Lynch et al., 2013).

As extensively discussed in the introduction, exercise is a complex intervention and it is hard to distinguish all mechanisms of action. Therefore, the investigation of single mechanisms like reward or stress may result in a simplified picture.

Unfortunately, the data from our fMRI studies reported so far only included men, and we can therefore not exclude the different effects it might have in women. Several rodent and human studies indicate that females and males differ with regard to their processing of reward (Spreckelmeyer et al., 2009), dysfunctions of reward processing (Fattore, Melis, Fadda & Fratta, 2014) and their striatal synaptic dopamine concentrations (Laakso et al., 2002). In line, exercise was found to differentially impact the reward processing of male and female rats (Cosgrove, Hunter & Carroll, 2002; Sanchez, Moore, Brunzell & Lynch, 2013). Similarly, the neural and physiological stress responses differ between men and women, and even between socialized gender roles (Dedovic, Wadiwalla, Engert & Pruessner,

2009; Duchesne, Tessera, Dedovic, Engert & Pruessner, 2012; Kelly, Tyrka, Anderson, Price & Carpenter, 2008), and some studies also found sex differences in the effects of exercise on cardiovascular stress responses (see review by Hamer et al., 2006).

In order to investigate groups with extremely different levels of habitual physical activity, subjects with an intermediate level of physical activity were excluded. This group however constitutes the majority of healthy young people (Lampert, Mensink, Romahn & Woll, 2007), and we can not exclude that we would have found fitness effects between this groups and the highly trained subjects on the one hand, or the untrained subjects on the other hand. Additionally, it appears problematic that the allocation to the HT or SED subsample was based on self-report (verified by exercise testing). To be eligible to participate in the study, it was mandatory to be either sedentary or highly trained. In the male samples reported here, even the subjectively sedentary subjects were remarkably fit, compared to other studies which report significantly lower VO_2max for their unfit participants (e.g. Deuster et al., 1989; Steptoe, Kearsley & Walters, 1993). It would have been more representative and reliable to recruit a large sample from the targeted student population and stratify them according to self-reported physical activity and aerobic capacity assessed in the medical examination.

Our MRI study consisted of three paradigms and a structural scan, resulting in a total scanning time of approximately 70 minutes. This may explain that subjects did not show a marked cortisol increase to the last paradigm, the MIST. It may also be

problematic that our data may be confounded with carry-over effects from one paradigm to the next. Although we applied the most demanding and stressful paradigm in the end of the testing session, we can not rule out mood or psychoneuroendocrine changes induced by one of the previous paradigms.

A further limitation is that the exercise conditions were not optimally controlled. For example, we did not assess the distance covered in the AER condition, nor did we record heart rate or blood pressure in any exercise condition. These factors may have contributed to the acute exercise effects we found in both paradigms, and could have been integrated as covariates. Furthermore, the assessment of the subjective hedonic or stressful properties of each exercise condition should have been assessed for each subject during exercise in order to control for them later. In line, we did not assess the subjective incentive value of the monetary gains or losses. Lacking this information, we do not know whether subjective reward or stress during exercise was also inversely related to subjective reward or stress during the MID task and the MIST.

In line, it would have strengthened our results to have a longer resting interval at the beginning of our testing, in order to let the participants recover from any previous stressors, and to closely monitor the subjective stressfulness of a) the mere participation in the study, b) the exercise intervention, and c) the anticipation of the MRI examination.

7.6. Outlook and Future Directions

The results of Articles III & IV need to be replicated in larger samples, including intermediate levels of habitual physical activity and female subsamples, and additionally considering the methodological limitations arising from our study design.

To establish ties to the clinical aspect, the hypothesis of acute exercise inducing alterations in (disorder-specific) reward processing should be tested, e.g. by examining neural responses to substance-related cues. Future studies could also address the question whether disturbed reward and stress processing which are found in many mental disorders (see above) can be restored by exercise interventions. Following the reasoning that these alterations constitute predisposing (i.e. risk) factors for several mental disorders (e.g. Ginty, 2013), one could even ask whether exercise could be used as a prevention strategy in pre-clinical populations.

With regard to the therapeutic use of exercise, evolving technologies open a variety of new research and clinical applications. Internet-delivered exercise programs and smartphone apps have been successfully tested in clinical populations (Mailey et al., 2010; Sparrow et al., 2011). In the long run, they allow not only individually tailored exercise interventions which may in turn increase adherence, but could also allow the investigation of SUD-related parameters (e.g. craving) or stress reactivity with questionnaires in a realistic setting outside of clinics and labs. Furthermore, accelerometers and comparable smartphone apps allow a quantification of physical activity in everyday life. Besides supervised

exercise programs, this may be a promising approach for interventions aiming to enhance the total amount of physical activity (Duda et al., 2014). Advantages here would be a higher temporal flexibility and exercise modes allowing the patients to be active in a self-paced way, tailored to their individual abilities and needs.

An increasing number of studies use mindfulness-based exercises instead of aerobic exercise, and find comparable or even superior results (e.g. Vancampfort et al., 2012). In China for example, Tai Chi has been shown to be a feasible intervention to reduce anxiety in older adults (Song et al., 2014). Despite different cultural backgrounds, this type of exercise should also be considered for scientific evaluation in western societies for several reasons: first, due to the slow movements and the low intensity, the risk of overstrain and injury is low. Second, low exercise intensities have been shown to be sufficient to induce mood enhancement (Reed & Ones, 2006). Third, comparable stress-reducing and anxiolytic action has been reported from studies using meditation or relaxation as control strategies (e.g. Murphy et al., 1986; Wedekind et al., 2010), which makes a combination of bodily movement and meditative components especially attractive. Fourth, coordination has been shown to be effective to improve cognition in older adults (Voelcker-Rehage, Godde & Staudinger, 2011), but has so far been neglected in previous studies on exercise in mental disorders in favour of anaerobic and aerobic exercise.

Since Articles I & II were published, evidence has fortunately extended a lot. Especially in dementia and mild cognitive impairment research there has been an

exponential increase in RCTs and published clinical trials and rationales (e.g., Hoffmann et al., 2013; Lowery et al., 2013; Schwenk et al., 2014). In anxiety disorders the first meta-analysis was recently published focusing only on aerobic exercise. The authors found no differences between aerobic exercise treatment and alternative interventions (Bartley, Hay & Bloch, 2013).

This raises hope that exercise recommendations for mental disorders will soon be based on a broader empirical basis. For example, there is a ongoing RCT on aerobic exercise as intervention in a large sample of methamphetamine-dependent subjects (Mooney et al., 2014), a so far neglected group of patients with particularly few pharmacological treatment options and poor treatment outcomes. Given the alarming increases of metamphetamine use and dependence in Germany (Drogen & Suchtbericht, 2013), results of this and similar trial can be eagerly awaited.

8. References

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Appendix

A Supplementary Material for Chapter 5 (Article III)

A1 Computation of literature based probabilistic ROIs

A-priori Regions of Interest (ROIs) for small volume alpha error adjustment were created combining anatomical hypotheses with functional findings for MID experiments as reported in the literature.

First, spatial coordinates for the ventral striatum (VSS) were taken from publications using the same task..

Secondly, anatomical ROIs for the left and right VSS were created using the bilateral Putamen and Caudate head as provided by the Anatomical Automatic Labeling brain atlas (AAL; http://www.cyceron.fr/web/aal_anatomical_automatic_labeling.html, Tzourio-Mazoyer et al. 2002).

Thirdly, based on this data set, we create the ROIs in a three-step process (Schubert et al., 2007):

(1) The probability that a voxel at a given position within the anatomical ROI showed neural activity regarding the corresponding literature was estimated by calculating a 3D normal (Gaussian) distribution G(x, y, z) as follows (Turkeltaub et al., 2002):

$$G(x,y,z) = \frac{1}{2\pi\sqrt{|Det(C)|}} \exp\left(-\frac{1}{2} \begin{bmatrix} x-\bar{x} & y-\bar{y} & z-\bar{z} \end{bmatrix} \right) C^{-1} \begin{bmatrix} x-\bar{x} \\ y-\bar{y} \\ z-\bar{z} \end{bmatrix}$$

where C is the covariance matrix for all coordinate triples x, y, z from the underlying literature and x, y, z are the mean values of the x, y, and z coordinates, respectively (Nielsen et al., 2002).

(2) The outer limits of the finally used ROI were defined by (a) the outer limits of the antomical ROI and (b) a threshold of 1.96 standard deviations (= 95% confidence interval) of the resulting 3D distribution.

(3) Finally a binary mask including all voxels spatially within these boundaries was formed.

ROI coordinates were extracted from the following publications:

Left ventral striatum (VS)

Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, et al. (2004) Incentive-elicited brain activation in adolescents: similarities and differences from young adults. J Neurosci 24: 1793-1802.

Bjork JM, Smith AR, Chen G, Hommer DW (2010) Adolescents, adults and rewards: comparing motivational neurocircuitry recruitment using fMRI. PLoS One 5: e11440.

Camara E, Rodriguez-Fornells A, Munte TF (2008) Functional connectivity of reward processing in the brain. Front Hum Neurosci 2: 19.

Cooper JC, Hollon NG, Wimmer GE, Knutson B (2009) Available alternative incentives modulate anticipatory nucleus accumbens activation. Soc Cogn Affect Neurosci 4: 409-416.

Dichter GS, Felder JN, Green SR, Rittenberg AM, Sasson NJ, et al. (2010) Reward circuitry function in autism spectrum disorders. Soc Cogn Affect Neurosci.

Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wustenberg T, et al. (2006) Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacology (Berl) 187: 222-228.

Juckel G, Schlagenhauf F, Koslowski M, Wustenberg T, Villringer A, et al. (2006) Dysfunction of ventral striatal reward prediction in schizophrenia. Neuroimage 29: 409-416.

Knutson B, Fong GW, Bennett SM, Adams CM, Hommer D (2003) A region of mesial prefrontal cortex tracks monetarily rewarding outcomes: characterization with rapid event-related fMRI. Neuroimage 18: 263-272.

Knutson B, Bjork JM, Fong GW, Hommer D, Mattay VS, et al. (2004) Amphetamine modulates human incentive processing. Neuron 43: 261-269.

Knutson B, Taylor J, Kaufman M, Peterson R, Glover G (2005) Distributed neural representation of expected value. J Neurosci 25: 4806-4812.

Knutson B, Rick S, Wimmer GE, Prelec D, Loewenstein G (2007) Neural predictors of purchases. Neuron 53: 147-156.

Knutson B, Bhanji JP, Cooney RE, Atlas LY, Gotlib IH (2008) Neural responses to monetary incentives in major depression. Biol Psychiatry 63: 686-692.

Muhlberger A, Wieser MJ, Gerdes AB, Frey MC, Weyers P, et al. (2011) Stop looking angry and smile, please: start and stop of the very same facial expression differentially activate threat- and reward-related brain networks. Soc Cogn Affect Neurosci 6: 321-329.

Ossewaarde L, Qin S, Van Marle HJ, van Wingen GA, Fernandez G, et al. (2011) Stress-induced reduction in reward-related prefrontal cortex function. Neuroimage 55: 345-352.

Rademacher L, Krach S, Kohls G, Irmak A, Grunder G, et al. (2010) Dissociation of neural networks for anticipation and consumption of monetary and social rewards. Neuroimage 49: 3276-3285.

Stark R, Bauer E, Merz CJ, Zimmermann M, Reuter M, et al. (2011) ADHD related behaviors are associated with brain activation in the reward system. Neuropsychologia 49: 426-434.

Stoppel CM, Boehler CN, Strumpf H, Heinze HJ, Hopf JM, et al. (2011) Neural processing of reward magnitude under varying attentional demands. Brain Res 1383: 218-229.

Right ventral striatum (VS)

Andrews MM, Meda SA, Thomas AD, Potenza MN, Krystal JH, et al. (2011) Individuals family history positive for alcoholism show functional magnetic resonance imaging differences in reward sensitivity that are related to impulsivity factors. Biol Psychiatry 69: 675-683.

Bjork JM, Knutson B, Fong GW, Caggiano DM, Bennett SM, et al. (2004) Incentive-elicited brain activation in adolescents: similarities and differences from young adults. J Neurosci 24: 1793-1802.

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Supplementary Table A2

Brain regions showing increased BOLD response to gain anticipation (cue(gain) > cue(neutral). One sample t-test for the whole sample, p <.001 (uncorr.), min cluster size = 10 voxels)

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FWE) SVC	MNI coord. (mm) x	y	z
Postcentral Gyrus Area 2 (80 %)	**L**	**229**	**5.02**	**<.001**		**-50**	**-21**	**41**
Postcentral Gyrus Area 3a (50 %)	L		4.55	<.001		-33	-25	48
Precentral Gyrus Area 4p (30 %)	L		4.32	<.001		-40	-11	38
dorsal ACC / Medial Frontal Gyrus	R		3.99	<.001		3	-4	55
Precentral Gyrus Area 6 (90 %)	L		3.98	<.001		-19	-21	69
Postcentral Gyrus Area 6 (30 %)	**R**	**32**	**4.54**	**<.001**		**24**	**-28**	**59**
Postcentral Gyrus Area 3b (60 %)	R		3.76	<.001		20	-35	62
Postcentral Gyrus Area 1 (60 %)	R		3.67	<.001		38	-32	62
Superior Parietal Lobule (7P) (70 %)	**R**	**19**	**3.65**	**<.001**		**13**	**-70**	**52**
Middle Cingulate Cortex SPL (5Ci) (40 %)	**R**	**17**	**4.38**	**<.001**		**10**	**-35**	**41**
Ventral Striatum	**R**	**16**	**3.68**	**<.001**	**.008**[1]	**17**	**11**	**-8**
Lingual Gyrus Area 17 (90 %)	**R**	**15**	**4.21**	**<.001**		**3**	**-67**	**6**
Lingual Gyrus Area 17 (90 %)	L		4.34	<.001		-5	-70	6
Ventral Striatum	**L**	**14**	**3.86**	**<.001**	**.022**[2]	**-19**	**18**	**-12**
Precuneus SPL (5M) (40 %)	**R**	**13**	**3.96**	**<.001**		**10**	**-49**	**59**
Precuneus Area 18 (60 %)	**R**	**12**	**4.57**	**<.001**		**27**	**-53**	**3**
Paracentral Lobule	**L**	**13**	**3.79**	**<.001**		**-1**	**-32**	**55**
Middle Cingulate Cortex SPL (5M) (50 %)	L		3.39	<.001		-8	-32	48
Calcarine Gyrus Area 17 (80 %)	**L**	**13**	**4.37**	**<.001**		**-12**	**-84**	**3**
Supramarginal Gyrus OP 1 (70 %)	**L**	**10**	**3.95**	**<.001**		**-54**	**-21**	**20**
Thalamus Th-Temporal (73 %)	**R**	**10**	**3.71**	**<.001**		**10**	**-18**	**13**

Abbreviations: CP % = cyto-architectonic probability in %; H = hemisphere; L = left; R = right; vox = voxel; SVC = small volume correction; FWE = family-wise error corrected. FWE correctable for ROI: [1] right Ventral Striatum-ROI; [2] left Ventral Striatum-ROI

Supplementary Table A3

Brain regions showing increased BOLD response during processing of gain feedback (gain vs. no-gain feedback; one sample t-test for the whole sample, p <.001 (uncorr.), min cluster size = 10 voxels)

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FWE) SVC	MNI coord. (mm) x	y	z
MPFC (ventral part)	**L**	**144**	**5.07**	**<.001**		**-5**	**49**	**-8**
MPFC	L		4.64	<.001		-1	63	13
ACC	**L**	**80**	**3.95**	**<.001**		**-5**	**-53**	**27**
Middle Cingulate Cortex	L		3.86	<.001		-1	-35	38
Ventral Striatum	**L**	**20**	**4.14**	**<.001**	**.001[1]**	**-5**	**11**	**-8**
Ventral Striatum	R		3.83	<.001	.011[2]	10	11	-12

Abbreviations: CP % = cyto-architectonic probability in %; H = hemisphere; L = left; R = right; vox = voxel; SVC = small volume correction; FWE = family-wise error corrected. FWE correctable for ROI; [1] left Ventral Striatal-ROI; [2] right Ventral Striatal-ROI

Supplementary Table A4

Brain regions showing increased BOLD response to gain anticipation cue(gain) > cue(neutral). 2 x 2 ANCOVA, main effect of treatment (PLAC > AER), p <.01 (uncorr.), min. cluster size = 10 voxels)

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FWE)	MNI coord. (mm) x	y	z
Precentral Gyrus	**L**	**58**	**3.82**	**<.001**		**-33**	**-7**	**59**
Area 6 (50 %)								
Superior Frontal Gyrus	L		3.49	<.001		-22	-11	69
Area 6 (60 %)								
Medial frontal gyrus	L		3.13	<.001		-8	-11	69
SMA – Area 6 (90 %)								
Lingual Gyrus	**L**	**39**	**3.18**	**<.001**		**-29**	**-46**	**-1**
Area 17 (30 %)								
Fusiform Gyrus	L		2.43	.007		-40	-49	-12
Middle Temporal Gyrus	**L**	**32**	**3.74**	**<.001**		**-57**	**-11**	**-19**
Precentral Gyrus	**L**	**26**	**3.04**	**.001**		**-29**	**-25**	**52**
Area 4a (30 %)								
Hippocampus	**R**	**26**	**3.60**	**<.001**		**27**	**-39**	**-5**
Hipp (FD) (70 %)								
Lingual Gyrus	R		2.78	.003		17	-42	-5
Middle Cingulate Cortex	**L**	**25**	**3.21**	**<.001**		**-8**	**-7**	**38**
Area 6 (50 %)	L		2.89	.002		-8	-7	48
Inferior Frontal Gyrus p. Triangularis –Area 45 (20 %)	**R**	**23**	**3.60**	**<.001**		**52**	**39**	**10**
Supramarginal Gyrus	**R**	**19**	**3.03**	**.001**		**48**	**-28**	**34**
IPC (PFt) (40 %)								
Postcentral Gyrus	R		3.03	.001		55	-25	45
Area 2 (50 %)								
Subgenual Anterior Cingulate Cortex	**L**	**18**	**3.15**	**<.001**		**-1**	**11**	**-12**
Caudate Nucleus	R		3.11	<.001		10	11	-12
Ventral Striatum	L		2.75	.003	**.029**[1]	-5	7	-8
Medial frontal gyrus – SMA	**R**	**15**	**3.87**	**<.001**		**10**	**-11**	**69**
Area 6 (100 %)								
Cuneus	**L**	**14**	**3.45**	**<.001**		**-8**	**-95**	**24**
Area 18 (40 %)								
Precuneus	**L**	**13**	**2.73**	**.003**		**-12**	**-46**	**66**
Area 3a (30 %)								
Paracentral Lobule	L		2.56	.005		-8	-39	62
Area 4a (70 %)								
Superior Parietal Lobule	L		2.52	.006		-22	-39	62
Area 3b (40 %)								
Superior Temporal Gyrus	**L**	**11**	**3.37**	**<.001**		**-43**	**-14**	**-5**

Abbreviation: CP % = cyto-architectonic probability in %; H = hemisphere; L = left; R = right; vox = voxel; SVC = small volume correction; FWE = family-wise error corrected. FWE correctable for ROI; [1] *left Ventral Striatum-ROI*

Supplementary Table A5

Brain regions showing increased BOLD response to processing of gain feedback (gain vs. no-gain feedback; 2 x 2 ANCOVA, main effect of treatment (PLAC > AER), p <.01 (uncorr.), min cluster size = 10 voxels)

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FWE) SVC	MNI coord. (mm) x	y	z
Subgenual Anterior Cingulate Cortex	**R**	**51**	**3.20**	**<.001**		**6**	**14**	**-12**
Ventral Striatum	R		3.14	<.001	**.025**[1]	6	7	-1
Ventral Striatum	L		3.07	.001		-12	14	-12
Caudate Nucleus	L		3.02	.001		-5	18	-5
Superior Orbital Gyrus	R		2.35	.009		20	25	-15
Hippocampus Hipp**ocampus** (SUB) (100 %)	**R**	**42**	**3.64**	**<.001**		**24**	**-28**	**-15**
Hipp**ocampus** Hipp**ocampus** (FD) (90 %)	R		3.18	<.001		31	-18	-19
Middle Temporal Gyrus	**R**	**28**	**3.09**	**.001**		**52**	**-4**	**-29**
Temporal Pole	R		2.98	.001		52	11	-22
Middle Temporal Gyrus IPC (PGa) (30 %)	**R**	**17**	**2.93**	**.002**		**45**	**-53**	**13**
Fusiform Gyrus	**L**	**27**	**3.18**	**<.001**		**-26**	**-35**	**-15**
Amygdala Amygdala (SF) (50 %) Hipp**ocampus** (EC) (30 %)	**R**	**19**	**3.27**	**<.001**		**20**	**-7**	**-22**
Anterior Cingulate Cortex	**R**	**17**	**2.87**	**.002**		**6**	**35**	**-5**
Precuneus	**R**	**14**	**2.95**	**.002**		**6**	**-60**	**24**
Superior Medial Gyrus	**L**	**13**	**3.03**	**.001**		**-1**	**53**	**17**
Angular Gyrus IPC (PGa) (50 %)	**R**	**11**	**3.24**	**<.001**		**48**	**-63**	**48**
Middle Occipital Gyrus	**L**	**10**	**2.85**	**.002**		**-36**	**-70**	**13**

Abbreviations: CP % = cyto-architectonic probability in %; H = hemisphere; L = left; R = right; vox = voxel; SVC = small volume correction; FWE = family-wise error corrected. FWE correctable for ROI: [1] right Ventral Striatum-ROI

B Supplementary Materials Chapter 6 (Article IV)

Supplementary Table B1: Main effect of stress level (stress > no stress)
Brain regions showing ***increased*** BOLD response to stress > (moderate stress + high stress). 2x2x3 ANCOVA, p <.001 (uncorr.), min cluster size = 10 voxels

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FDR)	p (FWE)	MNI coord. (mm) x	y	z
Anterior Cingulate Cortex	L	473	5.71	<.001	<.001	<.001	-5	25	31
Anterior Cingulate Cortex	L		5.18	<.001	<.001	.003	-5	35	20
Middle Cingulate Cortex	R		5.07	<.001	<.001	.006	3	32	31
SMA Area 6 (30 %)	R						3	14	45
Middle Cingulate Cortex	L						-1	14	38
Anterior Cingulate Cortex	R						13	39	3
Insula Lobe	L	151	5.29	<.001	<.001	.002	-29	25	-8
Inferior Frontal Gyrus (p. Orbitalis)	L		4.88	<.001	.001	.015	-40	39	-5
Insula Lobe	L		4.56	<.001	.001	.072	-33	21	3
Postcentral Gyrus Area 4p (60 %)	L	129	5.09	<.001	<.001	.005	-40	-21	48
Postcentral Gyrus Area 1 (60 %)	L		3.69	<.001	.008	.872	-50	-18	45
Inferior Parietal Lobule Area 2 (70 %)	L						-54	-21	38
Superior Frontal Gyrus Area 6 (10 %)	L						-19	4	59
Insula Lobe	R	75	4.94	<.001	.001	.011	34	25	3
Insula Lobe	R		4.82	<.001	.001	.021	41	18	-1
Inferior Frontal Gyrus (p. Opercularis) Area 44 (40 %)	R		3.59	<.001	.009	.936	52	14	3
Superior Temporal Gyrus IPC (PF) (40 %)	L	46	4.85	<.001	.001	.018	-57	-39	20
SupraMarginal Gyrus IPC (PFcm) (40 %)	L		3.89	<.001	.005	.658	-54	-35	31
Middle Cingulate Cortex SPL (5M) (20 %)	L	28	4.84	<.001	.001	.019	-1	-46	48
Middle Cingulate Cortex SPL (5Ci) (60 %)	R		3.15	<.001	.026	1	10	-39	48
Caudate Nucleus	R	16	3.93	<.001	.004	.616	6	18	3
SupraMarginal Gyrus IPC (PF) (90 %)	R	14	3.75	<.001	.007	.818	66	-32	31
Superior Temporal Gyrus IPC (PF) (80 %)	R		3.43	<.001	.014	.988	62	-39	20

Abbreviations: CP % = cyto-architectonic probability in %; H = hemisphere; L = left; R = right; vox = voxel; FDR = false-discovery rate corrected, FWE = family-wise error corrected

Supplementary Table B2: Main effect of stress level (no stress > stress)

Brain regions showing ***decreased*** BOLD response to stress > (moderate stress + high stress). 2x2x3 ANCOVA, p <.001 (uncorr.), min cluster size = 10 voxels

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FDR)	p (FWE)	MNI coord. (mm) x	y	z
Superior Frontal Gyrus	R	505	6.72	<.001	<.001	<.001	31	63	13
Superior Frontal Gyrus	R		6.31	<.001	<.001	<.001	20	67	13
Mid Orbital Gyrus	L		5.85	<.001	<.001	<.001	-5	67	-5
Superior Medial Gyrus	L						-8	63	27
Middle Frontal Gyrus	R						38	56	20
Rectal Gyrus	R						6	46	-19
Amygdala									
Amyg (CM) (60 %)	L	36	4.2	<.001	.002	.305	-22	-7	-8
Putamen	L		4.1	<.001	.003	.402	-26		-5
Putamen	L		3.81	<.001	.007	.759	-15	11	-8
Putamen	R	28	4.44	<.001	.001	.133	24	7	3
Putamen	R		3.76	<.001	.007	.802	31	4	13
Putamen	R		3.13	<.001	.038	1	34		6
Amygdala									
Amyg (SF) (60 %)	R	13	3.76	<.001	.008	.807	17	-7	-19
Amygdala									
Amyg (LB) (80 %)	R		3.57	<.001	.013	.948	24	-7	-26
Inferior Parietal Lobule									
IPC (PFm) (60 %)	L	11	3.84	<.001	0.006	0.723	-57	-49	41
Inferior Parietal Lobule									
IPC (PGa) (70 %)	L		3.19	<.001	0.034	1	-47	-60	45
Middle Temporal Gyrus	L	10	3.93	<.001	0.005	0.616	-61	-60	3

Abbreviations: CP = cytoarchitectonic probability, H = hemisphere, L = left, R = right, vox = voxels, FDR = corrected for false discovery rate, FWE = corrected for family-wise error, MNI = Montreal Neurological Institute

Supplementary Table B3: Main Effect of Exercise Treatment (AER > PLAC)

Brain regions with higher sustained BOLD response in the AER > PLAC group. 2x2x3 ANCOVA, p <.001 (uncorr.), min cluster size = 10 voxels

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FDR)	p (FWE)	MNI coord. (mm) x	y	z
Middle Temporal Gyrus	L	247	4.43	<.001	.01	.134	-54	-18	-15
Hippocampus Hipp (SUB) (90 %)	L		4.27	<.001	.013	.246	-26	-21	-19
Hippocampus Hipp (CA) (50 %)	R	62	4.57	<.001	.01	.07	38	-25	-19
ParaHippocampal Gyrus Hipp (SUB) (100 %)	R		4.13	<.001	.017	.371	24	-21	-19
Middle Temporal Gyrus IPC (PGa) (50 %)	R	13	3.87	<.001	.025	.679	52	-49	20
Middle Temporal Gyrus hOC5 (V5) (50 %)	R	13	3.77	<.001	.029	.795	45	-63	3
Middle Temporal Gyrus	R	10	3.69	<.001	.033	.872	55	-42	-5

Abbreviations: CP = cytoarchitectonic probability, H = hemisphere, L = left, R = right, vox = voxels, FDR = corrected for false discovery rate, FWE = corrected for family-wise error, MNI = Montreal Neurological Institute, AER = aerobic exercise treatment, PLAC = placebo intervention

Supplementary Table B4 Main Effect of Exercise Treatment (PLAC > AER)

Brain regions with higher sustained BOLD response in the PLAC > AER group. 2x2x3 ANCOVA, p <.001 (uncorr.), min cluster size = 10 voxels

Brain structure (CP %)	H	Cluster size (vox)	Z (peak)	p (uncorr.)	p (FDR)	p (FWE)	MNI coord. (mm) x	y	z
Paracentral Lobule Area 6 (70 %)	L	159	4.35	<.001	.031	.19	-19	-25	73
Precentral Gyrus Area 6 (100 %)	R		4.15	<.001	.031	.35	20	-21	73
Paracentral Lobule Area 6 (50 %)	L		4.14	<.001	.031	.36	-1	-25	62
Superior Frontal Gyrus Area 6 (20 %)	R	103	4.04	<.001	.033	.473	20	7	59
Middle Frontal Gyrus Area 6 (10 %)	R		3.86	<.001	.033	.697	38	0	59
Middle Cingulate Cortex Area 6 (20 %)	R		3.85	<.001	.033	.708	13	14	45
Postcentral Gyrus Area 3b (100 %)	R	35	3.96	<.001	.033	.569	38	-32	55
Inferior Parietal Lobule Area 2 (90 %)	R		3.89	<.001	.033	.656	45	-39	55
Inferior Frontal Gyrus (p. Opercularis) Area 44 (10 %)	R	26	4.55	<.001	.031	.078	34	11	34
Middle Frontal Gyrus	R		4.3	<.001	.031	.221	41	14	38
Middle Cingulate Cortex	R	18	4.53	<.001	.031	.084	10	-11	41
Middle Frontal Gyrus	R	14	3.78	<.001	.034	.789	41	28	31
Anterior Cingulate Cortex	L	12	3.69	<.001	.034	.871	-1	21	31
Precuneus Area 3a (50 %)	R	10	3.56	<.001	.037	.954	10	-46	59
Postcentral Gyrus Area 3a (30 %)	L	10	3.95	<.001	.033	.59	-29	-35	48

Abbreviations: CP = cytoarchitectonic probability, H = hemisphere, L = left, R = right, vox = voxels, FDR = corrected for false discovery rate, FWE = corrected for family-wise error, MNI = Montreal Neurological Institute, AER = aerobic exercise treatment, PLAC = placebo intervention

C List of Abbreviations

5-HT	5-Hydroxytryptamine = Serotonin
ACC	Anterior Cingulate Cortex
ACSM	American College of Sports Medicine
AER	Aerobic Exercise (Intervention)
Amyg	Amygdala
AN	Anorexia Nervosa
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ANP	Atrial Natriuretic Peptide
BDI	Beck's Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BED	Binge Eating Disorder
BMI	Body Mass Index
BN	Bulimia Nervosa
BOLD	Blood Oxygen Level Dependent
CBT	Cognitive-Behavioural Therapy
CRF / CRH	Corticotropin-Releasing Factor / Hormone
DA	Dopamine
EC	Endocannabinoid(s)
ED	Eating Disorder
EO	Endogenous Opioid
EPI	Echo-Planar Imaging
EX	Exercise
FKK	Fragebogen für Kompetenz- und Kontrollüberzeugungen (Questionnaire of Competence and Control)
fMRI	functional Magnetic Resonance Imaging
FWHM	Full-Width Half-Maximum
GLM	General Linear Model
Hipp	Hippocampus
HPA	Hypothalamus-Pituitary-Adrenal (Axis)
HRF	Hemodynamic Response Function
HT	Highly Trained (Participants)
Hz	Hertz

ICBM	International Consortium of Brain Mapping
IPC	Inferior Parietal Cortex
lol	Laughing Out Loud
MdFG	Medial Frontal Gyrus
ME	Main Effect
MID	Monetary Incentive Delay (Task)
MIST	Montreal Imaging Stress Task
MSWS	Multidimensionale Selbstwertskala (Multidimensional Self-Esteem Scale)
NAS	Numerical Analogous Scale
NE	Norepinephrine
NRT	Nicotine Replacement Therapy
OCD	Obsessive-Compulsive Disorder
PA	Physical Activity
PANAS	Positive Affect Negative Affect Schedule
PET	Positron-Emission Tomography
PLAC	Placebo (Intervention)
PTSD	Post-Traumatic Stress Disorder
rACC	Rostral Anterior Cingulate Cortex
RT	Reaction Time
SED	Sedentary (Participants)
sgACC	Subgenual Anterior Cingulate Cortex
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SNS	Sympathetic Nervous System
SPL	Superior Parietal Lobe
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Substance Use Disorder
TE	Time to Echo
TR	Time to Repetition
TSST	Trier Social Stress Test
VO_2max	maximal oxygen uptake ; aerobic capacity
VDM	Voxel Displacement Map
vox	Voxel
VS	Ventral Striatum
WHO	World Health Organization

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F Curriculum Vitae

Der Lebenslauf ist in der Online-Version aus Datenschutzgründen nicht enthalten.

G List of Publications

Publications Included into Dissertation

Zschucke E, Gaudlitz K, Ströhle A (2013). Exercise and Physical Activity in Mental Disorders: Clinical and Experimental Evidence. *J Prev Med Public Health 2013;46*: S12-S21

Zschucke E, Heinz A, Ströhle A (2012). Exercise and physical activity in the therapy of substance use disorders. *The Scientific World Journal 2012*: 901741.

Bothe N*, **Zschucke E***, Dimeo F, Heinz A, Wüstenberg T, Ströhle A (2013). Acute Exercise Influences Reward Processing in Highly Trained and Untrained Men. *Med Sci Sports Exerc 2013; 45(3),* 583–591 (***authors contributed equally**)

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Other Publications

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H Anteilserklärung Article III

Anteilserklärung für die Publikation *„Acute Exercise Influences Reward Processing in Highly Trained and Untrained Men“*, erschienen in *Medicine and Science in Sports and Exercise* 2013; 45(3):583–591

Dipl.-Psych. Elisabeth Zschucke (EZ) und Dr. Nina Bothe (NB) trugen im Rahmen ihrer Doktorarbeiten gleichermaßen zur Entstehung der obengenannten Publikation bei, was durch eine geteilte Erstautorschaft gekennzeichnet ist. Die Einzelbeiträge der beiden Autorinnen sind im folgenden detailliert aufgeschlüsselt.

Zwei inhaltlich verwandte Fragestellungen wurden für das Projekt untersucht:

I. Akute Auswirkungen aerober körperlicher Aktivität auf die neuronale Belohnungsverarbeitung und Stimmung bei körperlich inaktiven Männern und Frauen (EZ)
II. Akute Auswirkungen aerober körperlicher Aktivität auf die neuronale Belohnungsverarbeitung und Stimmung bei hochtrainierten Männern (NB)

Um die Effekte akuter körperlicher Aktivität zwischen trainierten und untrainierten (männlichen) Probanden vergleichen zu können und potentielle Interaktionen zwischen Trainingszustand und akutem Sport zu analysieren, wurden beide Forschungsfragen zu einer gemeinsamen Publikation zusammengefasst.

Die Gesamtstudie wurde von EZ und Prof. Dr. Andreas Ströhle konzipiert. EZ plante den Studienablauf im Detail, einschließlich der folgenden Aufgaben:

- Schreiben des Ethikantrags und Vorstellung des Projekts vor der Ethikkommission der Charité Berlin, Anpassungen des Studienprotokolls an deren Auflagen
- Auswahl der Persönlichkeits- und State-Fragebögen
- Adaptation des bereits existierenden fMRT-Paradigmas (Monetary Incentive Delax Task) an die spezifischen Fragestellungen dieser Studie (gemeinsam mit Dr. Torsten Wüstenberg)
- Implementatierung des fMRT-Paradigmas am 1.5 T Siemens Sonata Magnetom Scanner (gemeinsam mit Dr. Torsten Wüstenberg)

Ab Beginn der Probandenrekrutierung und Datenerhebung war auch NB an der Studie beteiligt.
EZ rekrutierte von Juni 2009-August 2010 die gesunde, untrainierte Teilstichprobe für Fragestellung 1. Dies beinhaltete die Aufklärung über Ablauf und Inhalt der Studie sowie ein

ausführliches telefonisches Screening zum Ausschluss regelmäßiger körperlicher Aktivität, psychischer oder neurologischer Störungen oder Kontraindikationen für die Sportintervention oder MRT-Untersuchung. Die Probandenzahlen der untrainierten Stichprobe können der untenstehenden Tabelle entnommen werden.

	Männer	Frauen	Gesamt
Teilnahmeinteressierte Probanden, mit denen das Telefonscreening durchgeführt wurde	114	137	251
Ausschluss aus medizinischen oder studienbezogenen Gründen (z.B. Linkshändigkeit, Rauchen, mittleres Level an körperlicher Aktivität, psychische oder neurologische Erkrankungen in der Vorgeschichte, Einnahme bestimmter Medikamente, Metall im/am Körper)	69	91	160
Dropouts vor oder während der Datenerhebung	15	16	31
Studienteilnahme; vollständige Datensätze	30	30	60

Zum Ausschluss medizinischer Bedenken gegen die Sportintervention und zur Erhebung der kardiovaskulären Fitness wurde durch PD Dr. Fernando Dimeo eine sportmedizinische Voruntersuchung am Campus Benjamin Franklin durchgeführt. EZ war bei den Voruntersuchungen der untrainierten ProbandInnen vor Ort, um Fragen zu beantworten, Kontraindikationen, Vorbehalte und entsprechende Vorsichtsmaßnahmen zu besprechen und eine mündliche und eine schriftliche Aufklärung über den Ablauf der Studie durchzuführen. Die gleichen Abläufe wurden von NB für die hochtrainierte Teilstichprobe durchgeführt.

EZ und NB führten die Datenerhebung aller unsportlichen (Männer und Frauen) und trainierten Probanden gemeinsam durch, wobei die Daten der weiblichen Teilstichprobe in der vorliegenden Publikation nicht berücksichtigt wurden. Jeweils eine Versuchsleiterin übernahm die Betreuung des Sports/Pseudosports (Überwachung und Anleitung der Sportintervention und der Beantwortung psychologischer Fragebögen), während die andere Versuchsleiterin die fMRT-Messung vorbereitete und durchführte. Aus praktischen- und Sicherheitsgründen wurden während der strukturellen und funktionellen MRT-Messungen zwei Versuchsleiterinnen benötigt. Die Auswertung der fMRT-Daten aller untrainierten ProbandInnen (n = 60) erfolgte durch EZ, einschließlich der folgenden Arbeitsschritte:

(1) Vorverarbeitung der Daten, Korrektur von Artefakten und Verbesserung des Signal-Rausch-Verhältnisses sowie Verfahren zur Sicherstellung der Datenqualität
(2) Einzelstatistik (First Level) für jeden Probanden, Erstellung und Erprobung verschiedener statistischer Modelle, um eine möglichst hohe Varianzaufklärung in den Daten zu gewährleisten (gemeinsam mit Dr. Torsten Wüstenberg).
(3) Gruppenstatistik (Second Level) zum Vergleichen der Sport- und der Placebointervention sowie der Geschlechtseffekte /- Interaktionen

(4) Regions-of-Interest (ROI) Analyse, um spezifische Effekte im Belohnungssystem näher zu untersuchen. Die Extraktion von Koordinaten aus der bisherigen Literatur zur Belohnungsverarbeitung sowie die technische Erstellung der ROIs wurden durch EZ und NB gemeinsam durchgeführt (mit Hilfe von Dr. Torsten Wüstenberg).

Analog wurde die Datenanalyse der hochtrainierten Teilstichprobe von NB durchgeführt.
Die Untersuchung von Interaktionen zwischen Trainingszustand und akuter körperlicher Aktivität (= Zusammenfassung beider Datensätze) erfolgte gemeinsam durch EZ und NB. EZ nahm die statistische Auswertung der psychologischen Fragebögen in SPSS 18 für die gesamte Stichprobe vor.

Bei der Erstellung des Manuskripts arbeiteten EZ und NB unter Supervision durch Dr. Torsten Wüstenberg und Prof. Dr. Andreas Ströhle eng zusammen. Theorie-, Methoden-, Ergebnis-, und Diskussionsteil wurden von den Autorinnen gemeinsam geschrieben, mit jeweils inhaltlichen Schwerpunkt auf untrainierten (EZ) und trainierten (NB) Probanden.
Das Manuskript wurde in seiner ursprünglichen Form im Dezember 2011 zunächst bei PLoS One eingereicht, dort aber abgelehnt. Beide Erstautorinnen arbeiteten gemeinsam mit Dr. Torsten Wüstenberg und Prof. Dr. Andreas Ströhle zu gleichen Teilen an der Überarbeitung des Manuskripts, der Einreichung bei MSSE sowie der nachfolgenden Revision.

Bremen, 15.05.14 E. Zschucke

Ort, Datum, Unterschrift Dipl.-Psych. Elisabeth Zschucke

Berlin, 17.05.14 N. Bothe

Ort, Datum, Unterschrift Dr. Nina Bothe

Berlin 20.5.14

Ort, Datum, Unterschrift Prof. Dr. Andreas Ströhle

I Selbstständigkeitserklärung

Hiermit versichere ich, dass ich die vorgeliegende Dissertation selbstständig verfasst habe und Zitate kenntlich gemacht habe. Es wurden keine anderen als die angegebenen Quellen und Hilfsmittel benutzt.

Die Arbeit ist in keinem früheren Promotionsverfahren angenommen oder abgelehnt worden.

Berlin, den 27.05.2014

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Elisabeth Zschucke