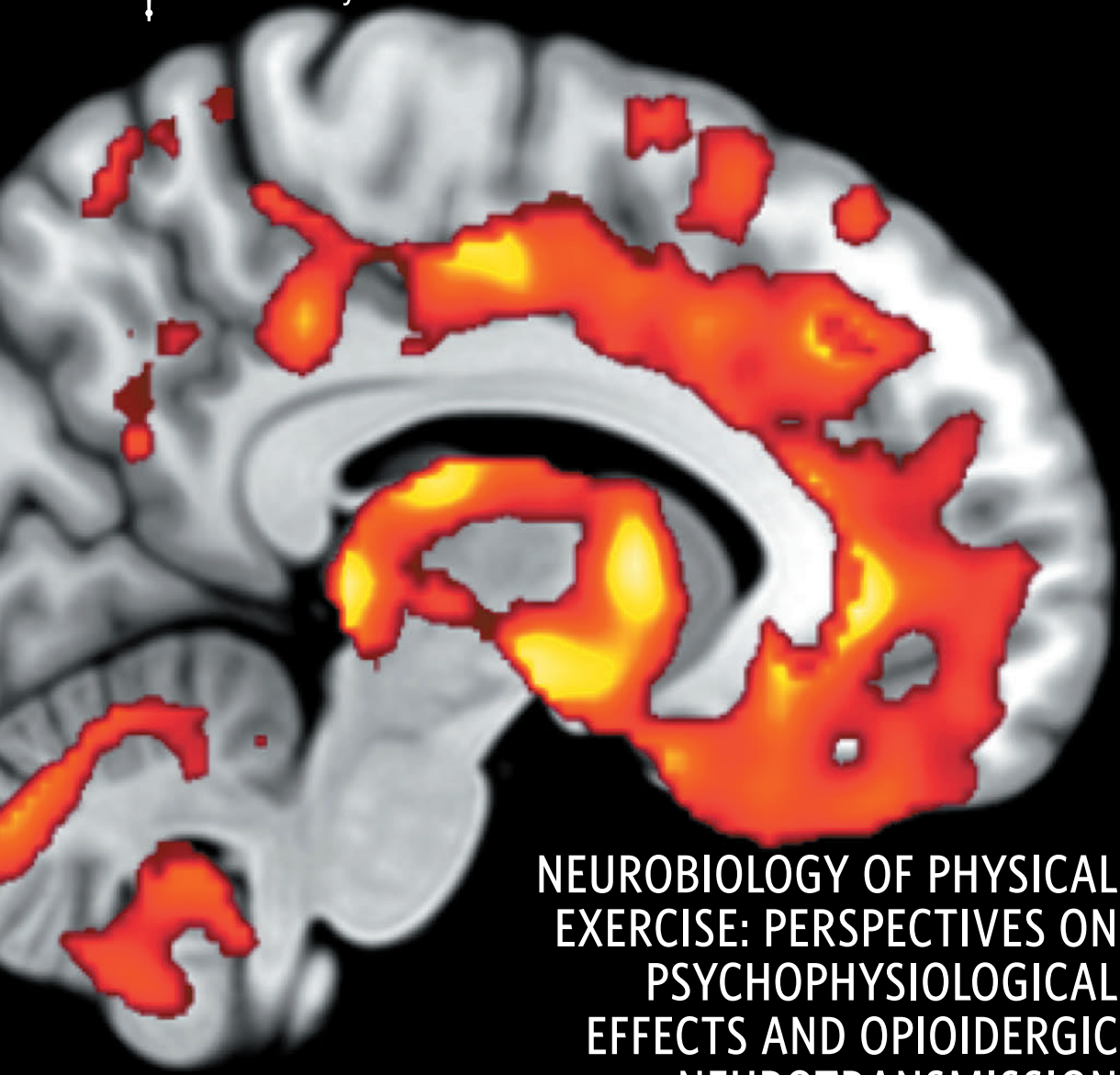
Turun yliopisto
University of Turku



NEUROBIOLOGY OF PHYSICAL EXERCISE: PERSPECTIVES ON PSYCHOPHYSIOLOGICAL EFFECTS AND OPIOIDERGIC NEUROTRANSMISSION

Tiina Saanijoki

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1363 | Medica - Odontologica | Turku 2018

Turun yliopisto
University of Turku

NEUROBIOLOGY OF PHYSICAL EXERCISE: PERSPECTIVES ON PSYCHOPHYSIOLOGICAL EFFECTS AND OPIOIDERGIC NEUROTRANSMISSION

Tiina Saanijoki

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
Sarja - ser. D osa - tom. 1363 | Medica - Odontologica | Turku 2018

University of Turku

Faculty of Medicine
Department of Clinical Physiology and Nuclear Medicine
Doctoral Programme in Clinical Research
Turku PET Centre

Supervised by

Adjunct Professor Kari Kalliokoski, PhD
Turku PET Centre
University of Turku
Turku, Finland

Adjunct Professor Jussi Hirvonen, MD, PhD
Department of Radiology
Turku University Hospital
Turku, Finland

Reviewed by

Adjunct Professor Jan Wikgren, PhD
Department of Psychology
University of Jyväskylä
Jyväskylä, Finland

Associate professor Simon Cervenka, MD, PhD
Department of Clinical Neuroscience
Karolinska Institutet
Stocholm, Sweden

Opponent

Professor Minna Huotilainen
Department of Education
Cognitive Brain Research Unit
University of Helsinki
Helsinki, Finland

Cover image by: Tiina Saanijoki

The originality of this thesis has been checked in accordance with the University of Turku quality assurance system using the Turnitin OriginalityCheck service.

ISBN 978-951-29-7282-1 (PRINT)
ISBN 978-951-29-7283-8 (PDF)
ISSN 0355-9483 (Print)
ISSN 2343-3213 (Online)
Painosalama Oy – Turku, Finland 2018

What a plot twist you were.
– faraway

ABSTRACT

Tiina Saanijoki

Neurobiology of physical exercise: Perspectives on psychophysiological effects and opioidergic neurotransmission

University of Turku, Faculty of Medicine, Department of clinical physiology and nuclear medicine; Doctoral programme in clinical research; Turku PET Centre, Turku, Finland

Regular physical exercise promotes health and prevents and treats multiple chronic diseases. Despite the well-acknowledged health benefits, many people remain physically inactive. Affective responses induced by exercise are believed to influence future exercise behaviour. Previous studies suggest that pleasurable sensations experienced in response to exercise are regulated by the endogenous opioid system. The opioid system is also involved in the reward processing, and may modulate food reward responses after exercise, possibly contributing to subsequent caloric intake and weight loss outcomes.

In this thesis, affective responses to high-intensity interval training (HIIT) and moderate-intensity continuous training (MICT) were investigated over a two-week training intervention in untrained healthy subjects and subjects with type 2 diabetes or prediabetes. Positron emission tomography (PET) was used to explore endogenous opioid release after HIIT and MICT in young healthy subjects. The interaction between exercise-induced opioid activation and changes in food reward processing were assessed using functional magnetic resonance imaging (fMRI).

HIIT generated a more negative overall affective experience in comparison with MICT; however, this lessened over the training period. Thus, HIIT appears as a tolerable exercise method for sedentary adults with and without diabetes. Furthermore, HIIT induced opioid release in key brain regions implicated in emotion and pain processing and the opioid release correlated with measures of negative emotionality. In contrast, MICT did not result in significant opioid release, although increased opioid activation correlated with increased euphoria after MICT as well as with increased neural responses to palatable foods. These results indicate that the intensity of the exercise regulates endogenous opioid release and concomitant changes in affect and reward processing. Taken together, these findings may have practical implications in developing more tolerable and likeable exercise programs to enhance physical activity participation in different population groups, as well as in optimising the efficient use of exercise in health care, for example in weight loss interventions and in the treatment of various affective disorders.

Keywords: high-intensity interval training (HIIT), affect, opioid system, reward processing, positron emission tomography, PET, functional magnetic resonance imaging, fMRI

TIIVISTELMÄ

Tiina Saanijoki

Liikunnan aiheuttamat psykofysiologiset vasteet ja aivojen opioidijärjestelmä

Turun yliopisto, Lääketieteellinen tiedekunta, Kliininen fysiologia ja isotooppilääketiede; Turun kliininen tohtoriohjelma; Valtakunnallinen PET-keskus

Säännöllinen liikunta ylläpitää terveyttä sekä ennaltaehkäisee ja hoitaa lukuisia sairauksia. Terveyshyödyistä huolimatta moni jää kuitenkin sohvaperunaksi. Liikunnan harrastaminen riippuu osin siitä, miltä liikunta tuntuu. Aikaisempien tutkimusten perusteella aivojen opioidijärjestelmän ajatellaan olevan liikunnasta saatavan mielihyvän taustalla. Opioidijärjestelmä säätelee myös ruuan ja syömisen aiheuttamaa mielihyvää, ja se voi siten muovata liikunnan aikaansaamia muutoksia ruuan palkitsevuudessa vaikuttaen näin syömiskäyttäytymiseen ja painonhallintaan.

Tässä väitöskirjatyössä tutkittiin, miltä kovatehoinen intervalliharjoittelu (*high-intensity interval training, HIIT*) ja keskitehoinen kestävyysharjoittelu (*moderate-intensity continuous training*) tuntuvat kahden viikon liikuntajakson aikana liikunnallisesti passiivisilla terveillä koehenkilöillä, sekä tyypin 2 diabeetikoilla ja esidiabeetikoilla. Lisäksi positroniemissiotomografia (PET) -kuvantamisella selvitettiin aivojen opioidijärjestelmän toimintaa HIIT ja MICT harjoitusten jälkeen terveillä nuorilla miehillä. Toiminnallisen magneettikuvantamisen (fMRI) avulla tutkittiin liikunnan vaikutuksia herkullisten ruokakuvien aikaansaamiin hermostollisiin vasteisiin aivoissa.

Lyhytkestoinen HIIT aiheutti huomattavasti negatiivisemman tunnekokemuksen kuin pitkäkestoinen MICT, mikä kuitenkin helpottui jo kahden viikon harjoittelujakson aikana niin terveillä kuin tyypin 2 diabeetikoilla ja esidiabeetikoilla. Näin ollen rankka HIIT voi soveltua liikuntavaihtoehdoksi myös aikaisemmin liikuntaa harrastamattomille. Lisäksi havaittiin, että liikunnan intensiteetti säätelee opioidijärjestelmän toimintaa. HIIT vapautti endogeenisiä opioideja tunteiden ja kivun säätelyyn liittyvillä aivoalueilla. Opioidien vapautuminen oli yhteydessä negatiivisiin tuntemuksiin. Vastaavaa opioidien vapautumista ei havaittu MICT:n jälkeen, joskin suurempi opioidiaktivaatio oli yhteydessä lisääntyneeseen euforisuuden tuntemukseen ja suurempiin hermostollisiin vasteisiin herkullisille ruokakuville pitkäkestoisen liikunnan jälkeen. Tutkimuksista saatuja tuloksia voidaan hyödyntää kehitettäessä uudenlaisia lähestymistapoja paitsi ihmisten liikunnalliseen aktivoimiseen, myös liikunnan tehokkaampaan hyödyntämiseen painonpudotuksessa ja esimerkiksi masennuksen ja riippuvuuksien hoidossa.

Avainsanat: kovatehoinen intervalliharjoittelu, HIIT, mieliala, opioidijärjestelmä, palkkiojärjestelmä, positroniemissiotomografia, PET, toiminnallinen magneettikuvaus, fMRI

TABLE OF CONTENTS

ABBREVIATIONS

ACC	Anterior cingulate cortex
ATP	Adenosine triphosphate
BMI	Body mass index
BOLD	Blood Oxygenation Level Dependent
BP_{ND}	Binding potential
CrP	Creatine phosphate
CVI	Continuous vigorous-intensity exercise
EIH	Exercise-induced hypoanalgesia
EPI	Echo-planar imaging
FDR	False discovery rate
fMRI	Functional magnetic resonance imaging
FOV	Field of view
FWHM	Full-width half-maximum
GLM	General linear model
HIIT	High-intensity interval training
HR	Heart rate
MCC	Middle cingulate cortex
MET	Metabolic equivalent
MICT	Moderate-intensity continuous training
MNI	Montreal Neurological Institute
MOR	μ-opioid receptor
MRI	Magnetic resonance imaging
OFC	Orbitofrontal cortex

OPRM1	Opioid receptor mu 1 gene
PAG	Periaqueductal gray matter
PANAS	Positive Affect and Negative Affect Schedule
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PSQ	Perceived Stress Questionnaire
RF	Radiofrequency
RMS	Root mean square
ROI	Region of interest
RPE	Rating of perceived exertion
SAM	Self-Assessment Manikin
SD	Standard deviation
SIT	Sprint interval training
SRTM	Simplified reference tissue model
T2DM	Type 2 diabetes mellitus
TAC	Time activity curve
TE	Echo time
TR	Repetition time
VAS	Visual analogue scale
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen uptake
vSTR	Ventral striatum

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the Roman numerals I–IV.

I Saanijoki T, Nummenmaa L, Eskelinen JJ, Savolainen AM, Vahlberg T, Kalliokoski KK, Hannukainen JC. 2015. Affective responses to repeated sessions of high-intensity interval training. *Medicine and Science in Sports and Exercise*, 47:2604-11.

II Saanijoki T, Nummenmaa L, Koivumäki M, Löyttyniemi E, Kalliokoski K, Hannukainen JC. 2018. Affective adaptation to repeated SIT and MICT protocols in insulin resistant subjects. *Medicine and Science in Sports and Exercise,* 50:18-27.

III Saanijoki T, Tuominen L, Tuulari JJ, Nummenmaa L, Arponen E, Kalliokoski K, Hirvonen J. 2018. Opioid release after high-intensity interval training in healthy human subjects. *Neuropsychopharmacology*, 43:246-254.

IV Saanijoki T, Nummenmaa L, Tuulari JJ, Tuominen L, Arponen E, Kalliokoski K, Hirvonen J. Aerobic exercise modulates anticipatory reward processing via the μ-opioid receptor system. *Human Brain Mapping* (in press).

1 INTRODUCTION

Physical activity is widely recognised for its numerous health benefits. Regular physical activity helps maintain both physical and mental functioning, and lowers the risk for several chronic diseases such as type 2 diabetes mellitus (T2DM) and coronary heart disease as well as reduces the risk of premature death (Physical Activitity Guidelines Advisory Committee, 2008). While the most physically active people appear to be at the lowest risk, the greatest health improvements are observed when people who are least fit become physically active (Warburton *et al*, 2006). Moderate-intensity continuous training (MICT), such as brisk walking, jogging, or cycling, is a traditional and efficient means for improving fitness and health (Penedo and Dahn, 2005). However, it is likely that additional health-benefits can be gained from more vigorous exercise. Consequently, high-intensity interval training (HIIT) has become a topic of intense interest for research over the last decade and emerged as an effective method for improving maximal oxygen uptake (VO_{2max}) in a variety of populations (Milanović *et al*, 2015; Ramos *et al*, 2015; Weston *et al*, 2014). In general, HIIT refers to alternating repeated bouts of high-intensity exercise with light-intensity recovery intervals. The modality of exercise can be anything from cycling, running, and burbees to functional training performed at high-intensity (Stork *et al*, 2017). Experimental work has demonstrated that HIIT improves cardio-metabolic risk factors at least equally well as MICT, but requires considerably less time-commitment. This is considered to be the significant appeal of HIIT, given that lack of time is cited as one of the major barriers for regular exercise participation (Aaltonen *et al*, 2012; Korkiakangas *et al*, 2011; Stutts, 2002). However, HIIT is a very strenuous exercise mode, which has raised concerns regarding its tolerability for sedentary and clinical populations (Hardcastle *et al*, 2014).

Aerobic activity also improves brain health. Abundant data indicates that exercise supports mood and cognition throughout the lifespan (Voss *et al*, 2013). Exercise modifies the structures and functions (i.e. physiological, psychological and biochemical) of the brain (Matta Mello Portugal *et al*, 2013), which enhances learning and memory, improves executive functions, counteracts age-related mental decline, and protects against neurodegeneration (Cotman *et al*, 2007). Furthermore, the psychophysiological benefits of exercise include mood elevation (Brown *et al*, 1995; Steptoe *et al*, 1989; Thayer *et al*, 1994), stress reduction (Tsatsoulis and Fountoulakis, 2006; Zschucke *et al*, 2015), anxiolysis (Gordon *et al*, 2017; Wipfli *et al*, 2008), and hypoalgesia (Naugle *et al*, 2012).

The effects of exercise on mood and emotional functioning have recently been examined not only from the aspect of potential tools for treating mental disorders

but in the context of exercise adherence. Regardless of the wide awareness of the health benefits of regular exercise, the rate of physical inactivity is high positing a substantial burden for public health and the economy (Ding *et al*, 2016; Lee *et al*, 2012). Furthermore, research indicates that 50% of those who begin exercise programs drop out within the first six months (Wienke and Jekauc, 2016) and that a relapse to less active or inactive state is common and occurs after the exercise intervention has finished (Amireault *et al*, 2013). The investigation of psychological responses to exercise and especially the exploration of affective responses to acute exercise has been of specific interest as the positive affect perceived during exercise appears to predict future exercise participation (Rhodes and Kates, 2015). Thus, it is believed that participation in regular exercise is partly dependent on how exercise makes an individual feel and that a greater understanding of the affective responses induced by exercise might provide new insights in resolving the problem of exercise adherence.

One potential neurobiological mechanism underlying the beneficial psychophysiological effects of exercise is the increased synthesis and release of neurotransmitters and neurotrophic factors (Dishman *et al*, 2006; Matta Mello Portugal *et al*, 2013). These mechanisms could contribute to enhanced neurogenesis, angiogenesis, and neuroprotective activity, which further promote cognitive, affective, and behavioural functioning. The most favoured theory with the general public is the 'endorphin hypothesis', which ascribes the mood improvements after a bout of exercise to an increased release of β-endorphins (Morgan, 1985; Yeung, 1996). Indeed, central endogenous opioid release has been demonstrated in the brains of endurance athletes after prolonged, 2-hours of running using positron emission tomography (PET), and associated with self-reported increases of euphoria (Boecker *et al*, 2008). Endogenous opioids are implicated in the modulation of emotions and pain (Leknes and Tracey, 2008; Nummenmaa and Tuominen, 2017), and research in both animals and humans highlight the importance of the opioid system and especially the μ-opioid receptor (MOR) in the pleasurable effects of external rewards like food, drugs, and social interaction. In this respect, exercise-induced changes in opioid action could also contribute to reward processing after exercise, which might have implications for example in weight management and treating addictions. Previous research has revealed altered hedonic and motivational responses to food following exercise (Finlayson *et al*, 2009; McNeil *et al*, 2015; Oh and Taylor, 2012), however the involvement of endogenous opioids remains unresolved. Clearly, more research is needed to explore the role of the opioid system in different psychophysiological effects promoted by various types of exercise. The experimental studies presented in this thesis aimed to investigate the psychophysiological responses to HIIT and MICT and the underlying brain function using multi-modal neuroimaging techniques including PET and functional magnetic resonance imaging (fMRI).

2 REVIEW OF THE LITERATURE

2.1 Physical activity and exercise

Physical activity refers to body movement that is produced by skeletal muscles, and which requires more energy expenditure than resting. Exercise and sports are subsets of physical activity that are intentional, structured, and repetitive and aim at improving or maintaining health and fitness. (Caspersen *et al*, 1985). A dose refers to the amount of physical activity performed, which is a function of its intensity, duration and frequency. In order to promote and maintain health, the prevailing recommendations for sufficient physical activity include accumulating either 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity physical activity per week along with strength training of a minimum of 2 days per week. Physical activity has a dose-response effect on the prospects of obtaining health benefits, and exceeding the minimum recommendation further decreases the risk of inactivity-related chronic diseases. (Haskell *et al*, 2007). However, the responsiveness to physical activity varies considerably between individuals (Bouchard and Rankinen, 2001).

2.1.1 Exercise intensity

Exercise intensity is an important determinant of the physiological training adaptations (Garber *et al*, 2011) as well as one of the key modulators of psychophysiological responses to exercise. Exercise intensity can be expressed as either an absolute measure, such as heart rate (HR) or metabolic equivalent (MET), or as a relative measure, for example a percentage of maximal HR (% HR_{max}) or a percentage of maximal oxygen uptake (% VO_{2max}, maximal aerobic capacity). MET is a measure of energy expenditure and refers to the absolute energy required to perform a given activity. One MET is equal to the oxygen uptake of 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ and describes the energy expenditure while sitting at rest. Thus, absolute measures do not consider individual physiological capabilities, whereas relative measures are proportional to an individual's maximal capacity. (Norton *et al*, 2010). Additionally, subjective measures such as perceived exertion can be used to determine exercise intensity. One of the most commonly used subjective tools is rating of perceived exertion (RPE) Borg 6–20 Category Scale (Borg, 1998). It has shown a strong correlation with heart rate and blood lactate concentration independently of gender, age and fitness status (Scherr *et al*, 2013), and thus provides a relatively good estimate of the exercise intensity level. A summary of the commonly used classifications of exercise intensities is shown in Table 1.

Table 1. Categories of exercise intensity and the objective and subjective measures. Subjective measures are from Borg (6–20) RPE Scale. (Adapted, with permission, from Norton *et al*, 2010).

Intensity category	METs	% HR_{max}	% VO_{2max}	Perceived exertion (RPE)
Sedentary	< 1.6	< 40 %	< 20 %	Very, very light (RPE < 8)
Light	1.6 < 3	40 < 55	20 < 40	Very light to fairly light (RPE 8−10)
Moderate	3 < 6	55 < 70	40 < 60	Fairly light to somewhat hard (RPE 11−13)
Vigorous	6 < 9	70 < 90	60 < 85	Somewhat hard to very hard (RPE 14−16)
High	≥ 9	≥ 90 %	≥ 85	Very hard (RPE ≥ 17)

The intensity categories are classified according the energy demands, and thus they reflect the gradient in metabolic and neurohumoral responses during activity. As the intensity of the exercise increases, many physiological responses show an accelerating, rather than linear pattern along with increased intensity: small increases in exercise intensity may lead to relatively large increases in the physiological and metabolic demands of the body, such as blood lactate concentration, respiratory rate, and stress hormones such as adrenaline and noradrenaline. These responses reflect physiological stress, that challenges body homeostasis. (Norton *et al*, 2010). They are also associated with the perceptual-cognitive sensation of exertion and pain as well as affective responses.

Skeletal muscle activity requires energy in the form of adenosine triphosphate (ATP). Three energy systems produce ATP in muscle: 1) creatine phosphate (CrP) breakdown, 2) anaerobic glycolysis, and 3) mitochondrial oxidative metabolism of carbohydrates and lipids. CrP pathway and glycolysis are independent of oxygen and are thus referred to as anaerobic systems, whereas mitochondrial oxidation requires oxygen and is called aerobic metabolism. These systems differ in the substrates used, the capacity of ATP regeneration, maximal rate of ATP regeneration, and metabolic products. (Baker *et al*, 2010). During moderate-intensity exercise, almost all the required ATP is provided by the aerobic system of oxidative metabolism of carbohydrates and lipids. Muscle glycogen, blood glucose, and free fatty acids are the major substrates for oxidation and because these energy resources are vast, moderate-intensity exercise can be sustained for long periods of time before exhaustion sets in. Blood lactate concentration elevates only a little (if at all) above the resting level. (Hargreaves, 2000). In con-

trast, during intense exercise all three energy systems contribute to different extents based on an interaction between the intensity and duration of the exercise. Short duration high-intensity exercise especially, relies extensively on fast anaerobic processes in replenishing ATP to power extremely high muscle force use and power outputs. As a result, lactate levels increase substantially and other metabolic by-products (e.g., inorganic phosphate, ^{+}H) accumulate in the muscle causing fatigue. (Baker *et al*, 2010; Glaister, 2005). The level of exercise intensity that corresponds to the transition from aerobic to anaerobic metabolism is referred to as the 2nd ventilatory threshold (also lactate threshold or anaerobic threshold). This is the point at which the ventilatory equivalent of oxygen increases in excess of the ventilatory equivalent of carbon dioxide and where blood lactate concentration starts to accumulate rapidly. (Mezzani *et al*, 2012).

2.1.2 Moderate-intensity continuous training (MICT)

Moderate-intensity continuous training (MICT) describes traditional endurance training protocols performed at constant intensity continuously at a steady state for a set duration, usually 45–60 minutes. Typical training modalities include brisk walking, jogging, and cycling, which are performed at an intensity that elicits a heart rate response of 55–69% HR_{max} or elevates the rate of oxygen consumption to 40–59% of VO_{2max}. (Norton *et al*, 2010).

Traditionally, moderate-intensity training has been the most common type of exercise recommended to improve physical fitness and overall health-related parameters. The effort-versus-benefit relationship promotes moderate-intensity activities, given that they are relatively easy to start and readily available. Nevertheless, MICT is considered time consuming, which may limit habitual exercise maintenance, given that a lack of time is perceived as major barrier in engaging in regular exercise (Babraj *et al*, 2009).

2.1.3 High-intensity interval training (HIIT)

According to the physical activity guidelines, vigorous-intensity activity can elicit health benefits in less time than moderate-intensity physical activity. The guidelines indicate that for improving cardiovascular fitness, 75 minutes of vigorous activity is equivalent to 150 minutes of moderate-intensity activity. In this respect, high-intensity interval training (HIIT) has emerged as a time-efficient means to achieve the health-related goals of exercise training, which additionally counters the often-cited problem of lack of time.

The concept of HIIT originates from the early 1900s and it is considered as one of the most powerful forms of exercise for improving physical performance in athletes (Billat, 2001a, 2001b; Buchheit and Laursen, 2013; Laursen and Jenkins, 2002). In the 1920s, Finnish track athlete Paavo Nurmi, who dominated middle and long-distance running by winning a total of nine gold Olympic medals, already included interval training in his training routines (Buchheit and Laursen, 2013). Today, different forms of interval training have become very popular among regular exercisers.

Generally, HIIT refers to any workout that consists of repeated, short bursts of activity performed at "all-out" effort or near-maximal intensity alternated with recovery periods of rest or light intensity activity. The term HIT (high-intensity training) is often used interchangeably with HIIT. Recent recommendations for a standardisation of terminology propose that the term HIIT should be used to describe interval training protocols consisting of 1−4 min bouts of activity performed at an intensity between 80-100 % of maximal heart rate, whereas the term "sprint interval training" (SIT) should be used when referring to exercise protocols using shorter (≤ 30 s) work intervals at maximal intensity in "all-out" manner. (Weston *et al*, 2014). For clarity and due to its better recognisability among lay audience, the term "HIIT" is used throughout this thesis.

Increasing evidence shows that HIIT elicit comparable or even superior metabolic and cardiovascular improvements to traditional MICT in healthy adults as well as in the sedentary population and in subjects with lifestyle-induced diseases (Jelleyman *et al*, 2015; Milanović *et al*, 2015; Ramos *et al*, 2015; Weston *et al*, 2014). However, there are numerous different interval training protocols and researchers continue to optimise practices that would maximise the physiological adaptations resulting from exercise, while minimising discomfort and the time and effort devoted to training. At least nine different variables can be chosen for a HIIT protocol (e.g., work and recovery interval durations and intensities, number of intervals in a set, exercise modality). A common HIIT protocol used in research is based on repeated Wingate tests, which progresses from four 30 s supramaximal "all-out" efforts separated by 4 min of rest or active recovery (Burgomaster *et al*, 2005; Gibala *et al*, 2006). Another, less demanding HIIT protocol involves 60 s bouts at the intensity of 90% of HR_{max} alternating with 60 s periods of recovery (Gibala *et al*, 2012). However, the optimal protocol is yet to be discovered and is likely highly individual (Weston *et al*, 2014).

2.2 Physical activity behaviour

The health benefits of exercise are widely acknowledged and dependent on regular exercise practice. Despite the broad awareness of this, the rate of physical activity worldwide is alarmingly low. Globally, more than one third of the adult population is insufficiently active and fail to meet the recommended volume in physical activity (Hallal *et al*, 2012). In Finland, 25 % of adults report that they do not perform any regular physical activity according to the Regional Health and Well-being Study (ATH Study) conducted by the National Institute for Health and Welfare (Murto *et al*, 2017). The societal costs of physical inactivity, poor cardiovascular fitness, and high rates of sedentary behaviour have been estimated to vary between 3.2 and 7.5 billion euros per year in Finland, and the costs are expected to increase due to aging and growing prevalence of many non-communicable diseases (Vasankari *et al*, 2018). Thus, physical inactivity and sedentary behaviour represent a major challenge for public health and economy worldwide and calls for actions for increasing physical activity levels (Baker *et al*, 2011; Tuso, 2015).

Physical activity is a complex behaviour that is influenced by numerous psychological, biological, and environmental factors and their interactions (Bauman *et al*, 2012). For some time now, research has aimed to understand determinants of physical activity that produce meaningful and sustainable improvements in physical activity practice (Allen and Morey, 2010; Heath *et al*, 2012). Among adults, the most often cited motives for physical activity participation are related to health and fitness as well as social and emotional aspects such as enjoyment (Aaltonen *et al*, 2012, 2014; Caglar *et al*, 2009; Dacey *et al*, 2008; Kolt *et al*, 2004; Korkiakangas *et al*, 2011; Sit *et al*, 2008). The most common barriers include tiredness and lack of time (Aaltonen *et al*, 2012; Ebben and Brudzynski, 2008; Fox *et al*, 2012; Korkiakangas *et al*, 2011; Reichert *et al*, 2007; Sit *et al*, 2008; Stutts, 2002).

Motivating individuals to adopt and maintain regular physical activity and exercise is a great challenge for health care professionals. Various behavioural theories have tried to reveal the most effective interventions for changing physical activity habits. These theories have traditionally emphasised cognitive factors (Ajzen, 1991; Bandura, 1998), however, also affective and emotional facilitators have recently been recognised in conceptual models of physical activity motivation. For instance, in line with hedonic theories of behaviour (Cabanac, 1992; Johnston, 2003), participation in regular exercise has been suggested to depend on how exercise makes one feel: affective response to exercise shapes the memory of the exercise experience and guide subsequent exercise behaviour (Figure 1). This approach posits that human behaviour is guided by a propensity

to maximise pleasure and minimise displeasure and pain, and consequently, affective responses direct individuals towards profitable or pleasurable stimuli and away from harmful or unpleasant stimuli (Kahneman, 1999). Hence, negative affective valence from unpleasant sensations during exercise would impair adherence to exercise, whereas a positive affective valence from enjoyable perceptions during exercise should engender greater adherence (Ekkekakis, 2003). Indeed, affective responses to exercise have been found to influence adherence to exercise programmes as well as a risk of dropping out from exercising (Lee *et al*, 2016; Rhodes and Kates, 2015). Williams and colleagues (2008) demonstrated that previously sedentary adults, who experienced greater pleasure during exercise, exercised more both 6 and 12 months later. An increase of one unit on the rating scale of affective valence during a session of MICT resulted in an additional 38 and 41 minutes of exercise per week at the 6 and 12 months follow-up, respectively. (Williams *et al*, 2008). In another study, one additional unit on the scale of affective valence during 10 minutes of moderate-intensity treadmill walk predicted additional 27–29 minutes of physical activity per week in healthy low-active adults. A higher positive affect during exercise was also coupled with an additional 15 minutes of exercise per week after six months. (Williams *et al*, 2012). Altogether research suggests that greater pleasure *during* a bout of exercise predicts increased adherence to exercise programs via anticipated affective response to future exercise, whereas *post-exercise* affective state has not shown such association (Kiviniemi *et al*, 2007; Kwan and Bryan, 2010; Rhodes and Kates, 2015; Williams, 2008; Williams *et al*, 2012). Overall, these studies support the relationship between affective response to physical activity and long-term physical activity behaviour.

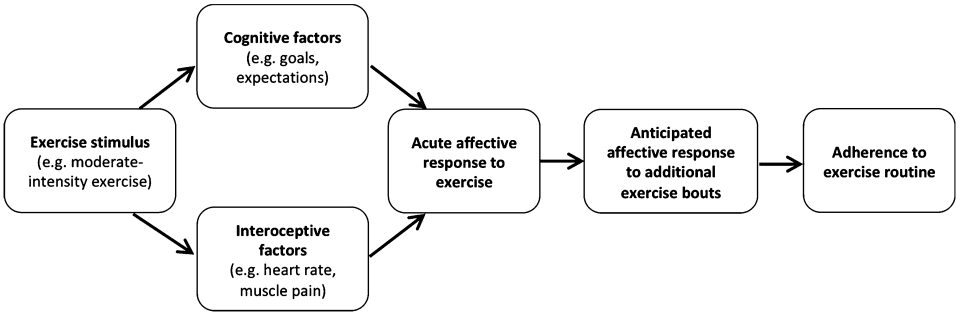


Figure 1. A model of affective response influencing exercise adherence. (Adapted, with permission, from Williams DM, 2008; Exercise, affect, and adherence: an integrated model and a case for self-paced exercise; *J Sport Exerc Psychol* 30: 471–496; http://dx.doi.org/10.1123/jsep.30.5.471).

2.3 Psychophysiological responses to exercise

In general, acute exercise is associated with increased positive affect and decreased negative affect (Ekkekakis and Petruzzello, 1999; Liao *et al*, 2015; Raedeke, 2007; Reed and Ones, 2006; Yeung, 1996), as well as alleviation of psychological and physiological responses to stress (Salmon, 2001; Zschucke *et al*, 2015). Exercise has also been found to be one of the most efficient behavioural strategies for self-regulation of mood in healthy adults (Edwards *et al*, 2017; Thayer *et al*, 1994). However, the transient affect modulation elicited by an acute bout of exercise is variable and can range from complete aversion (Lee *et al*, 2016) to intense sensations of euphoria, often referred to as runner's high (Dietrich and McDaniel, 2004; Morgan, 1985). Such sensations may be experienced as rewarding. In rodents, physical exercise such as wheel running, has reinforcing properties for which animals are willing to work and show conditioned place preference (Belke and Wagner, 2005; Greenwood *et al*, 2011). The rewarding component of exercise may contribute to addictive behaviour (Berczik *et al*, 2012) and athletes have reported withdrawal-like symptoms when deprived of their habitual level of exercise (Aidman and Woollard, 2003).

2.3.1 Affect

The term "affect" is often used to mean anything emotional (Barrett, 2006). In its most basic form affect ("core affect" or "basic affect") is considered as the general neuropsychological state and the elemental component of emotions and moods. It consists of all possible combinations of valenced (positive or negative, pleasant or unpleasant) and activated (high arousal or low arousal) states including states that would not be called emotions, such as calm, drowsiness or liveliness. Basic affect *per se* is not about anything, instead, it can be experienced without any internal or external stimulus. Thus, basic affect is experienced constantly, although the intensity of affect can vary over time. (Barrett, 2006; Fernández-Dols and Russell, 2003; Russell, 2003).

Basic affect also guides human behaviour. It represents different scenarios of action on a single dimension, namely pleasure−displeasure, and thus, provides a means of assessing resources when planning or deciding on behaviour. The pleasure−displeasure dimension has been considered to be a psychological currency that facilitates comparison between different options. Typically, although not always, people tend to seek pleasure and avoid displeasure. Physical exercise, listening to music, consuming specific foods, smoking cigarettes, and looking for

particular companions are, at least in part, methods for regulating basic affect. (Fernández-Dols and Russell, 2003).

Emotions and moods, which include basic affect, are much more complex affective phenomena. Emotions are typically about something. They are induced by external or internal stimuli, and temporally follow these eliciting stimuli quickly or even instantly. Compared to emotions, moods are more long-lasting and are less closely related to external or internal stimuli, and are thus more remote from their initial cause. (Ekkekakis, 2013). In exercise studies, investigating basic affect (valence and activation) rather than specific emotions would likely be more beneficial (Ekkekakis and Petruzzello, 2000).

2.3.2 Perceived exertion

Perceived exertion is a subjective measure that describes the subjective intensity of effort, strain, and/or fatigue that is experienced during physical activity or exercise (Robertson and Noble, 1997). It comprises detecting and interpreting physiological, psychosocial, performance-related, and symptomatic processes arising from the body during physical activity. Perceived exertion is mostly based on physiological sensations and exertional symptoms experienced during exercise, such as increased heart and breathing rate, increased sweating, and muscle fatigue, which ultimately shape the perceptual response. However, the sense of effort is also subject to psychosocial mediators, which include affective mediators, cognitive mediators, and social/situational mediators such as music. Variables that provide feedback from e.g. heart rate or distance travelled are performance-related exertional mediators, which further modify the perceptual response of exertion. (Eston, 2012; Haile *et al*, 2015).

Perceived exertion can be assessed during any type of exercise or daily activities. The level of perceived exertion can be assessed by selecting a number, or rating of perceived exertion (RPE), from a numerical range displayed on a perceived exertion scale. The most commonly used psychophysical tool to assess RPE in adults is the Borg 6–20 Category Scale. (Eston, 2012; Haile *et al*, 2015). The Borg (6–20) RPE Scale strongly correlates with heart rate and blood lactate concentration independently of gender, age and fitness status (Scherr *et al*, 2013), and thus provides a relatively robust estimate of the exercise intensity level. Consequently, RPE is a valid tool for monitoring, prescribing, and regulating exercise intensity and assessing training load (Eston, 2012).

2.3.3 Pain

Pain is integral element of sports and exercise. Phrases describing the perceptions of exercise-induced pain have become clichés (e.g. “no pain, no gain”). (Cook *et al*, 1997). The perception of naturally occurring muscle pain during exercise in healthy people is well-recognised and distinct from perceived exertion (Cook *et al*, 1997; Haile *et al*, 2015). Muscle pain threshold during exercise shows a large inter-individual variation and pain intensity increases as a positively accelerating function of the power output (Cook *et al*, 1997). Exercise-induced pain may reduce a person’s willingness to perform exercise or hamper performance and thus it may have implications for adoption and maintenance of regular exercise (Haile *et al*, 2015).

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey *et al*, 1994), suggesting that experience of pain is subjective, it involves an affective component, and may not be related to actual tissue damage (Haile *et al*, 2015; O’Connor and Cook, 1999). Pain experience is a complex perceptual process that originates in the brain and is strongly modulated by interactions between peripheral nociceptive input and modulatory processes at the spinal and supraspinal levels. The endogenous pain modulatory system within the nervous system includes inhibitory and excitatory functions, and involves multiple neurotransmitters and neuromodulators. During exercise, the mechanical pressure of the working muscles, and/or the noxious metabolic by-products such as bradykinin stimulate nociceptors within the afferent nociceptive pathways, and send information from active skeletal muscle to the central nervous system via group III and IV afferent nerve fibres. In the brain, pain modulation occurs in the cortical, hypothalamic, midbrain, and brainstem structures. (O’Connor and Cook, 1999).

Physical exercise can also shape endogenous pain modulation (Drury *et al*, 2005; O’Connor and Cook, 1999). Exercise-induced hypoalgesia (EIH) occurs when a noxious stimulus is perceived as less painful during or after a bout of exercise. EIH has also been characterised by increases in pain thresholds and tolerance, as well as by reductions in ratings of pain intensity. (Koltyn, 2000; Koltyn *et al*, 2014). Meeting the physical activity guidelines have been associated with a reduction in pain sensitivity in healthy women (Ellingson *et al*, 2012), and therapeutic exercise programmes may be an important element also in the treatment of many chronic pain syndromes (Mior, 2001). In patients with chronic pain, evidence indicates an inverse relationship between physical activity and pain sensitivity. It has been shown that regular physical activity is associated with decreased symptoms and improved functioning in patients with several chronic

pain conditions (Bidonde *et al*, 2017; Landmark *et al*, 2011; Mior, 2001). Although the processes responsible for EIH are poorly understood, multiple analgesia mechanisms, including opioid and non-opioid systems, have been suggested to contribute to changes in pain sensitivity resulting from exercise (Koltyn *et al*, 2014; Smith and Lyle, 2006; Sparling *et al*, 2003).

2.3.4 Modulators of affective and perceptual responses

Numerous factors influence affective and perceptual responses to exercise (Reed and Ones, 2006). These include contextual factors (e.g., exercise setting, music, weather), aspects of the exercise stimulus (e.g., intensity, duration, mode), and individual differences (e.g., fitness level, age, gender, affective state prior to exercise session, genes). In general, better physical fitness level and current participation in physical activity have been associated with more pleasant affective responses to exercise. (Magnan *et al*, 2013). Aerobic fitness appears as an important mediator of affective responses especially at high exercise intensities and larger exercise doses (Ekkekakis and Petruzzello, 1999). Habitually more active individuals report higher levels of positive affect and tranquillity and lower levels of negative affect and fatigue during a session of moderate-intensity exercise in comparison with less active individuals (Magnan *et al*, 2013). A single session of moderate-intensity exercise improves vigour and decreases fatigue more as well as results in higher improvements in disturbances in mood in regular exercisers than non-regular exercisers (Hoffman and Hoffman, 2008). Regular exercisers also respond positively to an acute bout of vigorous-intensity exercise, reporting less state anxiety and fatigue and more vigour in comparison to non-regular exercisers, who responded with an initial reduction in positive mood states, followed by a rebound to baseline levels 25 minutes after the cessation of exercise (Hallgren *et al*, 2010). Similarly, a bout of interval training results in more negative affective responses in insufficiently active individuals compared with active ones (Frazão *et al*, 2016).

Furthermore, high body weight may also modify perceptions of exercise (Ekkekakis and Lind, 2006; Hulens *et al*, 2003). It also predicts lower levels of physical activity participation and lower adherence to exercise programmes (Bish *et al*, 2007; Tryon *et al*, 1992). Overweight individuals report higher perceived exertion (Ekkekakis and Lind, 2006; Hulens *et al*, 2003) and obese individuals experience more displeasure during exercise than normal weight individuals (Ekkekakis *et al*, 2010). Overweight individuals tend to experience more musculoskeletal aches and pains as well as other physical discomforts such as skin fric-

tion and urinary stress incontinence (Hulens *et al*, 2001, 2003), which may further deteriorate the affective experience.

Additionally, various chronic diseases may also influence the perceptual responses to exercise due to both physiological and psychological factors. For instance, cardiovascular disease patients may experience pain during exercise at a certain level of exertion or exercise intensity due to ischemia. Pain is common also in diabetic patients who suffer from peripheral neuropathies and various types of arthritides. (Haile *et al*, 2015). Furthermore, increased feelings of fatigue, which accompany many common clinical conditions such as T2DM and fibromyalgia, may increase perceived exercise effort (Huebschmann *et al*, 2015) and further interfere with exercise tolerance and adherence (Busch *et al*, 2009; Fritschi and Quinn, 2010).

Affective responses to exercise appear complex and versatile, suggesting that they are driven by various underlying mechanisms. The dual-mode hypothesis by Ekkekakis (Ekkekakis, 2003) suggests that both physiological and social-cognitive cues are important modulators of affective response to exercise and neither alone entirely dictates the affective response. In addition to physical factors described above (higher BMI, poorer physical fitness and clinical conditions), other physical determinants that are associated with acute affective response include interoceptive cues from the body during exercise, such as increased respiration, HR, and body temperature, as well as sweating and muscle pain. Moreover, cognitive factors such as self-efficacy, personal goals, and expectations, further shape the affective experience. For example, exercise self-efficacy, which is situation-specific self-confidence in one's abilities to perform or engage in exercise, has shown to be an important cognitive determinant of the affective response to exercise (Bryan *et al*, 2007; Focht *et al*, 2007). Higher physical activity levels have also been associated with higher exercise self-efficacy (Fallon *et al*, 2005; Rose and Parfitt, 2012).

Exercise intensity is a key modulator of perceptual and affective responses to exercise. Affective changes from pre- to various post-exercise time points are robustly positive, regardless of exercise intensity. A positive shift in affect has been described following brief self-paced low-intensity walks (Ekkekakis *et al*, 2000) as well as after a bout of moderate- and vigorous-intensity exercise. The responses of affect during exercise however, show a much more diverse and intensity-dependent pattern (Ekkekakis and Petruzzello, 1999). Moderate-intensity exercise, though commonly assumed to induce positive affective response in most individuals, has a huge variation in affective responses during exercise. This has been demonstrated in a study where 44% of participants experienced a progressive enhancement in affective valence, whereas 41% experienced a pro-

gressive deterioration of affect during a 30 minute session of moderate-intensity cycling (Van Landuyt *et al*, 2000). The dual-mode model proposes that exercise intensity at which the transition from aerobic to anaerobic metabolism occurs is crucial as regards affect. Moderate-intensity training, which is sustained by aerobic metabolism for long periods of time, is typically associated with positive affective changes, whereas higher intensities at the anaerobic threshold (lactate threshold/ventilatory threshold) results in variable affective responses of which some report positive and some report negative affective changes. The variation at this intensity level is likely due to different perceptions of the metabolic transition from aerobic to anaerobic metabolism. Suprathreshold intensities consistently result in a deterioration of affective responses during exercise. (Ekkekakis *et al*, 2005). Given that an affective response is thought to arise from the interplay between interoceptive (e.g., heart rate, muscle pain) and cognitive factors (e.g., self-efficacy, personal goals, expectations), the factor making the greatest impact on affect at a given moment is posited to depend on the intensity of the exercise and upon the stress that is being placed on bodily homeostasis. Thus, according to the dual mode theory, defining exercise intensity with respect to a fixed metabolic marker such as the lactate/ventilatory threshold is important, instead of the percentage of maximal capacity. This would ensure that the intensity is physiologically equivalent between individuals. (Rose and Parfitt, 2008). Interestingly, affect-regulated exercise has been suggested as one approach for use in the clinical practice of prescribing and advising on exercise and physical activity. Exercising at the intensity where affect remains "good" or "very good" has been shown to be sufficient regarding the physical activity recommendations in overweight and obese individuals. (Costa *et al*, 2015).

Affective responses induced by interval training have also gained considerable interest recently. In general, HIIT has been considered as a very demanding and unpleasant exercise method. However, recovery periods interspersed with work intervals may alleviate the displeasure associated with high-intensity exercise (Oliveira *et al*, 2013) and variety in the protocol may increase exercise motivation (Wisloff *et al*, 2007). According to the dual-mode hypothesis, the very high exercise intensity utilised in HIIT protocols would predict negative affective experience. Indeed, the early studies found that during exercise, HIIT (1 min at 100% W_{peak} and 1 min at 20% W_{peak} for 20 min) elicits more displeasure compared to MICT (40 min at 40% W_{peak}), yet more pleasure than continuous vigorous-intensity exercise (CVI; 20 min at 80% W_{peak}) in inactive adults. Despite the negative affective response during exercise, HIIT was perceived as more enjoyable than MICT or CVI and ranked as the preferred exercise modality. (Jung *et al*, 2014). Another study comparing the affective responses to HIIT and CVI applied a different HIIT protocol (2 minute high-intensity intervals with less than 60 seconds of recovery periods), and found an opposite pattern of affective responses

indicating that affect was more positive during CVI than HIIT (Oliveira *et al*, 2013). Such equivocal findings are probably a result of methodological differences: given the numerous variations of HIIT methods, the protocol that elicits the highest positive affective responses remains unknown.

2.4 Endogenous opioid system

The endogenous opioid system is an essential modulatory mechanism that is involved in the regulation of pain, pleasure, and diverse autonomic functions. It consists of G-protein-coupled opioid receptors (μ, δ- and κ-receptors), which interact with their endogenous ligands (endorphins, enkephalins, dynorphins, and endomorphins), which in turn have different affinity profiles for different opioid receptors. Opioid peptides derive from the proteolytic cleavage of large protein precursors; for example β-endorphin, which possesses the highest affinity for μ-opioid receptors (MORs), is derived from alternative splicing of pro-opiomelanocortin. Both opioid peptides and receptors are ubiquitous and located with varying densities throughout the central, peripheral, and autonomic nervous systems as well as in different organs such as the heart, lungs, liver, and gastrointestinal tracts. This widespread distribution is consistent with the involvement of opioids in diverse pleiotropic effects; they are essential for supraspinal, spinal, and peripheral pain modulation, and regulate many other physiological processes, including stress responses, respiration, cardiovascular functions, gastrointestinal transit, as well as endocrine and immune functions. Furthermore, opioid peptides and receptors are rich in limbic brain areas, which posits the endogenous opioid system in a key role in reward and emotion processing and drug addiction. In general, activation of opioid receptors attenuates neuronal action by pre- and postsynaptic mechanisms, which include the release of inhibitory neurotransmitters and alterations in neuronal excitability. (Benarroch, 2012; Feng *et al*, 2012).

2.4.1 Opioid system in pain and pleasure

Of the three types of opioid receptors, MOR subtypes have been most extensively studied. MOR is encoded by the opioid receptor mu 1 gene (OPRM1) and is widely expressed in both cortical and subcortical regions of the brain. MORs mediate the effects of endogenous opioids (e.g., β-endorphins) and of exogenous opioid agonists (e.g., morphine), and thus are well-acknowledged for their role in processing analgesic, euphoric, and addictive functions. MORs are abundantly expressed at all levels of the complex central pain controlling network, including the anterior cingulate cortex, amygdala, hypothalamus, periaqueductal grey mat-

ter (PAG), and rostral ventromedial medulla, and engage in multiple aspects of pain modulation. Human neuroimaging studies using positron emission tomography (PET) support the fundamental role of MORs in central analgesia mechanisms. For example, sustained moderate-intensity muscular pain induces dynamic changes in the MOR mediated neurotransmission in multiple brain areas related to pain (Scott *et al*, 2007; Zubieta, 2001). The pain relieving effects of placebo (Wager *et al*, 2007) and transcranial magnetic stimulation (Lamusuo *et al*, 2017) have also been shown to involve MOR action. Furthermore, MOR activation has been found to be associated with reductions in the unpleasantness of pain, suggesting that analgesic effects of MORs include not only attenuation of nociception but blunting of the distressing, affective component of pain as well (Zubieta, 2001).

Another main aspect of opioid system is its emotion-regulating properties. MOR system is an important component of dispersed interconnected neurocircuitry involved in the regulation of specific emotion systems as well as pleasure and reward. Emotional stimulation induces MOR activation in the key components of the emotion circuit, including regions involved in emotional saliency encoding and fear learning (i.e. amygdala and hippocampus), arousal and alertness modulation (i.e. thalamus) and appetitive motivation and reward (i.e. ventral and dorsal striatum). The effects of opioids are not limited to any specific feelings, instead MOR actions influence various emotions. (Nummenmaa and Tuominen, 2017). While the involvement of the MOR system is most well-recognised in pleasurable feelings associated with reward, MOR action has also been linked to fear and anxiety (Liberzon *et al*, 2007; Wilson and Junor, 2008), sadness and depression (Hsu *et al*, 2013, 2015; Zubieta *et al*, 2003), as well as anger and aggression (Berman *et al*, 1993; Spiga *et al*, 1990).

Normal pleasure responses are essential for well-being (Berridge and Kringelbach, 2008). The mesolimbic reward system guides motivated behaviour, and highly pleasurable sensations upon receiving or consuming rewards reinforce subsequent repetition of the behaviour. Although dopamine is often regarded as the primary neurotransmitter responsible for reward processing, accumulating evidence suggests that dopamine is more likely to be central in motivational drive, such as craving and desire, rather than in actual pleasure. Instead, MOR stimulation appears to be more closely involved in generating liking and hedonic responses (Berridge and Kringelbach, 2015; Berridge and Robinson, 2016) and opioids can generate reward independently of dopamine (Hnasko *et al*, 2005). Animal studies indicate that MORs are primary mediators of the rewarding effects of exogenous opiates (Bozarth and Wise, 1981), ethanol, nicotine, and psychostimulants (Benarroch, 2012), yet MOR system is closely involved also in the hedonic effects of natural rewards. For example, social interaction is crucial for

mammalian survival and thus highly motivating and rewarding (Trezza *et al*, 2011). Social acceptance (Hsu *et al*, 2013) and social laughter (Manninen *et al*, 2017) induces MOR activation in humans, and both in animals and humans social bonding has been found to be linked to the MOR system (Burkett *et al*, 2011; Loseth *et al*, 2014; Nummenmaa *et al*, 2015, 2016).

Feeding is another natural stimulus that engages the MOR system. Although homeostatic processes constitute the basis of appetite regulation, the brain's reward mechanisms and especially the MOR system drive both incentive motivation and generation of pleasurable sensations upon food consumption (Peciña and Smith, 2010). In animals, MOR stimulation increases both food intake and hedonic reactions to food (Berridge *et al*, 2010; Gosnell and Levine, 2009; Peciña and Smith, 2010), and may increase the preference especially for a high fat diet (Katsuura *et al*, 2011). Human PET studies have revealed that food consumption induces MOR activation (Burghardt *et al*, 2015; Tuulari *et al*, 2017) and that continuous overstimulation of the MOR system following excessive eating may result in subsequent downregulation of the MOR in obesity (Karlsson *et al*, 2015, 2016) indicating a link between MOR and food consumption in humans.

2.4.2 Opioidergic effects of physical exercise

The neurobiological mechanisms underlying the affective responses to exercise have been primarily attributed to changes in brain neurochemical concentrations (Basso and Suzuki, 2016; Dishman *et al*, 2006; Matta Mello Portugal *et al*, 2013). The most popular theory, the 'endorphin hypothesis' ascribes the exercise-induced euphoria and mood improvements to increased release of β-endorphin (Morgan, 1985; Yeung, 1996), and hence, to opioidergic neurotransmission. Indeed, plasma β-endorphin concentration is elevated after prolonged (Heitkamp *et al*, 1993; Petraglia *et al*, 1990) and intense exercise (Farrell *et al*, 1987; Gambert *et al*, 1981; Rahkila *et al*, 1988). These responses, however, show a large inter individual variability (Farrell *et al*, 1982) and a poor correlation with exercise-induced affective responses (Farrell *et al*, 1982; Kraemer *et al*, 1990). While the exercise-induced perceptual and affective responses likely engage the opioidergic system, the blood borne responses of raised opioid levels may not serve as representative markers of the brain, given that the direct effects of peripheral endorphin on the brain is limited by the blood brain barrier (Banks and Kastin, 1990).

Studies using opioid antagonists have attempted to indirectly elucidate central opioidergic involvement in exercise. Opioid antagonists such as naloxone, block the effects of β-endorphin and should therefore diminish the possible endorphin-

dependent mood-enhancing effects of exercise. Findings have remained inconclusive: some studies have demonstrated attenuated mood-improvements after blocking opioid receptors with opioid antagonist (Daniel *et al*, 1992; Janal *et al*, 1984; Järvekülg and Viru, 2002), whereas others have found no effect of opioid antagonists on affective responses (Farrell *et al*, 1986; Markoff *et al*, 1982). Indecisive findings also link opioidergic mechanisms to perceived effort and endurance. Some studies, but not all (Koglin and Kayser, 2013), have found that opioid receptor blockade with naloxone results in increased ventilation (Grossman *et al*, 1984) and breathlessness (Mahler *et al*, 2009) as well as in increased ratings of perceived exertion at high levels of power output (Grossman *et al*, 1984; Sgherza *et al*, 2002). Discrepancies in these findings may be at least partly due to genetic variance, given that the rare G allele of the MOR gene OPRM1 has been found to be associated with greater changes in perceived exertion and lactate during exercise (Karoly *et al*, 2012).

Multiple animal studies have confirmed central opioidergic involvement in exercise. Increased β-endorphin levels were found in nucleus accumbens in rats after a fatiguing 2-hours of forced treadmill running (Blake *et al*, 1984), whereas increased opioid receptor binding was demonstrated after 2-hours but not 1-hour of forced swimming with non-selective opioid receptor antagonist [^{3}H]diprenorphine (Sforzo *et al*, 1986) and after a few repeated low-intensity exercise sessions (7 days, 1 hour per day) with selective MOR agonist [^{3}H]DAMGO (Arida *et al*, 2015). Similarly, increased MOR expression was found in rat hippocampal formation in response to acute, moderate-intensity, both voluntary and forced exercise (de Oliveira *et al*, 2010). These findings, however, only demonstrate exercise-induced opioid modulation, but fail to link opioidergic neurotransmission to behavioural or emotional responses. Recently, elevated expression of MOR gene OPRM1 mRNA was found in nucleus accumbens of rats, which were selectively bred for high levels of voluntary wheel running in comparison with low voluntary wheel running rats, which suggests that MOR may be implicated in motivation for exercise in the long term (Ruegsegger *et al*, 2015). Interestingly, β-endorphin and the MOR system have also been found to be pivotal for exercise-induced promotion of hippocampal neurogenesis (Koehl *et al*, 2008). This however, appears to be susceptible to exercise intensity: in rats, high-intensity exercise such as HIIT does not promote adult hippocampal neurogenesis like moderate-intensity exercise does, perhaps due to stress induced by higher exercise intensity (Inoue *et al*, 2015; Nokia *et al*, 2016). Chronic exposure to exogenous opioids such as morphine has been shown similar inhibition on neurogenesis in rat hippocampus (Eisch *et al*, 2000), thus increased MOR activation followed by repeated high-intensity exercise could weaken hippocampal neurogenesis.

The first evidence that endogenous opioids are released in human brain in response to prolonged exercise was provided by a seminal investigation measuring brain opioid receptor binding with non-selective radioligand [^{18}F]FDPN using PET-imaging (Boecker *et al*, 2008). The study included ten trained distance runners who were chosen for the study based on their prior runner's high experiences. Brain opioid receptor binding was measured in two separate conditions: at baseline (without sportive activity for >24h) and 30 minutes after 2 hours of running. Running reduced opioid receptor binding, indicating endogenous opioid release, in frontolimbic regions of the brain, and this reduction correlated with increases of self-reported euphoria. Although this study supports the idea that the endogenous opioid system is closely involved in the runner's high phenomenon, it is unlikely that the association with euphoria can be generalised to a typical exerciser, given that sensations of euphoria are not common even among long-distance runners (Dishman and O'Connor, 2009). Furthermore, two-hour exercise sessions are not applicable for most regular exercisers, and thus the effects of exercise duration and intensity on the brain opioid system remain unknown.

2.5 Effects of exercise on food reward processing

People make over 200 food-related choices per day of which they are aware of only a fraction (Wansink and Sobal, 2007). Food decisions are made in the brain and they integrate multiple hormonal and neural signals that reflect internal state and the environment (Smeets *et al*, 2012). These decisions concern when, what, and how much to eat, and they determine the final food intake (Van Meer *et al*, 2016). Overconsumption occurs when more energy is consumed than expended. Overconsumption leads to a positive energy balance and weight gain, and is considered to be the main cause of obesity (Blundell and King, 1996). The anticipation phase, when food or food-related cues are perceived or thought of, initiates the process of food choice (Van Meer *et al*, 2016). For example, palatable foods bear strong automatic incentives, and a mere glimpse of a delicious dessert or the smell of pizza may trigger a strong urge for eating. Hence, perception of a food cue activates various processes in the brain including hedonic evaluation of food and preparation for food ingestion (van der Laan *et al*, 2011). Previous fMRI studies have demonstrated that individuals who show greater brain reactivity to high-caloric food images consume more snacks after the experiment (Lawrence *et al*, 2012), have higher BMI (Stoeckel *et al*, 2008), and poorer weight loss outcomes (Murdaugh *et al*, 2012). As a result, sensitivity to anticipatory food cues may be predictive of actual food consumption and weight gain/loss outcomes. Furthermore, obesity has been suggested to reflect problems in dealing with food cues and the desire to eat, instead of increased pleasure derived from eating or a

stronger preference for energy-dense foods (Van Meer *et al*, 2016; Mela, 2001). Examining brain responses to food cue exposure may help unravel the mechanisms underlying eating behaviours.

Physical exercise can modulate eating behaviours and play a role in weight loss and management. Exercise modulates food intake not only by affecting various physiological signalling pathways that govern energy homeostasis and regulate appetite (Schubert *et al*, 2014) but also by inducing alterations in the subjective hedonic responses to food. Human behavioural and neuroimaging studies have demonstrated altered hedonic and motivational responses to food after exercise. A single exercise session abates chocolate craving and consumption (Oh and Taylor, 2012) as well as reduces preference for high versus low-fat foods (McNeil *et al*, 2015). At the neuronal level, functional magnetic resonance imaging (fMRI) studies have shown altered haemodynamic responses to pictures of high versus low caloric foods within brain regions implicated in reward processing following acute (Crabtree *et al*, 2014; Evero *et al*, 2012) and long-term exercise (Cornier *et al*, 2012), indicating changes in anticipatory food reward processing.

However, it appears that physical exercise alone, without calorie restriction is an ineffective means for weight loss (Shaw *et al*, 2006; Swift *et al*, 2014). One reason may be because individuals reward themselves through compensation for physical exertion and overestimate calories expended relative to the calories consumed (King, 1999). Moreover, exercise-induced changes in hedonic processing and a craving for food following exercise is likely to influence compensatory responses in dietary caloric intake, which may also contribute to modest efficiency of exercise interventions without energy restriction for weight loss outcomes (Thomas *et al*, 2012). Energy intake and food craving after exercise have been shown to vary considerably between individuals. For example, a single session of exercise was shown to increase food palatability and craving as well as preference for energy dense appetising foods in individuals who were more prone to increase their post-exercise energy intake in comparison with individuals whose energy intake did not change or even declined (Finlayson *et al*, 2009). Furthermore, increased food palatability and increased preference for high-fat sweet foods acutely after exercise has been found to predict smaller weight loss outcomes after 12-week exercise intervention in obese individuals (Finlayson *et al*, 2011). Despite progress in understanding the effects of exercise on hedonic processing of food, the underlying neurochemical mechanisms remain unknown. Given that endogenous mesolimbic opioid system and particularly the MORs are involved in both motivational processing and hedonic evaluation of food as well as in rewarding aspects of physical exercise, the interaction between opioid re-

lease following physical exercise and food reward processing seems plausible, yet unresolved.

2.6 Summary of the literature

Affective responses induced by physical exercise are associated with future exercise participation. Exercise intensity is a key modulator of the affective response during exercise. Altogether, higher exercise intensity elicits more negative affective response during exercise, whereas moderate-intensity exercise may result in improvements in affect. The affective responses to versatile protocols of HIIT remain less understood, but of importance, because HIIT has shown to be an efficient exercise strategy in healthy and clinical populations and it tackles one of the often-cited barriers for physical activity, namely the lack of time. Furthermore, the research regarding the neurochemical mechanisms underlying the affective responses to exercise is sparse. While animal studies indicate a role of endogenous opioid system in exercise, in humans, only one study has demonstrated central opioidergic involvement after a prolonged, 2-hours of running. The opioid action in different exercise settings and its role in affective responses as well as in food reward processing following exercise thus remain unclear.

3 OBJECTIVES OF THE STUDY

This thesis set out to investigate the affective and perceptual responses to physical exercise performed at different intensities, because these responses may influence adaption and adherence to regular exercise. Additionally, the aim was to explore the involvement of the endogenous opioid system in the brain in exercise-induced affective and perceptual responses, as well as in exercise-induced alterations in food reward processing; this was done using a multimodal neuroimaging approach with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI).

The specific objectives of this thesis were:

1) To study affective adaptation in healthy inactive males over a two-week period of HIIT and MICT (I).

2) To study affective adaptation in males and females with type 2 diabetes mellitus or prediabetes over a two-week period of HIIT and MICT (II).

3) To investigate exercise-induced opioidergic action in the human brain at different exercise intensities (III).

4) To investigate whether exercise-induced opioid release predicts changes in anticipatory food reward processing (IV).

4 GENERAL METHODOLOGY

4.1 Subjects

Subjects were collected from two larger studies, "The effects of short-time high-intensity interval training on tissue glucose and fat metabolism in healthy subjects and in patients with type 2 diabetes; "HITPET" (NCT01344928), and "Molecular and Functional Neurobiology of Physical Exercise; "EXEBRAIN" (NCT02615756) (http://www.clinicaltrials.gov). Altogether 28 healthy, middle-aged untrained men (Study I), 26 middle-aged men and women with insulin resistance (Study II), and 24 healthy young men (Studies III-IV) were studied. Characteristics of the subjects are presented in Table 2.

The inclusion criteria for the healthy subjects in Study I were male sex, age 40–55 years, BMI 18.5–30 $kg \cdot m^2$, normal fasting blood glucose concentration, and sedentary lifestyle. For the insulin resistant subjects in Study II, the inclusion criteria included male or female sex, BMI 18.5–35 $kg \cdot m^2$, impaired glucose tolerance according to the criteria of American Diabetes Association, and physically inactive lifestyle ($VO_{2peak} < 40$ $ml \cdot kg^{-1} \cdot min^{-1}$). Exclusion criteria for Studies I and II consisted of high blood pressure (>140/90 mmHg for healthy and >160/100 for insulin resistant subjects) and other chronic diseases or medical defect requiring medical treatment.

The inclusion criteria for the healthy subjects in the Studies III-IV were male sex, age 18–65 years, BMI ≤ 27 $kg \cdot m^2$, and good health. The exclusion criteria were current medication affecting central nervous system, history of or current neurological or psychiatric disease, and any chronic medical defect or injury, which hindered or interfered with everyday life.

For all subjects the exclusion criteria also included regular use of tobacco products or illicit drugs, heavy alcohol consumption, poor compliance, history of other nuclear imaging studies, and presence of ferromagnetic objects or notable claustrophobia, which would contraindicate MR imaging.

The studies were conducted according to the Declaration of Helsinki. The ethical committee of the Hospital District of the Southwest Finland approved the study protocols. All the subjects signed the ethics committee approved informed consent form.

Table 2. Baseline characteristics of the participants in each study.

	Study I	Study II	Study III	Study IV
Health status	healthy	T2DM or prediabetes	healthy	healthy
Number of subjects (male/female)	28/0	16/10	22/0	24/0
Age (years)	48 (5)	49 (4)	26 (5)	27 (5)
Body mass (kg)	84 (9)	92 (13)	78 (9)	78 (9)
Height (cm)	179 (4)	173 (8)	182 (7)	182 (7)
BMI ($kg \cdot m^2$)	26.1 (2.5)	30.5 (2.7)	23.4 (1.7)	23.5 (1.6)
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	34.2 (4.1)	27.2 (4.6)	48.9 (6.2)	47.2 (8.3)

Values are presented as mean (SD). T2DM, type 2 diabetes; BMI, body mass index; VO_{2peak}, peak oxygen uptake

4.2 Overall study designs

The imaging studies and training interventions were conducted at the Turku PET Centre, Turku, Finland. The VO_{2peak} tests were performed at the Paavo Nurmi Centre, University of Turku, Turku, Finland.

4.2.1 HITPET

HITPET was conducted in two phases as a parallel-group randomised controlled trial. In the first phase, the subjects were healthy untrained middle-aged men (n=28, Study I) and in the second phase the subjects were untrained men and women with T2DM or pre-diabetes (n=26, 10 women, Study II). The study design is illustrated in Figure 2. In both phases the subjects were randomised with 1:1 allocation ratio for HIIT and MICT training interventions. During intervention, the subjects completed six supervised training session within two weeks, with at least one recovery day between exercise sessions. Peak O_2 uptake was determined in a VO_{2peak} test prior to and after intervention, and perceptual and affective responses were assessed with questionnaires before, during, and after each training session. Blood lactate concentration was determined from capillary blood samples before and after each training session.

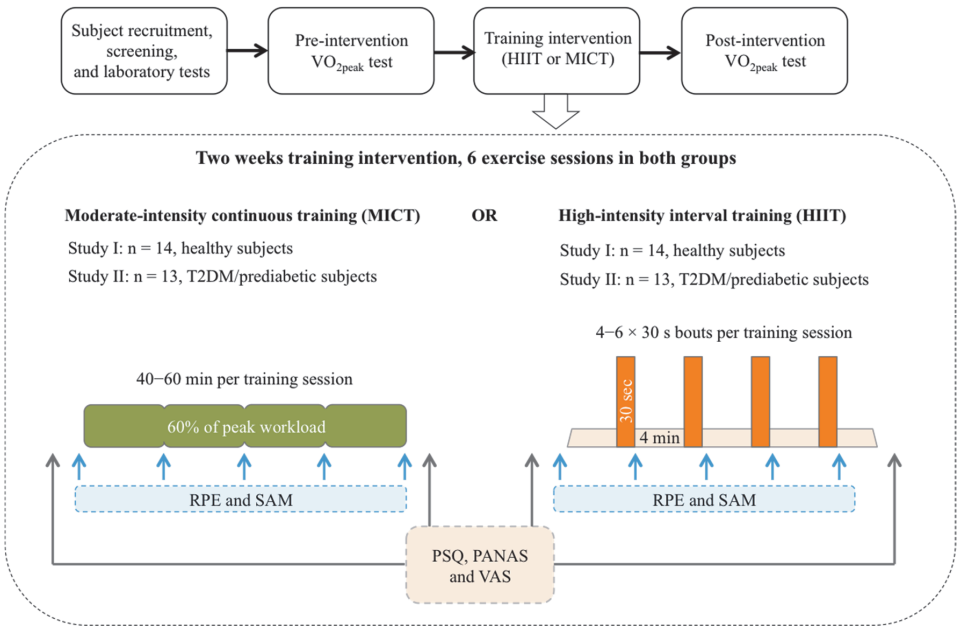


Figure 2. HITPET study design. VO_{2peak}, peak oxygen uptake; RPE, Rating of Perceived Exertion; SAM, Self-Assessment Manikin; PSQ, Perceived Stress Questionnaire; PANAS, Positive and Negative Affect Schedule, VAS, visual analogue scale.

Training interventions were conducted as described previously (Eskelinen *et al*, 2016; Heiskanen *et al*, 2017). The HIIT protocol was based on repeated Wingate tests. The HIIT session consisted of a warm-up and 4−6 bouts of all-out cycling efforts for 30 seconds with 4 minutes of recovery between the bouts, during which subjects remained still or did unloaded cycling (Monark Ergomedic 894E, Vansbro, Sweden). Each bout started with a few seconds of acceleration to maximal cadence without any resistance, followed by a sudden increase of the load and maximal cycling continued for 30 seconds. The number of bouts started from four and increased to five and six after every other training session. For the healthy subjects the load was 7.5% of the body weight and for the insulin resistant subjects the load was 10% of the fat free mass in kg. The subjects were familiarised with HIIT protocol during the screening phase.

In the MICT group, subjects performed continuous aerobic cycling for 40–60 min at moderate intensity (60 % of peak workload) with an electrically-braked cycle ergometer (Tunturi E85, Tunturi Fitness, Almere, The Netherlands). Training duration was increased from initial 40 min to 50 min and further to 60 min after every other training session.

4.2.2 EXEBRAIN

EXEBRAIN was conducted as a randomised crossover trial. Schematic illustration of the study design is illustrated in Figure 3. After the clinical screening, laboratory tests and VO_{2peak} tests, all subjects (n=24) underwent PET and MRI studies after rest and a session of MICT, and 12 subjects additionally after a session of HIIT, on separate days. The order of the studies was counterbalanced across subjects.

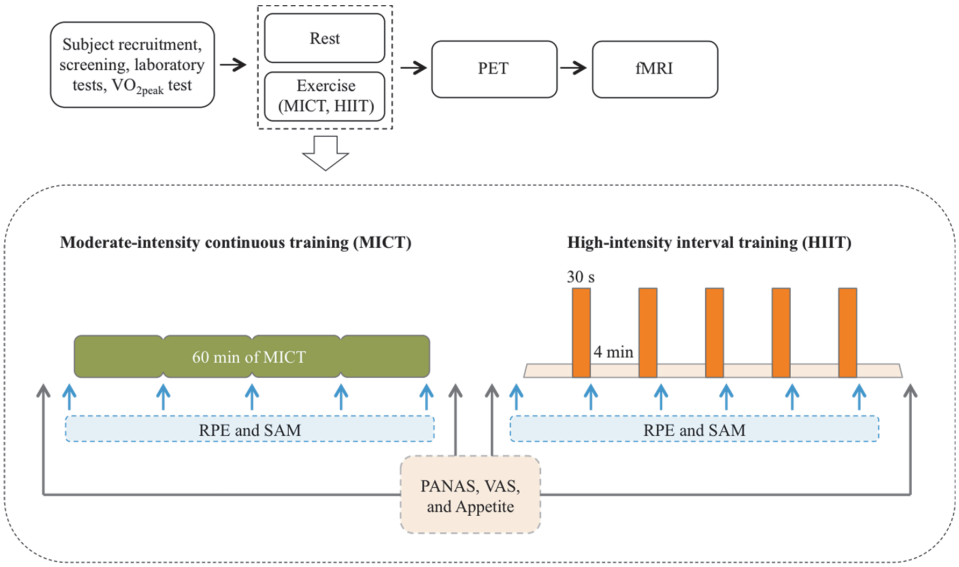


Figure 3. EXEBRAIN study design. VO_{2peak}, peak oxygen uptake; RPE, Rating of Perceived Exertion; SAM, Self-Assessment Manikin; PSQ, Perceived Stress Questionnaire; PANAS, Positive and Negative Affect Schedule, VAS, visual analogue scale.

The MICT session consisted of continuous aerobic cycling for 60 minutes at a workload in the middle between aerobic and anaerobic thresholds (Tunturi E85, Tunturi Fitness, Almere, The Netherlands). The HIIT session consisted of a warm-up and five bouts of all-out cycling efforts for 30 seconds against resistance of 7.5% of body weight with 4 minutes of unloaded recovery between the bouts (Monark Ergomedic 894E, Vansbro, Sweden) performed as described in the previous section (HITPET). Perceptual and affective responses were assessed with questionnaires before, during, and after the training sessions. Blood lactate concentration was determined from capillary blood samples before and after each training session. The PET scan began within 15−36 min after the exercise cessation and the fMRI took place immediately after the PET, 80−110 min after the completion of the exercise. During rest, the subjects sat or lay down

passively for 60 minutes before the PET and MRI studies. Music, television, reading, or mobile entertaining devices were not available to the subjects during exercise sessions or rest.

4.3 Perceptual and affective measurements

During exercise, perceived exertion was assessed using Borg's rating of perceived exertion (RPE) 6−20 scale with anchors ranging from "No exertion at all" (6) to "Maximal exertion (20). Subjective feelings of emotional valence (pleasant versus unpleasant) and arousal (calm versus excited) were assessed using the Self Assessment Manikin (SAM) rating scale (Bradley and Lang, 1994). SAM is a nine-point pictorial assessment tool to measure basic affect. RPE and SAM were administered within 5 seconds after each 30 second bouts during HIIT sessions and in every 10 minutes in HITPET MICT sessions and every 15 minutes in the EXEBRAIN MICT session (Figure 2 and Figure 3).

The subject's level of perceived stress was measured using the Perceived Stress Questionnaire (PSQ) (Levenstein *et al*, 1993). Subjects rated each of the 30 items on a 4-point Likert response scale ranging from "Disagree" (1) to "Agree" (4) in terms of how they felt at that moment. Higher scores indicate higher perceived stress. PSQ was administrated before and after exercise sessions in the HITPET study (Figure 2).

Positive and negative affect was assessed using the Positive and Negative Affect Schedule (PANAS) (Watson *et al*, 1988). PANAS lists 20 affect-related adjectives for positive activated affect and negative activated affect. Subjects were asked to respond to each item by how they were feeling "right now". Positive activated affect reflects affective states that are positive in valence (i.e., pleasant) and high in activation, such as excitement and alertness, whereas negative activated affect reflects affective states that are negative in valence (i.e., bad) and high in activation, such as distress and upset. Higher scores indicate greater positive activated affect and greater negative activated affect. PANAS was administrated before and after each exercise session (Figure 2 and Figure 3) and before rest in EXEBRAIN.

The visual analogue scale (VAS) with contrasting statements anchored at each end (i.e. not at all irritated to extremely irritated) was used for subjective ratings of selected emotions (separate scales for tension, irritation, pain, exhaustion, satisfaction, motivation to exercise, in EXEBRAIN also euphoria and energy were included). Subjects were asked to respond to each scale in terms of how they felt

at that moment. VAS was administrated before and after each exercise session (Figure 2 and Figure 3) and before rest in EXEBRAIN.

Subjective current level of appetite sensations (i.e. hunger, satiation, prospective food consumption) were recorded on VAS (Flint *et al*, 2000) with extreme statements anchored at each end (i.e. "I am not hungry at all" and "I have never been more hungry"). Appetite VAS was utilised in EXEBRAIN and administrated before and after each exercise session (Figure 3) and before rest.

4.4 Measuring μ-opioid receptor availability − Positron emission tomography (PET)

PET is a nuclear imaging technique that enables investigation of various physiologic, metabolic, and functional processes *in vivo*. PET is based on positron-emitting radionuclides, most commonly ^{18}F ($t_{½}$ = 109.8 min), ^{11}C ($t_{½}$ = 20.4 min), or ^{15}O ($t_{½}$ = 2.03 min), which are used to label biological substrates of pharmaceuticals to produce molecules called radioligands. A trace amount of radioligand is administrated into human body, where the unstable radioisotope emits a positron. In tissue, the emitted positron rapidly loses its energy and combines with its antiparticle, an electron, triggering an annihilation, in which the masses of these particles are converted into electromagnetic energy in the form of two 511 keV photons travelling to opposite directions. These high-energy photons escape the body and are detected in coincidence by the scintillation detector ring of the PET scanner surrounding the imaging object. The spatial location of the annihilation can be determined based on the two simultaneous events detected on opposite sides of the detector ring (Figure 4). A typical PET scan consists of a detection of large number of pairs of annihilation photons (10^6−10^9), which are registered and corrected for multiple factors, such as scatter, attenuation and random coincidence. Finally, an image reconstruction algorithm is applied to produce 3D tomographic images representing radioactivity distribution. Thus, PET image indirectly maps the functional process that created the distribution of the radionuclide. (Cherry and Dahlbom, 2004; Townsend, 2004).

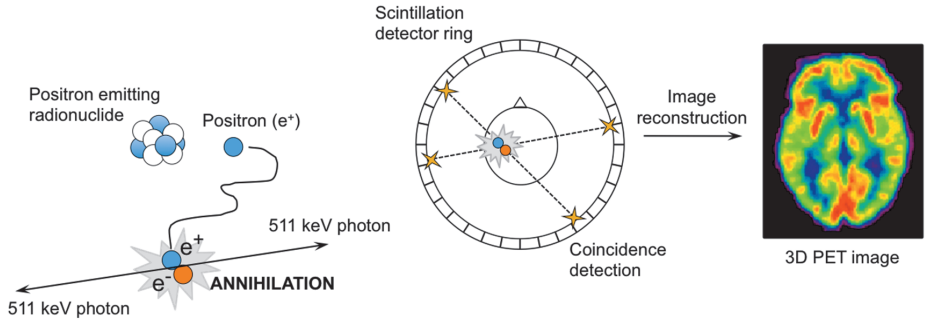


Figure 4. Schematic illustration of the basis of PET imaging.

The function of opioidergic system in the brain can be studied with a number of different radioligands by using PET. Here, we used [^{11}C]carfentanil, which is a high-affinity agonist selective to μ-opioid receptors (Frost *et al*, 1989; Titeler *et al*, 1989) and which has a high test-retest reliability (Hirvonen *et al*, 2009). [^{11}C]carfentanil binding is sensitive to endogenous opioids, as it decreases during stimuli such as pain, that putatively increases the endogenous opioid tone in the brain resulting in activation of the MOR system (Scott *et al*, 2007). Acute increases in [^{11}C]carfentanil binding would then manifest an acute reduction in endogenous opioid tone, and thus, a deactivation of MOR mediated neurotransmission (Nummenmaa *et al*, 2016; Prossin *et al*, 2010; Zubieta *et al*, 2003). Thus, these bidirectional changes in [^{11}C]carfentanil binding between baseline and challenge conditions are thought to reflect the challenge-induced changes in endogenous opioid release and changes in neurotransmission (Colasanti *et al*, 2012; Mick *et al*, 2014; Zubieta *et al*, 2003).

4.4.1 PET image acquisition (Studies III-IV)

Production of [^{11}C]carfentanil is described in detail in the original article III. The injected dose, specific radioactivity, and the injected mass of the radioligand did not differ between the scans. The radioligand was administrated intravenously as a bolus injection via a catheter placed in the left arm at tracer doses with no expected pharmacological side effects. The targeted injection dose was 250 MBq. Radioactivity data acquisition in the brain started concomitantly with the injection of the radiotracer and was measured with the Philips Ingenuity TF PET/MR (Philips Healthcare, Cleveland, OH, USA) scanner. Total scanning time was 51 minutes, during which 13 time frames were collected (3×1 min, 4×3 min, 6×6 min). PET data was corrected for dead-time, decay, and photon attenuation using

MR-based attenuation correction technique that is based on image segmentation, and images were reconstructed using time-of-flight information. A T1-weighted MR images (1 mm^3 voxel size) were acquired for anatomical reference using repetition time (TR) = 25 ms, echo time (TE) = 4.6 ms, flip angle = 30°, scan time 376 s.

4.4.2 PET data analysis (Studies III-IV)

A reconstructed PET image represents regional radioactivity concentration distribution. In order to convert radioactivity concentration into biologically meaningful pharmacokinetic information such as receptor binding in the brain, kinetic compartment models are used (Gunn *et al*, 2001; Heiss and Herholz, 2006). In these models, the compartments represent different pharmacokinetic pools into which the radioligand is distributed after being administrated, such as arterial plasma and the positions of the ligand in free and bound states. The model defines radioligand kinetics into and out of each compartment by rate constants (k). Here, a two-tissue compartment model called simplified reference tissue model (SRTM) (Lammertsma and Hume, 1996) was utilised (Figure 5) to obtain regional binding potential (BP_{ND}), which is the ratio of specific to non-displaceable binding in the brain (Innis *et al*, 2007).

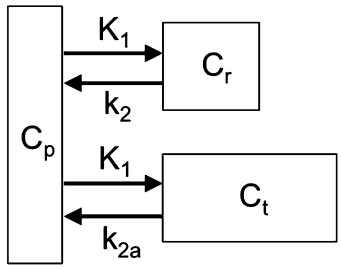


Figure 5. Schematic illustration of the compartments and rate constants of the simplified reference tissue model. C_p, radioligand concentration in the arterial plasma; C_r, radioligand concentration in the reference region, comprised of non-displaceable uptake (free and non-specifically bound ligand in the tissue); C_t, radioligand concentration in the tissue, comprised of specifically bound ligand, non-specifically bound ligand and free ligand in the tissue; K_1, rate constant for transfer from arterial plasma to tissue; k_2, rate constant for transfer from tissue to plasma; k_{2a}, apparent rate constant for transfer from tissue to plasma.

BP_{ND} is the characteristic measurement from reference tissue methods such as STRM, as it compares the radioligand concentration in receptor-rich with receptor-free regions (Innis *et al*, 2007).

$$BP_{ND} = f_{ND} \times \frac{1}{K_d} \times B_{max}$$

In the equation, f_{ND} denotes the free fraction of the ligand in the non-displaceable compartment, $\frac{1}{K_d}$ stands for receptor affinity and B_{max} is the density of available receptors.

SRTM enables quantification of receptor availability without the need for arterial blood sampling, because the time activity curve (TAC) from a specific reference region, which is a region almost completely devoid of receptors of interest, serves as input data. Thus, SRTM is based on the comparison of radioligand concentration between receptor-rich and receptor-free regions. (Gunn *et al*, 1997). However, SRTM relies on several assumptions on the modelled biological system. The reference region is assumed to be virtually devoid of target receptors and thus has only non-specific binding of the ligand. The degree of non-specific binding is assumed to be similar in both reference and target regions. SRTM does not differentiate between free ligand and non-specifically bound ligand, and thus the exchange between these compartments is assumed to be sufficiently fast to be approximated as one compartment. (Gunn *et al*, 1997; Lammertsma and Hume, 1996)

The preprocessing of the reconstructed PET images, which addresses head motion during scanning as well as individual differences in brain anatomy, was carried out using Statistical Parametric Mapping 8 (SPM8) software (www.fil.ion.ucl.ac.uk/spm/), running on Matlab R2012a (The MathWorks Inc., Natick, MA, USA). To correct for head motion during the scanning, all the volumes of the dynamic PET scan were realigned frame-to-frame. Then, the summation image was calculated from realigned frames and co-registered with subject's T1-weighted MR image. The occipital cortex, which was used as a reference region, was manually drawn on the co-registered T1 image using the PMOD 3.3 software (PMOD Technologies, Zürich, Switzerland) to produce TAC for subsequent SRTM. The resulting parametric BP_{ND} images generated using SRTM were normalised to the Montreal Neurological Institute (MNI) space using deformation fields obtained by segmenting the T1-weighted images. Normalised parametric images were smoothed with a Gaussian kernel of 7 mm full-width half-maximum (FWHM).

In the full-volume statistical analyses, voxel-wise differences in [^{11}C]carfentanil BP_{ND}s between rest, MICT, and HIIT conditions were tested with repeated

measures one-way ANOVA and paired samples t test in SPM8. The threshold for statistical significance was set at $p < 0.05$, with a false discovery rate (FDR) corrected at cluster level (Study III). Associations between BP_{ND}s, exercise-induced perceptual and affective changes, as well as biological variables were tested using exploratory whole-brain analysis in SPM8, with a statistical threshold set at $p < 0.05$, FDR corrected at cluster level (Study III).

Additionally, for Study IV, anatomical regions of interest (ROIs) in key components of the reward and emotion circuits (ventral striatum, dorsal caudate nucleus, putamen, amygdala, thalamus, insula, orbitofrontal cortex, and anterior, middle, and posterior cingulate cortex) were generated using the AAL (Tzourio-Mazoyer *et al*, 2002) and Anatomy (Eickhoff *et al*, 2005) toolboxes. Subject-wise BP_{ND} were extracted for each ROI from rest and MICT conditions using Marsbar toolbox for SPM (http://marsbar.sourceforge.net/) (Study IV).

4.5 Measuring anticipatory food reward – functional magnetic resonance imaging (fMRI)

Magnetic resonance imaging (MRI) enables the studying of the anatomical structure and functions of the central nervous system non-invasively without radiation exposure. MRI uses strong (typically ≥ 1.5 T) magnetic fields to create high-contrast images of biological tissue. It utilises the nuclear magnetic resonance properties of hydrogen, which is abundant in human body as part of water and lipids. Hydrogen atom nucleus consists of a single positively charged particle, a proton. The proton rotates, or spins, at high speed on its axis producing an electrical current and thereby generating a tiny magnetic field called magnetic moment. Magnetic moments are normally randomly orientated, but when placed in an external strong magnetic field (B_0) such as MRI scanner, they align either with (parallel) or against (antiparallel) the external field. Slightly more magnetic moments align with B_0 than against it because it requires less energy. This creates a net longitudinal magnetisation in the direction of the field. To generate the MR signal, rotating magnetic field B_1 is applied for a short duration by radiofrequency (RF) pulsations, which tilts the net magnetisation away from B_0. Once the excitation RF pulses stop, the system seeks to return to equilibrium in a process called relaxation. This results in the restoration of the longitudinal magnetisation along with B_0 in a process referred to as longitudinal (T1 or spin-lattice) relaxation, while the transverse magnetisation decreases and disappears in a process known as transverse (T2 or spin-spin) relaxation. These create a signal that can be measured using a receiver coil. T1-weighted images provide excellent discrimination between water and fat, and thus good anatomic detail, and differenti-

ation of for example the grey and white matter in the brain is possible. (Hendee and Morgan, 1984; McRobbie *et al*, 2006; Seeger, 1989).

Brain activation can be studied using functional MRI (fMRI). It measures dynamic changes in blood oxygenation and blood flow related to neuronal activity, either in response to a certain task or when at rest. The most common method for performing fMRI uses the Blood Oxygenation Level Dependent (BOLD) contrast. BOLD utilises differences in the magnetic properties of oxygenated and deoxygenated haemoglobin: deoxyhemoglobin is paramagnetic, and thus differs substantially from water and surrounding tissues in its magnetic properties. This creates small inhomogeneities in the magnetic field that affect the BOLD signal. Increased neural activity stimulates an increase in the local blood flow in order to meet the larger metabolic demand for oxygen and nutrients in stimulated regions of the brain. This results in a net increase in the balance of oxygenated arterial blood to deoxygenated venous blood at the capillary level: since more oxygen is supplied than actually consumed, this leads to a decrease in the concentration of deoxygenated hemoglobin, which leads to an increase in BOLD signal. The spatial resolution of fMRI is on the order of millimetres, while temporal resolution typically varies between 1-3 seconds. (Huettel *et al*, 2014; Kim and Ogawa, 2012).

4.5.1 Experimental design (Studies IV)

The fMRI experiment was performed as previously described (Nummenmaa *et al*, 2012). Experimental design for fMRI is summarised in Figure 6. The fMRI stimuli were full-colour photographs of palatable foods (e.g. strawberries, chocolate cake, sundae), non-palatable foods (e.g., crackers, lentils, aubergine), and non-food objects (cars) matched with respect to low-level visual features such as mean luminosity, root mean square (RMS) contrast, and global energy. Previous evaluations show that palatable foods are rated as more pleasant than non-palatable foods, $t(28) = 10.97$, $p < 0.001$ (Nummenmaa *et al*, 2012). During the fMRI, the participants viewed alternating 15.75-second epochs with six stimuli from one category (palatable foods, non-palatable foods, cars), each shown for 1 s and intermixed with fixation cross visible for a random time (0.75 – 1.75 s; mean = 1.25 s). The order of the stimuli during each epoch was randomised. A car stimulus epoch was always presented between the palatable and non-palatable stimulus epochs to maximise the power of the design and to prevent carryover effects of viewing the food pictures. To ensure that the participants paid attention to the stimuli, the images were placed slightly to the left or to the right of the screen and the participants were instructed to press the left or right

response button according to which side the stimulus was presented. Altogether there were a total of 72 palatable food trials (in 12 epochs), 72 non-palatable food trials (in 12 epochs) and 144 car trials (in 24 epochs). The starting epoch was counterbalanced across the participants. The total task duration was 14 minutes. (Nummenmaa *et al*, 2012).

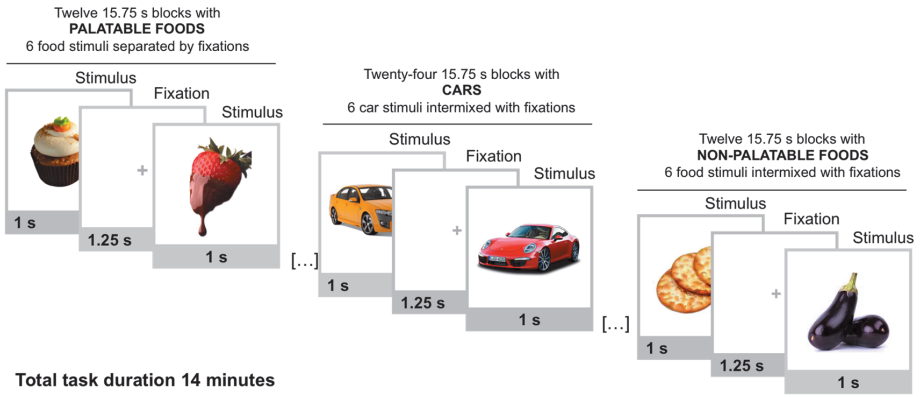


Figure 6. Experimental design for fMRI. Participants viewed alternating 15.75-s blocks with palatable foods, non-palatable foods, or cars. Each block contained 6 stimuli from one category, intermixed with fixation crosses (modified from original publication IV).

4.5.2 MR Image acquisition (Study IV)

MR imaging was performed using the 3T Philips Ingenuity TF PET/MR scanner. Whole-brain functional data in a total of 430 functional volumes were acquired with echo-planar imaging (EPI) sequence, sensitive to the blood-oxygen-level-dependent (BOLD) signal contrast with following parameters: TR = 2000 ms, TE = 20 ms, 90° flip angle, field of view (FOV) 240 × 240 × 140 mm, 80 × 80 acquisition matrix, 53.4 kHz bandwidth, 3 mm × 3 mm in plane matrix and 4.0 mm slice thickness with no gaps between slices, 35 slices acquired in ascending order. T1-weighted MR images with 1 mm^3 resolution were acquired for anatomical reference (TR = 8.1 ms, TE = 3.7 ms, flip angle 7°, scan time 263 s).

4.5.3 fMRI data analysis (Study IV)

Data were preprocessed and analysed using SPM8 as described previously (Nummenmaa *et al*, 2012). The EPI images were sinc interpolated in time to cor-

rect for slice time differences and realigned to the first scan image by rigid body transformations to correct for head movements. EPI and structural images were co-registered and normalised to the T1 standard template in MNI space using linear and non-linear transformations, and smoothed with a Gaussian kernel of 8 mm FWHM.

A whole-brain random effects model was implemented using a two-stage process (first and second level). This random-effects analysis assesses the effects on the basis of inter-subject variance and thus allows inferences at population level. For each participant, a general linear model (GLM) was used to assess regional effects of task parameters on BOLD indices of activation. The model included three experimental conditions (palatable foods, non-palatable foods, and cars) and effects of no interest (six realignment parameters) to account for motion-related variance. Low-frequency signal drift was removed using a high-pass filter (cut-off 128 s), and autoregressive AR(1) modelling of temporal autocorrelations was applied. Subject-wise contrast images were generated using the contrast palatable minus non-palatable foods. Furthermore, to test exercise-dependent changes in anticipatory reward, we modelled the interaction contrasts (palatable versus non-palatable foods) × (rest versus exercise) and (foods versus cars) × (rest versus exercise). The second level analysis used these contrast images in a new GLM to generate statistical t test images. With balanced designs at the first level, this second level analysis closely approximates a true mixed effects design, with both within and between subject variance. The threshold for the data was set at $p < 0.05$, and FDR corrected at the cluster level.

The effects of exercise-induced changes in regional MOR availability on anticipatory reward responses to palatable foods in fMRI were tested. The difference scores (MICT minus rest) of the subject-wise BP_{ND}s in each generated ROIs from rest and MICT conditions were used in a full-volume linear regression analysis to predict the voxel-wise contrast estimates (SPM contrast images) for the interaction contrasts (palatable vs. non-palatable foods) × (rest vs. exercise) and (foods versus cars) × (rest versus exercise). Each ROI was used as a predictor in a separate model because of the high between-regions co-dependency of [^{11}C]carfentanil binding potentials (Tuominen *et al*, 2014, 2015).

5 RESULTS

5.1 Perceptual and affective responses to repeated HIIT and MICT (Studies I-II)

We examined the perceptual and affective responses to repeated HIIT and MICT protocols in physically untrained healthy (Study I) and insulin resistant (Study II) subjects. The healthy group (Study I) consisted of male subjects, while both male and female subject were included in the insulin resistant group (Study II). Within studies, the HIIT and MICT groups did not differ significantly in age, BMI, or VO_{2peak} before the training intervention. Between subject comparison showed that insulin resistant subjects had significantly higher BMI (26.1 in healthy vs. 30.5 in insulin resistant) and lower VO_{2peak} (34.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in healthy vs. 27.2 $ml \cdot kg^{-1} \cdot min^{-1}$ in insulin resistant) than healthy subjects. The physiological training adaptations are summarised in Table 3. In healthy subjects, the training intervention improved VO_{2peak} and $Load_{peak}$ and not differently between the HIIT and MICT groups (both $p < 0.001$ for the training effect) (Study I). In insulin resistant subjects, the response of VO_{2peak} was different between the HIIT and MICT groups ($p = 0.050$ for the group × training interaction), and only HIIT improved the VO_{2peak} ($p = 0.013$ for the training effect for HIIT), while $Load_{peak}$ improved similarly in response to both HIIT and MICT ($p < 0.001$ for the training effect) (Study II). Lactate was higher after HIIT than the MICT sessions in both healthy and insulin resistant subjects ($p < 0.001$ for the training group × time interaction).

Perceptual and affective responses during exercise sessions: Overall, healthy and insulin resistant subjects responded to HIIT and MICT similarly (Figure 7): perceived exertion, displeasure, and arousal were higher during HIIT compared with MICT sessions (all $p < 0.01$ for the training group × bout interaction). However, the comparison between the insulin resistant and healthy subjects revealed that while perceived exertion and arousal were at a similar level over the course of the training intervention, insulin resistant subjects experienced markedly lower subjective pleasantness during HIIT and higher pleasantness during MICT than healthy subjects ($p = 0.018$ for the training group × health status interaction) (Study II). Perceived exertion, displeasure, and arousal experienced during the exercise sessions alleviated over the training period of six days in both healthy and insulin resistant subjects, and the effect was similar for HIIT and MICT (all $p < 0.001$ for the training session).

Table 3. Characteristics of healthy and insulin resistant subjects (Studies I and II) and their training adaptations to HIIT and MICT. (Modified from Original publication II.)

	HIIT		MICT		
	Pre	**Post**	**Pre**	**Post**	
Study I (Healthy subjects)					
n	14	13	14	13	
Age, year	47 (45, 50)		48 (45, 51)		
Height, cm	180 (177,182)		179 (176, 181)		
Weight, kg	83.1 (78.2, 88)	82.6 (77.7, 87.4)	84.1 (79.2, 89.1)	84.1 (79.3, 88.9)	
BMI	25.9 (24.5, 27.2)	25.7 (24.3, 27)	26.4 (25, 27,7)	26.4 (25, 27.7)	
Fat, %	22.2 (19.8,24.6)	21.2 (18.8, 23.6)	22.9 (20.5, 25.3)	22.1 (19.7, 24.5)	***
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$	34.7 (32.4, 37.1)	36.7 (34.1, 39.3)	33.7 (31.4, 35.9)	34.7 (32.2, 37.2)	***
$Load_{peak}$, W	225 (206, 244)	245 (227, 262)	224 (205, 243)	238 (220, 255)	***
Study II (Insulin resistant subjects)					
n	13	11	13	10	
men/women, *n*	9/4	7/4	7/6	6/4	
T2DM/ prediabetes, *n*	11/2	10/1	6/7	4/6	
Age, year	49 (47, 51)		49 (46, 51)		
Height, cm	173 (168, 179)		172 (167, 176)		
Weight, kg	88.9 (80.6, 97.2)	88.4 (80.1, 96.7)	91.5 (84.5, 98.6)	91.1 (84.0, 98.1)	
BMI	30.5 (28.5, 32.5)	30.3 (28.4, 32.3)	31.0 (29.4, 32.7)	30.8 (29.2, 32.5)	
Fat, %	34.8 (31.4, 38.5)	33.8 (30.5, 37.5)	33.8 (30.8, 36.9)	32.9 (30.0, 36.0)	*
VO_{2peak}, $ml \cdot kg^{-1} \cdot min^{-1}$	25.7 (23.2, 28.2)	27.0 (24.6, 29.5)‡	27.0 (24.9, 29.2)	26.9 (24.6, 29.1)§	†
$Load_{peak}$, W	173 (153, 193)	187 (167, 207)	190 (173, 208)	201 (183, 219)	***

Age and height values are means (95% confidence interval, CI), all other values are model-based means (95% CI). BMI, body mass index; VO_{2peak}, peak oxygen uptake; $Load_{peak}$, peak workload.
* $p \leq 0.05$ for the training effect
*** $p \leq 0.001$ for the training effect
† $p \leq 0.05$ for the group × training interaction
‡ HIIT time effect, $p = 0.013$
§ MICT time effect, $p = 0.75$

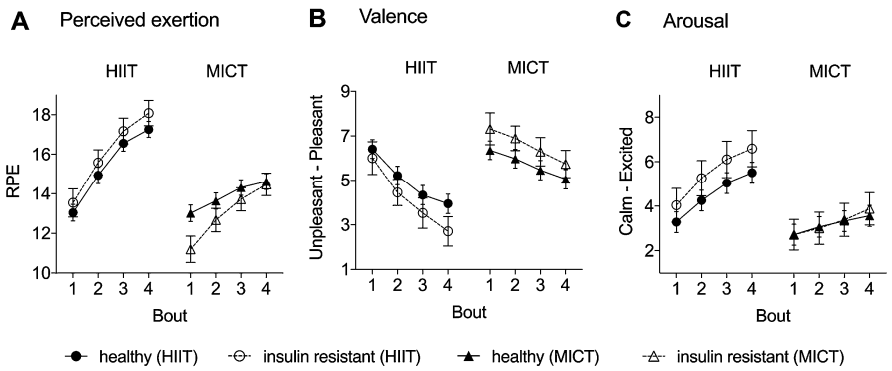


Figure 7. Perceived exertion (A) and arousal (C) increased more, and affective valence decreased more (B) during HIIT compared with MICT sessions in both healthy and insulin resistant subjects. Bout: 1−4 30 s maximal sprints in the HIIT group, and 10 min, 20 min, 30 min, 40 min time intervals in the MICT group.

Affective responses before and acutely after exercise: In general, healthy and insulin resistant subjects showed similar acute affective responses to HIIT and MICT, and especially in the beginning of the intervention the overall affective state was more negative after HIIT compared with MICT. In healthy subjects (Study I), perceived stress, tension, and irritation were higher, and PANAS positive score was lower acutely after HIIT over the training period, while no significant changes in these were recorded after MICT (all $p < 0.05$ for the training group × time interaction). Participants in the HIIT group reported higher PANAS negative scores, more pain and less satisfaction than participants in the MICT group (all $p < 0.05$ for training group). Both PANAS positive and negative scores declined during the training intervention in healthy subjects (all $p < 0.001$ for session). In insulin resistant subjects (Study II), perceived stress remained unaffected over the training period in the MICT group, but increased significantly after the first two sessions of HIIT, after which stress declined to the level comparable with MICT ($p = 0.035$ for the training group × session × time interaction). The PANAS positive score significantly decreased after the first two sessions of HIIT, and then increased over the training period, whereas after MICT, the PANAS positive score declined towards the end of the intervention ($p = 0.014$ for the training group × session × time interaction) in insulin resistant subjects. Furthermore, satisfaction was higher after, as compared with before, MICT sessions over the course of the intervention and both pre and post HIIT satisfaction increased throughout the training period in insulin resistant subjects ($p = 0.031$ for the training group × session × time interaction). Pain increased in both groups after the training sessions but more in the HIIT group, yet alleviated in the HIIT group during the training period ($p = 0.033$ for the training group × session × time interaction). Motivation to exercise increased more after MICT than after

HIIT ($p = 0.006$ for the training group × time interaction) and pre-training ratings of motivation to exercise declined during the training period until the last training session, whereas post-training ratings increased during the intervention similarly between the groups ($p = 0.047$ for the session × time interaction). In insulin resistant subjects, neither HIIT nor MICT significantly affected the feeling of irritation, and in both training groups the PANAS negative score and feeling of tension varied between the training sessions ($p = 0.006$ and 0.008, for session, respectively). Acute affective responses were not associated with changes in lactate, VO_{2peak} or $Load_{peak}$ in either healthy or insulin resistant subjects.

Comparison of affective responses between healthy and insulin resistant subjects (Study II) showed that PANAS positive scores after HIIT significantly increased throughout the training intervention in insulin resistant subjects, while they remained unaltered in healthy subjects, whereas after MICT, PANAS positive scores decreased in both healthy and insulin resistant subjects during the intervention ($p = 0.002$ for the session × training group × health status interaction). Pain ratings after HIIT remained unaffected in healthy subjects but decreased significantly in insulin resistant subjects during the intervention, while after MICT, pain ratings did not change over the training period in either healthy or insulin resistant subjects ($p = 0.005$ for the session × training group × health status interaction) (Figure 8).

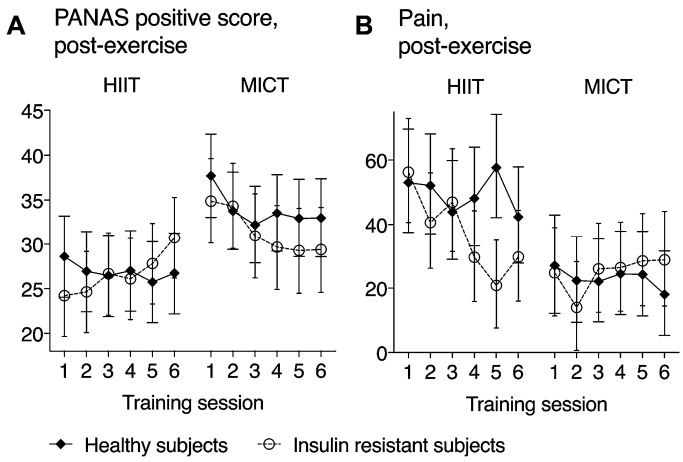


Figure 8. PANAS positive (A) and pain scores (B) after HIIT and MICT in healthy and insulin resistant subjects. The values are least squares means and the error bars represent 95% confidence intervals (modified from Original publication II).

5.2 HIIT releases endogenous opioids in human brain (Study III)

In this study, MOR binding and affective responses after a single session of HIIT and MICT were examined in healthy subjects in a crossover fashion. After HIIT, [^{11}C]carfentanil BP_{ND} values were significantly lower than after rest or MICT in widespread regions of the brain, according to full-brain voxel-based analysis using repeated measures one-way ANOVA for the subset of participants who completed all three studies (n=11) ($p < 0.05$, FDR corrected). These areas included cortical regions, such as prefrontal cortex, anterior cingulate cortex, and insula, and subcortical brain regions such as hippocampus, thalamus, amygdala, ventral striatum, periaqueductal grey matter in the brainstem, and cerebellum (Figure 9). The average change of [^{11}C]carfentanil BP_{ND} was -19 ± 14 % (range -50 % to 0 %). HIIT did not induce increases of [^{11}C]carfentanil binding. In contrast, [^{11}C]carfentanil BP_{ND} values were not significantly changed after MICT compared to rest, either for the whole group (n=21) using paired t test or in the repeated measures one way ANOVA for the subset of participants who performed all three scans (n=11). Although no significant differences in BP_{ND} values between MICT and rest conditions were observed at group level, this response showed a notable variation between participants: MOR binding decreased in some individuals and increased in others in response to MICT.

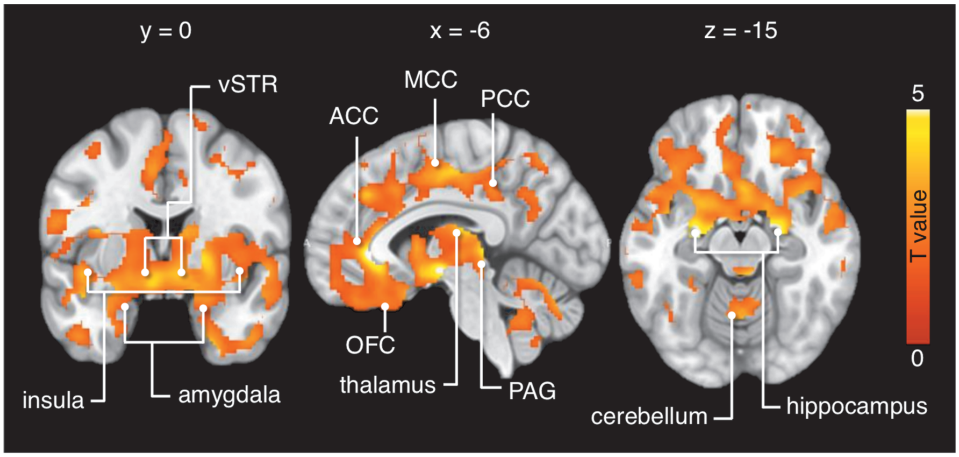


Figure 9. Brain regions showing significantly decreased MOR binding after HIIT in comparison with rest ($p < 0.05$, FDR corrected). vSTR, ventral striatum; ACC, anterior cingulate cortex; MCC, middle cingulate cortex; PCC, posterior cingulate cortex; OFC, orbitofrontal cortex; PAG, periaqueductal grey matter.

Acute affective responses to HIIT and MICT: In the subset of participants who completed both exercise modes (n=12), HIIT increased perceived exertion and arousal more and decreased affective valence more than MICT during exercise ($F_{1,11} = 31.71$, $p < 0.001$; $F_{1,11} = 6.44$, $p = 0.028$; and $F_{1,11} = 13.44$, $p = 0.004$, respectively). PANAS positive score was higher after MICT that after HIIT ($F_{1,11} = 10.01$, $p = 0.009$), and PANAS negative score was higher after HIIT than MICT ($F_{1,11} = 29.37$, $p < 0.001$). Satisfaction ratings increased after MICT and decreased after HIIT ($F_{1,11} = 7.60$, $p = 0.019$) and euphoria ratings were higher in MICT than in HIIT condition ($F_{1,11} = 4.74$, $p = 0.052$), and higher after exercise ($F_{1,11} = 6.00$, $p = 0.032$). Exhaustion ratings were higher after HIIT than after MICT ($F_{1,11} = 6.92$, $p = 0.023$) and the feeling of energy was higher after MICT than after HIIT ($F_{1,11} = 14.98$, $p = 0.003$). Irritation ratings were higher after HIIT than after MICT ($F_{1,11} = 10.91$, $p = 0.007$), and tension ratings were higher under HIIT than MICT conditions, but the pre- and post-exercise ratings did not differ significantly from each other ($F_{1,11} = 13.49$, $p = 0.004$). Pain ratings were higher after exercise, but not differently so between MICT and HIIT ($F_{1,11} = 9.62$, $p = 0.01$). Motivation to exercise was lower under HIIT than MICT conditions and there were no differences in ratings between before and after exercise ($F_{1,11} = 10.14$, $p = 0.009$). Lactate was higher after HIIT than after MICT ($F_{1,11} = 923.62$, $p < 0.001$). MICT-induced affective responses in the participants who performed only MICT (n=10) did not differ from those of the participants who performed both MICT and HIIT (all $p > 0.05$).

Associations between exercise-induced affective responses and changes in MOR binding: Exploratory whole-brain analysis revealed that after MICT, increased euphoria ratings correlated with decreased BP_{ND} in the dorsal prefrontal cortex (r = 0.81) and precuneus (r = 0.80) (Figure 10A). Lower ratings of affective valence during MICT correlated positively with decreased BP_{ND} in the orbitofrontal regions of the brain (r = 0.76). Higher ratings of perceived exertion during MICT predicted decreased BP_{ND} in the frontal (r = 0.77) and parietal regions (r = 0.71) of the brain. After HIIT, increased negative affect (Figure 10B) and tension correlated with decreased BP_{ND} in the frontal cortex (r = 0.75 and r = 0.90, respectively). Lower ratings of affective valence during HIIT and decreased satisfaction after HIIT predicted decreased BP_{ND} in the dorsal prefrontal cortex (r = 0.71) and thalamus (r = 0.76), respectively. Inverse correlations were not recorded.

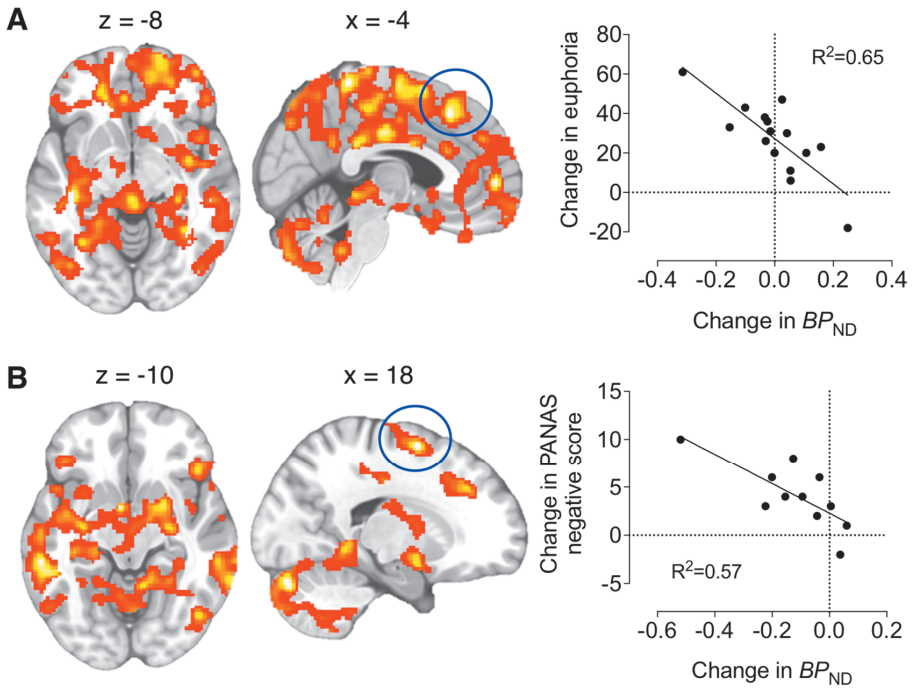


Figure 10. Whole brain exploratory analysis revealed that decreased [^{11}C]carfentanil BP_{ND} predicts increased euphoria after MICT (A) and increased negative affect after HIIT (B). Circles denote the clusters where BP_{ND} changes are shown against euphoria (A) and negative affect (B) in the scatterplots, however the inference is based on the full-volume SPM analysis and the scatterplots are shown for visual purposes only. (Modified from original publication III).

5.3 Associations between anticipatory food reward responses and exercise-induced changes in MOR binding (Study IV)

In this study, we tested whether MICT-induced changes in MOR binding correlate with changes in anticipatory reward processing using [^{11}C]carfentanil PET and fMRI methods. Physical exercise *per se* did not significantly influence brain responses to anticipatory food reward, compared with rest. In general, higher neuronal responses to foods versus cars was observed in the network of brain regions, including the supplementary motor area, sensory motor and premotor cortices, and parietal cortices. Furthermore, contrasting palatable versus non-palatable foods resulted in robust activation of the reward and emotion circuit, where activation foci were observed in the medial prefrontal cortex, bilateral caudate, bilateral hippocampus, posterior cingulate, bilateral fusiform, and precuneus. As reported in a previous section (Study III), a group level whole brain analysis revealed no significant differences in [^{11}C]carfentanil BP_{ND} values between MICT and rest.

To investigate whether MICT-induced regional changes in MOR binding would be associated with changes in anticipatory reward responses measured with fMRI, the BOLD responses to palatable versus non-palatable foods and foods versus cars in MICT versus rest condition were predicted with regional BP_{ND} difference in each ROI using a full-volume linear regression analysis. MICT-induced change in MOR binding in eight out of ten ROIs correlated negatively with the difference between MICT and rest conditions in BOLD responses to palatable versus non-palatable foods. These findings indicate that increased exercise-induced opioid release predicts higher brain responses to palatable versus non-palatable foods. This effect was observed in widespread brain regions including both cortical regions (i.e. prefrontal cortex, anterior cingulate cortex, and insula), as well as subcortical regions (i.e. hippocampus, thalamus, amygdala, ventral striatum, periaqueductal grey matter in the brainstem, and cerebellum) (Figure 11 and Figure 12). Opposite correlations were not recorded.

Similarly, the MICT-induced change in MOR binding in four out of ten ROIs associated negatively with the difference in BOLD responses to foods versus cars between MICT and rest conditions showing that increased opioid release after MICT predict higher responses to food versus non-food objects. This effect was found in frontal, temporal, parietal and occipital cortices, anterior and middle cingulate, supplementary motor areas, and left thalamus and caudate (Figure 11).

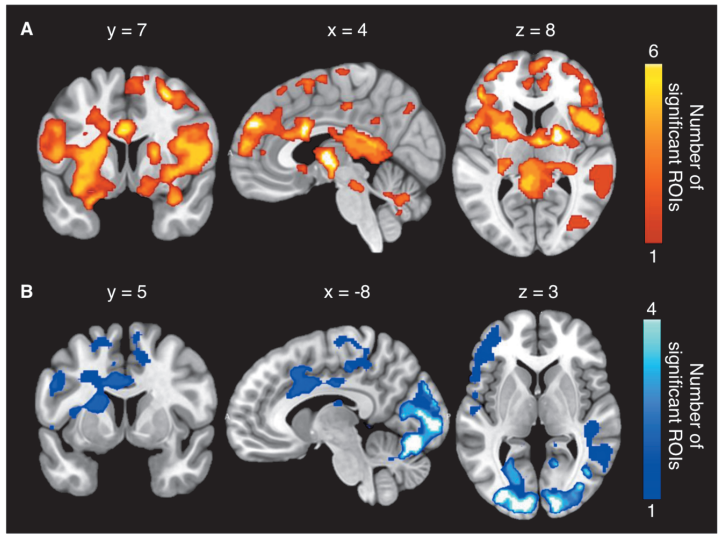


Figure 11. Cumulative maps showing the number of ROIs (out of 10) whose [^{11}C]carfentanil BP_{ND} correlated with BOLD responses to (A) palatable versus non-palatable foods between MICT and rest conditions and to (B) foods versus cars between MICT and rest conditions, $p < 0.05$, FDR corrected (modified from original publication IV).

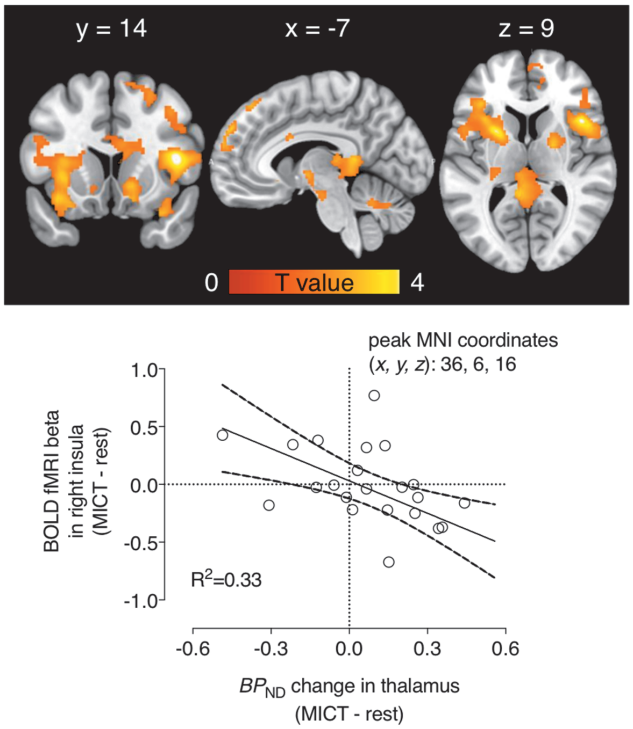


Figure 12. Brain regions where MICT-induced change in thalamic MOR binding of [^{11}C]carfentanil is associated with the difference in BOLD-fMRI responses to palatable versus non-palatable foods between MICT and rest conditions. The scatterplots show least-square regression lines with 95% confidence intervals and are shown for visual purposes only, statistical inference is based on the full-volume SPM analysis (modified from original publication IV).

Associations between perceptual responses and functional responses: MICT acutely increased the ratings of hunger, prospective food consumption, desire to eat, and reduced satiety (all $p < 0.05$). Whole brain exploratory analysis revealed that decreased MOR binding after MICT predicted decreased fullness (Figure 13A) and satiety and increased hunger and prospective food consumption (Figure 13B) after MICT. Moreover, reduced fullness (Figure 13C) and increased prospective food consumption (Figure 13D) as well as increased positive affect after MICT and higher perceived exertion during MICT predicted higher responses to palatable versus non-palatable foods after MICT compared with rest.

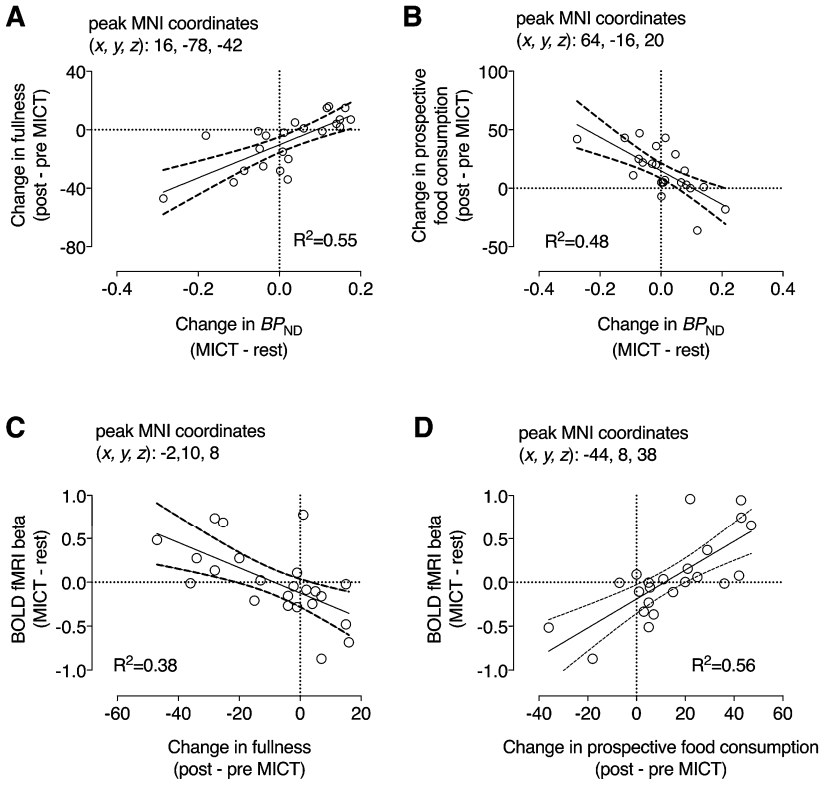


Figure 13. MICT-induced change in MOR binding correlated positively with decreased fullness (A) and negatively with prospective food consumption (B). Negative change in BP_{ND} is consistent with increased endogenous opioid release. Furthermore, reduction in fullness (C) and increase in prospective food consumption (D) after MICT predicted higher BOLD fMRI responses to palatable vs. non-palatable foods after MICT compared with rest. The scatterplots show least-square regression lines with 95% confidence intervals and are shown for visual purposes only, statistical inference is based on the full-volume SPM analysis (all $p < 0.05$, FDR corrected) (modified from original publication IV).

6 DISCUSSION

The main findings of this thesis were:

1) HIIT, based on repeated Wingate tests, generates overall a more negative affective experience in comparison with MICT. We showed that during exercise, HIIT increases perceived exertion, displeasure, and arousal significantly more than MICT. Negative affect and tension are higher acutely after HIIT than MICT, whereas satisfaction and positive affect are higher acutely after MICT than HIIT. These acute responses were similar in healthy, habitually active young adults as well as in untrained healthy and insulin resistant overweight adults. In insufficiently active subjects, the HIIT-induced negative affective experience already starts to improve within a few exercise sessions.
2) Endogenous opioid release in response to physical exercise depends on the intensity of exercise and on the concomitant affective changes. We showed that HIIT induces opioid release in human brain, as evidenced by decreased MOR binding of [^{11}C]carfentanil measured with PET, in key brain regions related to reward and pain processing. Reduced MOR binding correlated with measures of negative emotionality. In contrast, MICT did not result in a significant overall change in MOR binding, although this response exhibited notable variation between individuals: the magnitude of MOR activation correlated with increased positive affect and euphoria after MICT.
3) Exercise-induced changes in endogenous opioid action are associated with anticipatory food reward processing. We showed that the MICT-induced changes in MOR binding correlate negatively with the exercise-induced changes in neural anticipatory food reward responses in fMRI. This effect was observed in widespread brain regions involved in homeostasis and reward processing, and it suggests that higher opioid release predicts higher brain responses to palatable versus non-palatable foods.

6.1 HIIT induces more negative affective response in comparison with MICT

Throughout the studies I–III, we observed that the levels of perceived exertion and arousal increased and the affective valence decreased during both exercise modes, but significantly more steeply during HIIT compared with MICT sessions in untrained healthy and insulin resistant adults, as well as in healthy habitually

active young men. In addition, immediately after exercise, the affective state in general was more negative after HIIT than MICT across the studies: HIIT evoked higher ratings of perceived stress, negative affect, irritation, tension, and exhaustion, whereas MICT resulted in higher ratings of positive affect, satisfaction, and energy. These findings are in line with several recent studies, which have demonstrated more negative affective responses during and immediately after HIIT in comparison with MICT in recreationally active and inactive adults as well as in overweight to obese individuals (Decker and Ekkekakis, 2017; Green *et al*, 2017; Jung *et al*, 2014; Thum *et al*, 2017). Nevertheless, some studies have reported similar affective responses to continuous and interval protocols in habitually active young men as well as in overweight to obese inactive adults (Kilpatrick *et al*, 2015a; Little *et al*, 2014). Although the interval training protocol that elicits the most positive affective responses remains unknown, the perceptual responses and enjoyment have been found more positive during shorter than longer intervals (Kilpatrick *et al*, 2015b; Martinez *et al*, 2015; Townsend *et al*, 2017). Thus, sprint bouts even shorter than 30 seconds might be favoured over a few minute intervals (Vollaard and Metcalfe, 2017).

The acute negative affective responses elicited by HIIT are considered to negatively impact the general perceptions toward exercise, and consequently to discourage exercise motivation and reduce the likelihood of future exercise participation (Biddle and Batterham, 2015; Hardcastle *et al*, 2014). Thus, the present findings together with findings of others would advocate MICT over HIIT. However, we demonstrated that perceived exertion, displeasure, and arousal already attenuated within six exercise sessions, regardless of the training mode, in both healthy and insulin resistant individuals (Studies I and II). Rapid attenuation of perceived exertion and leg pain in response to six days of HIIT have also been previously reported in young active individuals (Astorino *et al*, 2012). Weakening of these perceptual responses over repeated exercise are likely due to rapid adaptations in physiological systems such as metabolic (Eskelinen *et al*, 2015), neuromuscular (Kinnunen *et al*, 2017), cardiovascular (Kiviniemi *et al*, 2014), and respiratory systems (Bailey *et al*, 2009), as well as improvements in pain tolerance (Drury *et al*, 2005; Koltyn, 2002) and in psychological and cognitive elements (Stork *et al*, 2017). Nevertheless, the positive progression of affective responses over six training sessions is encouraging as regards the adoption of new exercise routines and suggests that even very intense HIIT may be a feasible exercise strategy for untrained individuals.

Interestingly, the adaptation to repeated HIIT appeared somewhat more positive in insulin resistant than healthy inactive subjects. While healthy subjects reported higher perceived stress and a lower positive affect acutely after HIIT versus MICT throughout the intervention, in insulin resistant subjects the disparities in

these measures between training groups abolished in fact after three exercise sessions and the positive affect and perceived stress after HIIT improved to a level comparable to MICT. Moreover, the notable drop in post-HIIT ratings of pain, as well as the pronounced enhancement of positive affect over six exercise sessions in addition to growing exercise motivation after HIIT may indicate that exercise enjoyment, although not directly measured, improved in response to repeated HIIT in insulin resistant subjects. This would be in line with recent work demonstrating that enjoyment of HIIT increases with repeated training over the first three to six weeks of training (Heisz *et al*, 2016; Smith-Ryan, 2017), whereas enjoyment of MICT remains constant and lower than HIIT (Heisz *et al*, 2016). We did not observe associations between affective responses and improvements in physiological parameters (e.g., VO_{2peak}, $Load_{peak}$), however, others have reported that increases in workload over the training period predicted increases in exercise enjoyment. This suggests that physiological adaptions in strength and perceived competence may be important for facilitating exercise enjoyment (Heisz *et al*, 2016). It must be noted that insulin resistant subjects included women, whereas the healthy group consisted of men only. This may have influenced the positive perceptual and affective adaptation observed among the insulin resistant group, given that women tend to experience greater exercise enjoyment (Green *et al*, 2017) and exercise-induced mood improvements (McDowell *et al*, 2016) as well as less intense muscle pain during exercise (Cook *et al*, 1998) in comparison with men. Nevertheless, the observed positive affective adaptation during and after HIIT likely promotes exercise adherence, as was recently shown in overweight to obese adults and people with prediabetes, who were able to sustain a regular HIIT programme independently for four to five weeks following a brief supervised laboratory intervention (Jung *et al*, 2015; Vella *et al*, 2017). Accordingly, HIIT appears to be adopted at least equally well, if not even better, by untrained insulin resistant individuals in comparison with healthy individuals.

The present results indicate that positive affective as well as physiological adaptations take place soon after initiating a new exercise regimen. Regarding health gains, HIIT is not imperative and thus, individuals can freely choose the exercise alternative that is the most convenient for them. However, the present findings of rapidly alleviating displeasure experienced during HIIT may encourage previously inactive adults to also try high-intensity exercise protocols. Moreover, as individual preferences and specific needs have to be taken into account in clinical practice when prescribing and advising on physical exercise, the apparent suitability of HIIT for insulin resistant adults may help to broaden the exercise strategies utilised in the health care of people with and at risk of T2DM. This could improve the physical activity participation in this population group.

6.2 Exercise intensity modulates endogenous opioid release in human brain

The novel finding of Study III was that the exercise intensity modulates MOR activation and the concomitant changes in affective states. High-intensity exercise, HIIT, elicits endogenous opioid release, as evidenced by significantly decreased MOR availability in the key brain regions of pain, reward, and emotion processing, such as the thalamus, ventral striatum, amygdala, anterior cingulate, orbitofrontal and insular cortices. Moreover, HIIT resulted in increased negative affect, irritation, and exhaustion and loss of energy. In contrast, moderate-intensity continuous exercise, a training protocol that reflects public health guidelines (MICT), did not result in any net change in MOR binding, although it did improve positive affect, satisfaction, and euphoria, and changes in these variables were associated with the change in MOR binding.

Decreased MOR binding detected after HIIT versus rest is indicative of increased endogenous opioid release (Henriksen and Willoch, 2008; Quelch *et al*, 2014). This finding is in accordance with the other PET studies that have been conducted in the field of exercise research, which also reported opioid release in response to strenuous exercise (Boecker *et al*, 2008; Hiura *et al*, 2017). The earliest PET study examining the opioidergic effects of physical exercise demonstrated a decade ago an increased opioid release after 2 hours of running in male endurance athletes with the non-selective opioid receptor radioligand [^{18}F]FDPN (Boecker *et al*, 2008). More recently, 20 minutes of continuous vigorous-intensity and severe-intensity cycling were shown to induce opioid release in recreationally active young men using [^{11}C]carfentanil (Hiura *et al*, 2017). In contrast to previous findings, one hour of indoor cycling did not result in activation of the MOR function, yet it increased self-ratings of positive affect, satisfaction and energy. Such milder affective improvements are typically reported to occur in response to low to moderate-intensity exercise and physical activity in general (Hall *et al*, 2002; Kilpatrick *et al*, 2007). Despite no net change in MOR availability after MICT, we detected a notable variation in MOR responses between individuals, and found that decreased binding predicted higher increases in ratings of euphoria following MICT. This suggests some level of emotional modulation by MOR action, although the affective responses after moderate-intensity exercise is likely modulated also by other neural factors and neurotransmitter systems, such as the endocannabinoid system (Dietrich and McDaniel, 2004). Interestingly, Raichlen and colleagues (2013) found that only moderate exercise intensities at 70−85 % of maximal HR increased the circulating levels of endocannabinoid anandamide, but neither low nor near-maximal exercise intensities affected anandamide concentrations. This suggests a role for the endocanna-

binoids in mediating the positive psychological responses elicited by moderate exercise. (Raichlen *et al*, 2013).

Opioid release after HIIT, but not MICT, indicates that the endogenous opioid action at the MOR sites in response to physical exercise may be relevant for more strenuous exercise regimens. This is supported by the previous reports of opioid release following demanding and exhaustive exercise protocols (Boecker *et al*, 2008; Hiura *et al*, 2017). In addition, peripheral levels of β-endorphin have been found to rise in response to high-intensity or prolonged exercise, but not in response to low or moderate-intensity exercise (Schwarz and Kindermann, 1992). Furthermore, endogenous opioids have been suggested to modulate perceptions of fatigue (Harber and Sutton, 1985), and blocking MOR with naloxone has been found to impair maximal cycle ergometry performance in healthy subjects mainly through increased perceived exertion rather than by physiological limits (Sgherza *et al*, 2002). Overall, these data imply that endogenous opioid activation after strenuous exercise is related to mechanisms of antinociception and stress relief. An acute bout of HIIT induces greater physiological (Wahl *et al*, 2013) and emotional stress and pain than MICT as shown in Studies I and II. Thus, it may well result in endogenous opioid release and MOR activation, which not only promotes analgesia, but also regulates the stress response by modulating behaviour and responses of the endocrine and autonomic nervous system. The lesser physiological and emotional demands of 1 hour of aerobic exercise may not generate such profound or persistent stimulation of the MOR system. Interestingly, MICT-induced MOR activation was associated with higher ratings of perceived exertion and lower affective valence during exercise, suggesting that higher perception of strenuousness during exercise resulted in increased MOR activation also after MICT. This finding further supports the hypothesis that activation of the MOR system has a suppressive effect on emotional and physical challenges that threaten organism homeostasis. However, more research is warranted on the underlying causes of divergent MOR responses to moderate-intensity exercise.

After HIIT, decreased MOR binding predicted higher negative affect and tension, and decreased satisfaction. Despite no net change in MOR binding after MICT, a notable variation in MOR responses was detected between individuals, and after MICT, decreased MOR binding predicted greater increases in ratings of euphoria. The exercise-induced changes in MOR binding were recorded specifically in the brain regions related to processing pain and analgesia: the thalamus, insula, anterior cingulate cortex, prefrontal cortex, basal ganglia, and periaqueductal grey matter (Duerden and Albanese, 2013; Zubieta, 2001). These regions are also primary for reward and emotions (Haber and Knutson, 2010) and manage both positive and negative affect (Saarimäki *et al*, 2016). Our findings of diverse as-

sociations between exercise-induced perceptual and affective changes and changes in MOR binding in these regions are consistent with a role of the endogenous opioid system for pain and pleasure (Leknes and Tracey, 2008). Interestingly, although HIIT-induced pain may have contributed to MOR function, we did not find a correlation between MOR activation and pain ratings after exercise. Others have reported similar observations, as no effect of either exogenous opioid agonist (codeine) or antagonist (naltrexone) treatment has been found on exercise-induced muscle pain (Cook *et al*, 2000; Ray and Carter, 2007). MOR activation in the anterior cingulate cortex and thalamus, however, is associated with attenuation of the affective component of pain (Zubieta, 2001), and hence, this could contribute also to tolerance for strenuous and painful high-intensity exercise such as HIIT. Nonetheless, ultimately, the specific contributions from pain, analgesia, and negative emotionality to the outcomes in this study setting cannot be separated, as all of these functions involve MOR activation in these brain regions.

Regarding appetite, decreased MOR availability after HIIT predicted reduced craving to eat following exercise, whereas after MICT, decreased MOR availability predicted increased hunger and prospective food consumption and decreased fullness and satiety following exercise. These observations accord with abundant data elucidating the close involvement of the opioid system in both homeostatic and hedonic aspects of feeding (Nogueiras *et al*, 2012).

6.3 Anticipatory food reward responses are associated with changes in MOR binding after MICT

In Study IV, we found a novel role for the brain MOR system in modulating anticipatory food reward following aerobic exercise. Changes in MOR binding after MICT, indicating changes in endogenous opioid release, were associated with changes in neural responses to foods images after exercise. Subjects who showed larger opioid release following MICT showed the largest increase in the anticipatory food reward responses following exercise. This effect was found in multiple brain regions implicated in food anticipation and reward processing, including the ventral striatum, thalamus and hypothalamus, and amygdala, as well as the medial prefrontal cortex, anterior cingulate, and insula. These findings suggest that individual variation in acute hedonic and motivational processing of food after exercise may be modulated by exercise-induced changes in the opioid system in the brain.

Hedonic aspects of food motivate feeding and may lead to overeating and weight gain. Both acute and chronic physical exercise has been shown to alter hedonic and motivational responses to food. On a neurochemical level, MOR action is

tightly involved in hedonic and motivational processing of food (Mendez *et al*, 2015; Peciña and Smith, 2010), and recently, we demonstrated in healthy subjects that lower baseline MOR binding predicts higher anticipatory food responses (Nummenmaa *et al*, 2018a), which suggests a direct link between brain opioid function and food reward processing. Although we did not find changes in anticipatory food reward following exercise in the main analyses, the change in MOR binding after MICT was associated with altered processing of anticipatory food reward between rest and MICT conditions. Thus, subjects who showed the largest increases in endogenous opioid release also had the highest anticipatory fMRI food reward responses to palatable versus non-palatable foods following the exercise session. These data are consistent with previous work showing that MOR stimulation increases food consumption and preference for palatable foods both in animals and humans, whereas conversely blocking opioid receptors with opioid antagonist prevents motivation towards food consumption (Cambridge *et al*, 2013; Giuliano *et al*, 2012; Mysels and Sullivan, 2010). Our findings also go beyond the previous data and suggest a role for physical exercise.

In contrast to our initial observation that anticipatory food reward responses on fMRI were unaffected by MICT, others have demonstrated changes in neuronal responsiveness to visual food cues following exercise. Aerobic exercise has been found to decrease neuronal activation to high-caloric foods vs. non-foods in bilateral insula and increase activation in the left precuneus (Evero *et al*, 2012), whereas high-intensity exercise has shown to induce decreased neuronal responsiveness to images of high caloric foods vs. non-foods in the orbitofrontal cortex and left hippocampus, as well as increased responsiveness in dorsolateral prefrontal cortex (Crabtree et al., 2014) immediately (within ten minutes) after exercise cessation. Extended periods between exercise and fMRI may compromise the detection of such changes, as no effect of exercise on haemodynamic responses to images of food was found, when the fMRI took place after 30 min of the completion of exercise (Cornier *et al*, 2012). Similarly, due to the 51 min PET scan prior to fMRI measurement, we may have lost some of the effects of MICT on brain responses. Nonetheless, the variation in palatable food reward responses between MICT and rest conditions was explained by exercise-induced change in MOR binding. Interestingly, neuronal activation to visual food cues in obese individuals was found to decrease in response to a six-month exercise intervention (5 days per week), however, an acute bout of aerobic exercise blunted these effects (Cornier *et al*, 2012); this could be explained by exercise-induced MOR action, according to the present findings.

The effects of exercise on weight-loss outcomes are typically modest and individually widely variable. This heterogeneity in weight loss suggests that some individuals may adopt compensatory behaviours, such as increasing energy in-

take in response to exercise. Compensatory eating following exercise could undermine the beneficial effect of exercise on energy balance, and consequently weaken the weight loss outcomes. (Melanson *et al*, 2013). The altered food reward processing after exercise, which also shows considerable inter-individual variability, may modulate compensatory energy intake propensity. Previous research has found that a single session of exercise increased palatability and craving for food as well as preference for high-caloric appetising foods in individuals who were more prone to increase their post-exercise energy intake in comparison with individuals whose energy intake did not change or even decreased (Finlayson *et al*, 2009). Moreover, increased food palatability together with increased acute preference for high-fat, sugary foods after exercise predicted smaller weight loss outcomes after a 12-week exercise intervention in obese individuals (Finlayson *et al*, 2011). Our findings of enhanced reward processing given sufficient opioidergic activation suggest one possible modulatory mechanism for food reward processing following exercise that may contribute to compensatory eating behaviours. Nevertheless, more research is needed to determine the modulatory role of MOR at higher exercise intensities and the effect of exercise on other physiological correlates that may influence food reward, such as leptin (Hopkins *et al*, 2014).

6.4 Limitations of the studies

Across all studies, we recorded perceptual and affective responses during exercise sessions and immediately after exercise (within 5 min), however data was not acquired while the subjects were recovering from exercise, or during the PET scans. Affect fluctuates continuously and dynamically, and although high-intensity exercise increases negative affect during and immediately after exercise, a rebound towards positive affect tends to arise during a recovery of 10–20 min (Hall *et al*, 2002). Furthermore, given the fluctuating nature of affect, all the changes observed in these measures may not be induced solely by exercise, which might have been controlled for by using a non-exercise control group. The exercise intervention of six training sessions in Studies I and II was short and may not reflect the long-term affective responses to HIIT. Generalisability is further limited by the tightly controlled training settings, as exercise modality was limited to the cycle ergometer and all the training sessions were carried out individually in a laboratory environment under supervision and encouragement. Whether HIIT can be initiated, adopted, and sustained independently in real life settings by inactive, healthy and overweight to obese people with T2DM or prediabetes requires further investigation.

The PET studies (Studies III and IV) include certain limitations. First, we used BP_{ND} as a measure of the MOR binding. This composite outcome measure does not differentiate between receptor density and affinity. Thus, changes in BP_{ND} may be due to changes in the receptor affinity, the amount of actual receptor proteins, receptor trafficking between cell surface and intracellular spaces, or the amount of endogenous ligand occupancy in the receptor proteins. Nevertheless, regardless of the exact mechanism, decreased BP_{ND} after exercise most likely reflects endogenous opioid actions on the MOR system (Boecker *et al*, 2008; Colasanti *et al*, 2012; Scott *et al*, 2007). Second, physical exercise may have influenced the radiotracer kinetics of [^{11}C]carfentanil. For example, altered cerebral blood flow could potentially influence both delivery and washout of the tracer, leading to artefactual changes in receptor binding estimates. While this confounding factor cannot be definitively ruled out on the basis of current data, it is unlikely that decreased blood flow would explain decreased BP_{ND} after HIIT, given that previous simulations (Endres *et al*, 2003; Frost *et al*, 1989; Liberzon *et al*, 2002) have demonstrated that reference tissue modelling of specific binding is relatively insensitive to changes in cerebral blood flow. Moreover, recent research using simultaneous measurement of brain perfusion (with arterial spin labelled MRI) and radioactivity uptake after tracer injection (with PET), convincingly shows no effect of altered cerebral blood flow on receptor binding with other reversibly binding radiotracers (Sander *et al*, 2017), which likely translates to [^{11}C]carfentanil as well (Nummenmaa *et al*, 2018b). Third, the time points of measurements may have affected the results. The PET scan started 20 minutes after exercise cessation and fMRI took place after the PET scan. Significant dilution of the BP_{ND} effect in the time between the exercise and the PET scan seems unlikely, as decreased BP_{ND} persists for 20–65min after pain stimulation (Scott *et al*, 2007). However, some of the effects of exercise on haemodynamic brain responses to food images have most likely been missed, due to the 51 min PET scan prior to fMRI measurement. Others have reported altered functional responses 10 minutes after exercise (Crabtree *et al*, 2014; Evero *et al*, 2012), but not 30 minutes after exercise (Cornier *et al*, 2012), paralleling our findings.

[^{11}C]carfentanil has a very high intra-class correlation coefficient and low variability, suggesting good reliability for both within-subject and between-subject study designs (Hirvonen *et al*, 2009). However, although mood questionnaires are common in exercise studies and the food image fMRI paradigms are widely used for examining the neural basis of food reward processing and ingestive behaviour, the reliability of these methods is not well understood. This may limit the statistical power of the present studies (Matheson, 2018), and thus, the results should be interpreted with caution.

Finally, the study groups may limit the generalisability of the findings regarding neural responses to exercise. In Studies III and IV, only young lean (non-obese) male subjects were studied. Given that age, obesity, and sex influence both MOR availability and the capacity to activate the MOR system (Burghardt *et al*, 2015; Gabilondo *et al*, 1995; Karlsson *et al*, 2015; Zubieta *et al*, 1999, 2002) as well as the responsiveness to visual food stimuli (Brooks *et al*, 2013; Chao *et al*, 2017), our findings may not directly generalise to females and other age and weight groups. Moreover, the physical activity background of the participants varied considerably in Studies III and IV (from no exercise at all to yoga, crossfit, and martial arts), yet the effect of cardiovascular fitness on MOR tone and activation capacity remains unknown. The anticipatory food reward responses following exercise were examined only after MICT but not after HIIT, given the small number of subjects who completed the HIIT session.

6.5 Practical implications and future directions

The prevalence of physical inactivity is alarming, and innovative new ideas are needed to increase the adoption and maintenance of regular exercise. The goals of exercise programmes are typically twofold, with emphasis on both health benefits and tolerability. The present findings suggest that HIIT is a feasible exercise alternative for sedentary adults and it can be implemented as part of the training routines of diabetic patients. This may broaden and individualise the exercise strategies utilised in diabetes care, which could possibly improve the levels of physical activity in this population group. Although perceptual responses and enjoyment appear more positive during shorter than longer intervals (Kilpatrick *et al*, 2015b; Martinez *et al*, 2015; Townsend *et al*, 2017), the optimal work and/or rest interval duration for maximising both physiological and psychological adaptations needs be determined in future studies. Moreover, future studies should also aim at investigating the best practices of HIIT in real world settings in order to maximise the feasibility and accessibility.

While affective responses during continuous exercise have shown to be predictive of future exercise participation and adherence (Kwan and Bryan, 2010; Rhodes and Kates, 2015; Williams *et al*, 2008), whether this predictive relationship applies to interval training remains unknown. The variable nature of interval exercise may complicate the evaluation of fluctuating affect, and its subsequent influence on future exercise behaviour. For example, intervals of varied length may exert distinct influence on physiological and metabolic strain in a manner that affects perceptions of effort differently than in continuous exercise. Breaking exercise into small, more achievable bouts may allow participants more opportu-

nities to experience mastery over completed sprints, which may lead to increased self-efficacy (Jung *et al*, 2014). This could be important especially for novice exercisers. Future research needs to explore how perceptual and affective responses both during and after HIIT may influence future exercise participation. This might also influence the implementation of HIIT protocols into physical activity recommendations.

The present findings indicate a novel role for the MOR system in modulating various psychophysical responses to acute exercise at different intensity levels. While high exercise intensity resulted in a robust release of endogenous opioids, moderate-intensity exercise showed both activation and deactivation of the MOR system. There are several interesting research aspects in these findings. First, lower BMI is linked to higher baseline MOR binding in amygdala (Nummenmaa *et al*, 2018a), but whether other factors related to exercise, such as better aerobic fitness or higher physical activity level affect baseline MOR availability, and whether these influence the MOR activation capacity in response to exercise remain unknown. Thus, future research should explore the potential mediators underlying the variable MOR responses induced by moderate-intensity exercise. Second, animal studies suggest that higher levels of exercise may produce greater compensatory responses within the MOR system. Future studies should determine whether in humans acute MOR responses to exercise are similar in individuals with opposing exercise backgrounds (e.g., competitive endurance athletes such as triathletes versus completely sedentary individuals) and whether long-term repeated exercise modulates MOR responses. This could provide insights on the neurobiological mechanisms that underlie the habituation to physical activity, maintenance of regular exercise participation, and exercise addiction. Third, MOR activation after acute aerobic exercise resulted in enhanced food reward and thus, anticipatory reward sensitisation. Whether exercise-induced MOR action is linked to other types of reward, such as monetary rewards or substance craving, needs to be established in future studies. Given that an altered MOR function has been associated with behavioural addictions such as pathological gambling and binge eating disorder (Joutsa *et al*, 2018; Majuri *et al*, 2017) as well as with substance abuse (Gorelick *et al*, 2005; Hermann *et al*, 2017), exercise might address these underlying mechanisms, and thus, possibly provides a potential tool for treating these conditions.

Moreover, dysfunctions in the MOR system have been associated with major depressive disorder (Kennedy *et al*, 2006), the leading cause of disability worldwide (WHO, 2017). Research has shown promise for the efficacy of physical exercise in alleviating symptoms of depression which may be comparable to psychotherapy and antidepressants (Kvam *et al*, 2016). One important future extension of the present work would be to determine whether exercise is capable of

affecting the dysfunctional MOR system in these patients, and whether exercise-induced adaptation in the MOR system is associated with the therapeutic effects of exercise.

Finally, the neurochemical mechanisms mediating motivational and affective behavioural processes of exercise are not exclusively posited on the opioidergic system. The dopamine system, for example, is undeniably a part of the reward system and likely involved in the positive psychological outcomes of exercise. Previous animal studies have revealed altered dopaminergic activity in response to acute and chronic exercise (Meeusen *et al*, 2001; Robison *et al*, 2018), however this has yet to be demonstrated in humans (Wang *et al*, 2000). The endocannabinoid system has also gained interest as a mediator of exercise-induced positive mood responses (Brellenthin *et al*, 2017; Raichlen *et al*, 2012). As a close interaction between opioid, dopamine, and endocannabinoid systems has been established (Wenzel and Cheer, 2017), they may also possess a synergistic functions in the psychological effects of exercise. All things considered, understanding the neurobiological underpinnings of the psychophysiological responses to exercise could provide new means for targeted and effective use of exercise in health care, for example in weight loss interventions and lifestyle changing programmes as well as in the treatment of various affective spectrum disorders.

7 CONCLUSIONS

The benefits of regular exercise are advantageous on a health promotion level only when exercise programmes are well tolerated and engaged in by the people who are the targets of public health recommendations. By this means, the findings of the present thesis suggest that although the perceptual and affective responses are more negative both during and acutely after HIIT compared with MICT, these responses show significant improvements already within six training sessions indicating rapid positive affective and physiological adaptations to continual exercise training. Accordingly, even very intense HIIT can be a tolerable exercise option for insufficiently active adults with and without insulin resistance, and thus, HIIT could be implemented as part of training routines of diabetic patients. These findings are valuable for the development of new time-efficient, yet pleasurable exercise strategies to increase exercise participation and physical activity level in general.

The positive psychophysiological effects of physical exercise have been proposed to involve central opioidergic mechanisms. The findings of this thesis strengthen previous data and beyond this, demonstrate for the first time that exercise intensity modulates acute MOR action and concomitant changes in affective states. High-intensity exercise, HIIT, elicited endogenous opioid release, as evidenced by significantly decreased MOR binding. Decreased MOR binding correlated with HIIT-induced increases in negative affect. In contrast, moderate-intensity exercise did not result in significant overall change in MOR availability, but it did improve the positive affect, satisfaction and euphoria, and changes in these measures correlated with changes in MOR binding. This pattern of results indicates that MOR may have a dual role at different levels of physical exercise: modulation of positive emotionality in moderate intensity exercise and modulation of negative emotionality in high-intensity exercise. These findings pave the way for a better understanding of the neurochemical basis of affective responses to exercise and its role in exercise behaviour.

Finally, physical exercise regulates appetite, modulates food reward, and helps control body weight. Differences in acute food reward responses following exercise possibly contribute to energy intake after training. Findings described in this thesis reveal a novel role for the brain MOR system in modulating anticipatory food reward following exercise. Changes in MOR binding after moderate-intensity exercise correlated negatively with the exercise-induced changes in anticipatory food reward responses in fMRI in such way that higher opioid release after exercise predicted higher brain responses to palatable versus non-palatable foods. This data suggest that altered MOR action induced by acute exercise may

modulate appetitive motivation and contribute to anticipatory reward sensitisation by enhancing food reward. Consequently, it may account for compensatory energy intake following exercise and compromise weight control. These findings may facilitate further understanding of the complexity of physical exercise in weight loss interventions.

ACKNOWLEDGEMENTS

Entering this ambiguous research project changed the course of my life. During the past years, I have found my passion for neuroscience and human behaviour, and I have grown enormously not only as a researcher but as person as well. I want to thank all the wonderful people who have supported me, guided me, believed in me, and stood in my corner through this challenging and rewarding journey.

First, I wish to express my deepest and heartfelt gratitude to my supervisors, the two true sportsmen, Adjunct Professors Kari Kalliokoski and Jussi Hirvonen. I highly respect your scientific expertise and immense input in my work. Moreover, I value your incredible patience with me, as well as all the freedom and independence you have given me during this process. Kari, I am forever thankful to you for seeing the potential in me from the very beginning, and for ultimately taking a chance and hiring me, a chemist with no experience in exercise physiology or neuroscience. Your belief in me made this work possible. Jussi, your impressive expertise in neuroreceptor research has been crucial to this work. I greatly appreciate your confident approach and positive mindset, which have helped me to overcome a number of challenges and moments of disbelief.

In addition to my supervisors, I want to thank Associate Professor Lauri Nummenmaa for adopting me as part of the Emotion team and becoming an extra mentor for me during the last couple of years. Lauri, your endless enthusiasm for science (especially for all the weird stuff) is truly inspiring! I appreciate your keen interest towards my work, as well as your patient guidance with fMRI analyses, and teaching me the valuable skills of data compression.

My warm thanks go to all the voluntary subjects of the present studies as well as to all my co-authors for the well-functioning collaboration. This thesis, as well as the top-quality research in “HIIT feels shit”, and the Exebrain projects would not have been possible without your invaluable contribution! Doctors Lauri Tuominen and Jetro Tuulari, it has been a great pleasure to work with you both, your dedication to science and high-quality work is admirable. Thank you for teaching and mentoring me during Exebrain and for being such superior company in and outside the office. To the radiochemistry department and especially Eveliina Arponen, an enormous thanks for the sound supply of [^{11}C]carfentanil which ensured smooth and successful imaging sessions. Joonas Eskelinen, I value your huge input in HITPET project and thank you for welcoming me as part of the exercise team, it was fun working side by side! Thank you for your friendship and warm support over these years. Jarna Hannukainen and Anna Savolainen, your encouragement and important input in HITPET study are highly appreciat-

ed. Biostatisticians Tero Vahlberg and Eliisa Löyttyniemi, thank you for handling the complex statistical analyses. Additionally, I want to thank exercise physiologist Jukka Kapanen from Paavo Nurmi Centre for taking care of the maximal exercise tests.

I express my gratitude to the official reviewers of this thesis, Adjunct Professor Jan Wikgren from the University of Jyväskylä and Associate Professor Simon Cervenka from the Karolinska Institutet in Stocholm. I appreciate their positive review and constructive feedback, which helped me to strengthen the scientific quality of this dissertation and to think in broader ways. I thank Elizabeth Nyman for thorough language check of this work. The Doctoral Programme in Clinical Research, at the University of Turku, and its director, Associate Professor Antti Saraste are acknowledged for providing educational opportunities. The coordinator of CLIDP, Kristiina Nuutila, and the Chief Academic Officer Outi Irjala are acknowledged for always being so helpful with matters related to doctoral studies. I thank Professor Minna Huotilainen from the University of Helsinki for accepting the invitation to act as my opponent in the public defence of this dissertation.

I am privileged to have been able to carry out this work in the excellent research facilities at Turku PET Centre, University of Turku and Turku University Hospital. For that, I wish to express my appreciation to Professor Jaakko Hartiala and Adjunct Professor Jukka Kemppainen from the Department of Clinical Physiology and Nuclear Medicine and to Professor Juhani Knuuti, the Director of Turku PET Centre.

I also want to warmly thank the personnel of Turku PET Centre for all the help and support they have given me throughout these years. I greatly value the forward-looking and problem-solving attitude as well as the kind and playful work atmosphere! And what's more, at PET parties the dance floor is never empty! My great appreciation goes to the resourceful medical laboratory technologists Eija Salo, Sanna Suominen, Emilia Puhakka, Heidi Partanen, Leena Tokoi-Eklund, Tiina Tuominen, and Hanna Liukko-Sipi, and radiographers Minna Aatsinki, Hannele Lehtinen, Tiina Santakivi, Anne-Mari Jokinen, Aliisa Jokinen, Pirkko Herranen, Silja Hälli, and Sofia Sinervo, for their skilled work and assistance with practical things during data collection. Many thanks go to physicists Virva Saunavaara for always being only a phone call away from handling all MRI-related problems, Jarmo Teuho for PET-image reconstructions, and Mika Teräs and Tuula Tolvanen for their help with other technical issues as well as constant support. Lenita Saloranta, Tarja Marttila, and Mirja Jyrkinen are thanked for secretarial matters, and Rami Mikkola and Marko Tättäläinen for their expertise in IT related issues.

Throughout these years, it has been an inspiration to also be surrounded by talented scientists. I want to thank Professor Anne Roivainen for introducing me to the world of PET imaging ten years ago and for encouraging me to pursue a scientific career. Thank you also to all the past and present members of Anne's gallium team for the projects and experiences we have shared together, especially Anu Autio, Pauliina Luoto and Henri Sipilä from my early years in radiochemistry, when all of us were young, wild, and free (at least I was!). I owe my warm thanks to all the brilliant members of the Emotion Lab. I have truly enjoyed our weekly sessions with sparkling and superb traditions such as lonkerotasting, gingerbread baking, and spurgulounas. I especially want to thank Lauri Nummenmaa, Tomi Karjalainen, Kerttu Seppälä, Matthew Hudson, Vesa Putkinen, Marco Bucci, Janne Isojärvi, Sanaz Nazari-Farsani, Lihua Sun, Sandra Manninen, Tatu Kantonen and Jouni Tuisku, the peer sufferers of the daily punishment, for fun times, great company, and for making rankkari more tolerable. Daddy-O-Travels and Father Henry Karlsson are acknowledged for the memorable travel arrangements and the traditional Pohjolan Pidot. Great thanks go also to all the other intelligent neuroscientists, Anniina Snellman, Laura Ekblad, Noora Lindgren, Juho Joutsa, Joonas Majuri, Kati Alakurtti, Eero Rissanen, and Jarkko Johansson, and other members of "PET boys and girls" with whom I have shared numerous laughs and unforgettable moments in lunches and coffee breaks, get-togethers, and conference trips. I thank the skilled and energetic exercise scientists Sanna Honkala and Marja Heiskanen for peer support during the doctoral studies, Kumail Motiani for always finding encouraging words, Minna Yli-Karjanmaa for being an excellent travel buddy, and Tuija Leskinen for all the conversations, company, and for being a friend when I needed one. All the other researchers in PET bunkkeri are also acknowledged for creating a relaxed and productive work atmosphere.

A special thank you to all my dear friends outside work. Noora Ottman, Elina Siirola, and Anu Autio, my intelligent and inspirational sisters in science, thank you for your friendship and all the captivating talks, crazy laughs, and hilarious times we have experienced together. Your support through challenges and roadblocks of life has been invaluable. My other Terbio friends, Tuija Orre, Johanna Mäkelä, Katri Kaunismaa, Aino Kopu, Jaakko Kopra, Henrik Paavilainen, Ville Ranta-Panula, Kati Räisänen, and Anna Knittle, with you I had a pleasure to build foundations for this work. Your positive and aspiring example and attitude in life has encouraged me to pursue this endeavour. My high school friends, especially Laura Åvall, thank you for your long-lasting friendship and ever so cheerful support.

My heart holds deep appreciation for my family. My parents Teija and Markku Saanijoki, you instilled in me the value of education and hard work, and have

always encouraged me with my studies. I have always been able to count on your loving support. My sister Jaana Saanijoki, the warmest and kindest person I know, you have been maybe the most supportive person in my life. Your willingness to always help in any possible way you can and you being proud of me means so much to me. Katja Ketolainen, my cousin, oldest friend, and my other sister, I am so happy to have you in my life. You are the one who takes me out to shake both booty and mind! Thank you for keeping me close through all the action and chaos of life. Finally, my dear companion on this journey, Mikko Koivumäki. I deeply appreciate your scientifically oriented mind and that you understand the details of my work. Your practical input to this project is undoubtedly huge, but beyond that, your unwavering support, patience, and love as my partner have mattered the most. I am so grateful for being able to share this experience, and life, with you.

This work was financially supported by the Academy of Finland, the Ministry of Education and Culture of Finland, the Paavo Nurmi Foundation, the Finnish Cultural Foundation, the Novo Nordisk Foundation, the Paulo Foundation, the Turku Collegium for Science and Medicine, the Hospital District of Southwest Finland, the Medical Imaging Centre of Southwest Finland, the European Foundation for the Study of Diabetes, the Finnish Cardiovascular Foundation, the Finnish Diabetes Foundation, the Emil Aaltonen Foundation, the Doctoral Programme in Clinical Research, and by personal grants to me from the Juho Vainio Foundation, the Paavo Nurmi Foundation, the Instrumentarium Science Foundation, the Veritas Foundation, the Orion Research Foundation, the Sports Institute Foundation, and the Yrjö Jahnsson Foundation.

Turku, May 2018

Tiina Saanijoki

REFERENCES

Aaltonen S, Leskinen T, Morris T, Alen M, Kaprio J, Liukkonen J, *et al* (2012). Motives for and barriers to physical activity in twin pairs discordant for leisure time physical activity for 30 years. *Int J Sports Med* **33**: 157–63.

Aaltonen S, Rottensteiner M, Kaprio J, Kujala UM (2014). Motives for physical activity among active and inactive persons in their mid-30s. *Scand J Med Sci Sports* **24**: 727–735.

Aidman E V., Woollard S (2003). The influence of self-reported exercise addiction on acute emotional and physiological responses to brief exercise deprivation. *Psychol Sport Exerc* **4**: 225–236.

Ajzen I (1991). The theory of planned behavior. *Organ Behav Hum Decis Process* **50**: 179–211.

Allen K, Morey MC (2010). Physical Activity and Adherence. In: Bosworth HB (Ed.), Improving Patient Treatment Adherence: A Clinician's Guide. New York, NY: Springer.

Amireault S, Godin G, Vézina-Im L-A (2013). Determinants of physical activity maintenance: a systematic review and meta-analyses. *Health Psychol Rev* **7**: 55–91.

Arida RM, Gomes da Silva S, Almeida AA de, Cavalheiro EA, Zavala-Tecuapetla C, Brand S, *et al* (2015). Differential effects of exercise on brain opioid receptor binding and activation in rats. *J Neurochem* **132**: 206–17.

Astorino TA, Allen RP, Roberson DW, Jurancich M, Lewis R, McCarthy K (2012). Attenuated RPE and leg pain in response to short-term high-intensity interval training. *Physiol Behav* **105**: 402–7.

Babraj JA, Vollaard NBJ, Keast C, Guppy FM, Cottrell G, Timmons JA (2009). Extremely short duration high intensity interval training substantially improves insulin action in young healthy males. *BMC Endocr Disord* **9**: 3.

Bailey SJ, Wilkerson DP, DiMenna FJ, Jones AM (2009). Influence of repeated sprint training on pulmonary O2 uptake and muscle deoxygenation kinetics in humans. *J Appl Physiol* **106**: 1875–1887.

Baker JS, McCormick MC, Robergs RA (2010). Interaction among Skeletal Muscle Metabolic Energy Systems during Intense Exercise. *J Nutr Metab* **2010**: 905612.

Baker PR, Francis DP, Soares J, Weightman AL, Foster C (2011). Community wide interventions for increasing physical activity. *Cochrane Database Syst Rev* CD008366.

Bandura A (1998). Health promotion from the perspective of social cognitive theory. *Psychol Health* **13**: 623–649.

Banks WA, Kastin AJ (1990). Peptide transport systems for opiates across the blood-brain barrier. *Am J Physiol* **259**: E1-10.

Barrett LF (2006). Solving the Emotion Paradox: Categorization and the Experience of Emotion. *Personal Soc Psychol Rev* **10**: 20–46.

Basso JC, Suzuki WA (2016). The Effects of Acute Exercise on Mood, Cognition, Neurophysiology, and Neurochemical Pathways: A Review. *Brain Plast* **2**: 127–152.

Bauman AE, Reis RS, Sallis JF, Wells JC, Loos RJF, Martin BW, *et al* (2012). Correlates of physical activity: why are some people physically active and others not? *Lancet* **380**: 258–71.

Belke TW, Wagner JP (2005). The reinforcing property and the rewarding aftereffect of wheel running in rats: a combination of two paradigms. *Behav Processes* **68**: 165–72.

Benarroch EE (2012). Endogenous opioid systems: current concepts and clinical correlations. *Neurology* **79**: 807–14.

Berczik K, Szabó A, Griffiths MD, Kurimay T, Kun B, Urbán R, *et al* (2012). Exercise Addiction: Symptoms, Diagnosis, Epidemiology, and Etiology. *Subst Use Misuse* **47**: 403–417.

Berman M, Taylor S, Marged B (1993). Morphine and human aggression. *Addict Behav* **18**: 263–8.

Berridge KC, Ho C-Y, Richard JM, DiFeliceantonio AG (2010). The tempted brain eats: Pleasure and desire circuits in obesity and eating disorders. *Brain Res* **1350**: 43–64.

Berridge KC, Kringelbach ML (2008). Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology (Berl)* **199**: 457–80.

Berridge KC, Kringelbach ML (2015). Pleasure Systems in the Brain. *Neuron* **86**: 646–664.

Berridge KC, Robinson TE (2016). Liking, wanting, and the incentive-sensitization theory of addiction. *Am Psychol* **71**: 670–679.

Biddle SJH, Batterham AM (2015). High-intensity interval exercise training for public health: a big HIT or shall we HIT it on the head? *Int J Behav Nutr Phys Act* **12**: 95.

Bidonde J, Busch AJ, Schachter CL, Overend TJ, Kim SY, Góes SM, *et al* (2017). Aerobic exercise training for adults with fibromyalgia. *Cochrane Database Syst Rev* **6**: CD012700.

Billat L V (2001a). Interval training for performance: a scientific and empirical practice. Special recommendations for middle- and long-distance running. Part I: aerobic interval training. *Sports Med* **31**: 13–31.

Billat L V (2001b). Interval training for performance: a scientific and empirical practice. Special recommendations for middle- and long-distance running. Part II: anaerobic interval training. *Sports Med* **31**: 75–90.

Bish CL, Blanck HM, Maynard LM, Serdula MK, Thompson NJ, Khan LK (2007). Activity/participation limitation and weight loss among overweight and obese US adults: 1999 to 2002 NHANES. *MedGenMed* **9**: 63.

Blake MJ, Stein EA, Vomachka AJ (1984). Effects of exercise training on brain opioid peptides and serum LH in female rats. *Peptides* **5**: 953–8.

Blundell JE, King NA (1996). Overconsumption as a cause of weight gain: behavioural-physiological interactions in the control of food intake (appetite). *Ciba Found Symp* **201**: 138-54; discussion 154–8, 188–93.

Boecker H, Sprenger T, Spilker ME, Henriksen G, Koppenhoefer M, Wagner KJ, *et al* (2008). The runner's high: opioidergic mechanisms in the human brain. *Cereb cortex* **18**: 2523–31.

Borg G (1998). Borg's Perceived exertion and pain scales. Champaign, IL: Human Kinetics.

Bouchard C, Rankinen T (2001). Individual differences in response to regular physical activity. *Med Sci Sports Exerc* **33**: S446-51; discussion S452–3.

Bozarth MA, Wise RA (1981). Intracranial self-administration of morphine into the ventral tegmental area in rats. *Life Sci* **28**: 551–5.

Bradley MM, Lang PJ (1994). Measuring emotion: The self-assessment manikin and the semantic differential. *J Behav Ther Exp Psychiatry* **25**: 49–59.

Brellenthin AG, Crombie KM, Hillard CJ, Koltyn KF (2017). Endocannabinoid and Mood Responses to Exercise in Adults with Varying Activity Levels. *Med Sci Sport Exerc* **49**: 1688–1696.

Brooks SJ, Cedernaes J, Schiöth HB (2013). Increased Prefrontal and Parahippocampal Activation with Reduced Dorsolateral Prefrontal and Insular Cortex Activation to Food Images in Obesity: A Meta-Analysis of fMRI Studies. *PLoS One* **8**: e60393.

Brown DR, Wang Y, Ward A, Ebbeling CB, Fortlage L, Puleo E, *et al* (1995). Chronic psychological effects of exercise and exercise plus cognitive strategies. *Med Sci Sports Exerc* **27**: 765–75.

Bryan A, Hutchison KE, Seals DR, Allen DL (2007). A transdisciplinary model integrating genetic, physiological, and psychological correlates of voluntary exercise. *Health Psychol* **26**: 30–9.

Buchheit M, Laursen PB (2013). High-Intensity Interval Training, Solutions to the Programming Puzzle. *Sport Med* **43**: 313–338.

Burghardt PR, Rothberg AE, Dykhuis KE, Burant CF, Zubieta J-K (2015). Endogenous Opioid Mechanisms Are Implicated in Obesity and Weight Loss in Humans. *J Clin Endocrinol Metab* **100**: 3193–201.

Burgomaster KA, Hughes SC, Heigenhauser GJF, Bradwell SN, Gibala MJ (2005). Six sessions of sprint interval training increases muscle oxidative potential and cycle endurance capacity in humans. *J Appl Physiol* **98**: 1985–90.

Burkett JP, Spiegel LL, Inoue K, Murphy AZ, Young LJ (2011). Activation of μ-Opioid Receptors in the Dorsal Striatum is Necessary for Adult Social Attachment in Monogamous Prairie Voles. *Neuropsychopharmacology* **36**: 2200–2210.

Busch A, Overend T, Schachter C (2009). Fibromyalgia treatment: the role of exercise and physical activity. *Int J Clin Rheumtol* **4**: 343–380.

Cabanac M (1992). Pleasure: the common currency. *J Theor Biol* **155**: 173–200.

Caglar E, Canlan Y, Demir M (2009). Recreational Exercise Motives of Adolescents and Young Adults. *J Hum Kinet* **22**: 83–89.

Cambridge VC, Ziauddeen H, Nathan PJ, Subramaniam N, Dodds C, Chamberlain SR, *et al* (2013). Neural and behavioral effects of a novel mu opioid receptor antagonist in binge-eating obese people. *Biol Psychiatry* **73**: 887–94.

Caspersen CJ, Powell KE, Christenson GM (1985). Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep* **100**: 126–31.

Chao AM, Loughead J, Bakizada ZM, Hopkins CM, Geliebter A, Gur RC, *et al* (2017). Sex/gender differences in neural correlates of food stimuli: a systematic review of functional neuroimaging studies. *Obes Rev* **18**: 687–699.

Cherry SR, Dahlbom M (2006). PET: Physics, Instrumentation, and Scanners. In: Phelps ME (Ed.), PET. New York, NY: Springer.

Colasanti A, Searle GE, Long CJ, Hill SP, Reiley RR, Quelch D, *et al* (2012). Endogenous opioid release in the human brain reward system induced by acute amphetamine administration. *Biol Psychiatry* **72**: 371–7.

Cook DB, O'Connor PJ, Eubanks SA, Smith JC, Lee M (1997). Naturally occurring muscle pain during exercise: assessment and experimental evidence. *Med Sci Sports Exerc* **29**: 999–1012.

Cook DB, O'Connor PJ, Oliver SE, Lee Y (1998). Sex differences in naturally occurring leg muscle pain and exertion during maximal cycle ergometry. *Int J Neurosci* **95**: 183–202.

Cook DB, O'Connor PJ, Ray CA (2000). Muscle pain perception and sympathetic nerve activity to exercise during opioid modulation. *Am J Physiol Regul Integr Comp Physiol* **279**: R1565-73.

Cornier M-A, Melanson EL, Salzberg AK, Bechtell JL, Tregellas JR (2012). The effects of exercise on the neuronal response to food cues. *Physiol Behav* **105**: 1028–34.

Costa EC, Sá JCF de, Costa IBB, Meireles R da SRV, Lemos TMAM, Elsangedy HM, *et al* (2015). Affect-regulated exercise: an alternative approach for lifestyle modification in overweight/obese women with polycystic ovary syndrome. *Gynecol Endocrinol* **31**: 971–975.

Cotman CW, Berchtold NC, Christie L-A (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends Neurosci* **30**: 464–472.

Crabtree DR, Chambers ES, Hardwick RM, Blannin AK (2014). The effects of high-intensity exercise on neural responses to images of food. *Am J Clin Nutr* **99**: 258–67.

Dacey M, Baltzell A, Zaichkowsky L (2008). Older adults' intrinsic and extrinsic motivation toward physical activity. *Am J Health Behav* **32**: 570–82.

Daniel M, Martin AD, Carter J (1992). Opiate receptor blockade by naltrexone and mood state after acute physical activity. *Br J Sports Med* **26**: 111–5.

Decker ES, Ekkekakis P (2017). More efficient, perhaps, but at what price? Pleasure and enjoyment responses to high-intensity interval exercise in low-active women with obesity. *Psychol Sport Exerc* **28**: 1–10.

Dietrich A, McDaniel WF (2004). Endocannabinoids and exercise. *Br J Sports Med* **38**: 536–41.

Ding D, Lawson KD, Kolbe-Alexander TL, Finkelstein EA, Katzmarzyk PT, Mechelen W van, *et al* (2016). The economic burden of physical inactivity: a global analysis of major non-communicable diseases. *Lancet* **388**: 1311–1324.

Dishman RK, Berthoud H-R, Booth FW, Cotman CW, Edgerton VR, Fleshner MR, *et al* (2006). Neurobiology of Exercise. *Obesity* **14**: 345–356.

Dishman RK, O'Connor PJ (2009). Lessons in exercise neurobiology: The case of endorphins. *Ment Health Phys Act* **2**: 4–9.

Drury DG, Greenwood K, Stuempfle KJ, Koltyn KF (2005). Changes in pain perception in women during and following an exhaustive incremental cycling exercise. *J Sports Sci Med* **4**: 215–22.

Duerden EG, Albanese M-C (2013). Localization of pain-related brain activation: a meta-analysis of neuroimaging data. *Hum Brain Mapp* **34**: 109–49.

Ebben W, Brudzynski L (2008). Motivations and barriers to exercise among college students. *J Exerc Physiol Online* **11**: 1–11.

Edwards MK, Rhodes RE, Loprinzi PD (2017). A Randomized Control Intervention Investigating the Effects of Acute Exercise on Emotional Regulation. *Am J Health Behav* **41**: 534–543.

Eickhoff SB, Stephan KE, Mohlberg H, Grefkes C, Fink GR, Amunts K, *et al* (2005). A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. *Neuroimage* **25**: 1325–35.

Eisch AJ, Barrot M, Schad CA, Self DW, Nestler EJ (2000). Opiates inhibit neurogenesis in the adult rat hippocampus. *Proc Natl Acad Sci U S A* **97**: 7579–84.

Ekkekakis P (2003). Pleasure and displeasure from the body: Perspectives from exercise. *Cogn Emot* **17**: 213–239.

Ekkekakis P (2013). The measurement of affect, mood, and emotion : a guide for health-behavioral research. New York, NY: Cambridge University Press.

Ekkekakis P, Hall EE, Petruzzello SJ (2005). Variation and homogeneity in affective responses to physical activity of varying intensities: an alternative perspective on dose-response based on evolutionary considerations. *J Sports Sci* **23**: 477–500.

Ekkekakis P, Hall EE, VanLanduyt LM, Petruzzello SJ (2000). Walking in (Affective) Circles: Can Short Walks Enhance Affect? *J Behav Med* **23**: 245–275.

Ekkekakis P, Lind E (2006). Exercise does not feel the same when you are overweight: the impact of self-selected and imposed intensity on affect and exertion. *Int J Obes* **30**: 652–660.

Ekkekakis P, Lind E, Vazou S (2010). Affective Responses to Increasing Levels of Exercise Intensity in Normal-weight, Overweight, and Obese Middle-aged Women. *Obesity* **18**: 79–85.

Ekkekakis P, Petruzzello SJ (1999). Acute aerobic exercise and affect: current status, problems and prospects regarding dose-response. *Sport Med* **28**: 337–74.

Ekkekakis P, Petruzzello SJ (2000). Analysis of the affect measurement conundrum in exercise psychology: I. Fundamental issues. *Psychol Sport Exerc* **1**: 71–88.

Ellingson LD, Colbert LH, Cook DB (2012). Physical Activity Is Related to Pain Sensitivity in Healthy Women. *Med Sci Sport Exerc* **44**: 1401–1406.

Endres CJ, Bencherif B, Hilton J, Madar I, Frost JJ (2003). Quantification of brain mu-opioid receptors with [^{11}C]carfentanil: reference-tissue methods. *Nucl Med Biol* **30**: 177–86.

Eskelinen JJ, Heinonen I, Löyttyniemi E, Hakala J, Heiskanen MA, Motiani KK, *et al* (2016). Left ventricular vascular and metabolic adaptations to high-intensity interval and moderate intensity continuous training: a randomized trial in healthy middle-aged men. *J Physiol* **594**: 7127–7140.

Eskelinen JJ, Heinonen I, Löyttyniemi E, Saunavaara V, Kirjavainen A, Virtanen KA, *et al* (2015). Muscle-specific glucose and free fatty acid uptake after sprint interval and moderate-intensity training in healthy middle-aged men. *J Appl Physiol* **118**: 1172–1180.

Eston R (2012). Use of ratings of perceived exertion in sports. *Int J Sports Physiol Perform* **7**: 175–82.

Evero N, Hackett LC, Clark RD, Phelan S, Hagobian TA (2012). Aerobic exercise reduces neuronal responses in food reward brain regions. *J Appl Physiol* **112**: 1612–9.

Fallon EA, Wilcox S, Ainsworth BE (2005). Correlates of Self-Efficacy for Physical Activity in African American Women. *Women Health* **41**: 47–62.

Farrell PA, Gates WK, Maksud MG, Morgan WP (1982). Increases in plasma beta-endorphin/beta-lipotropin immunoreactivity after treadmill running in humans. *J Appl Physiol* **52**: 1245–9.

Farrell PA, Gustafson AB, Garthwaite TL, Kalkhoff RK, Cowley AW, Morgan WP (1986). Influence of endogenous opioids on the response of selected hormones to exercise in humans. *J Appl Physiol* **61**: 1051–7.

Farrell PA, Kjaer M, Bach FW, Galbo H (1987). Beta-endorphin and adrenocorticotropin response to supramaximal treadmill exercise in trained and untrained males. *Acta Physiol Scand* **130**: 619–625.

Feng Y, He X, Yang Y, Chao D, Lazarus LH, Xia Y (2012). Current research on opioid receptor function. *Curr Drug Targets* **13**: 230–46.

Fernández-Dols, J. and Russell, J. A. (2003). Emotion, Affect, and Mood in Social Judgments. In Weiner IB (Ed.), Handbook of Psychology. New York, NY: Wiley.

Finlayson G, Bryant E, Blundell JE, King NA (2009). Acute compensatory eating following exercise is associated with implicit hedonic wanting for food. *Physiol Behav* **97**: 62–67.

Finlayson G, Caudwell P, Gibbons C, Hopkins M, King N, Blundell J (2011). Low fat loss response after medium-term supervised exercise in obese is associated with exercise-induced increase in food reward. *J Obes* **2011**: 615624.

Flint A, Raben A, Blundell JE, Astrup A (2000). Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes* **24**: 38–48.

Focht BC, Knapp DJ, Gavin TP, Raedeke TD, Hickner RC (2007). Affective and Self-Efficacy Responses to Acute Aerobic Exercise in Sedentary Older and Younger Adults. *J Aging Phys Act* **15**: 123–138.

Fox AM, Mann DM, Ramos MA, Kleinman LC, Horowitz CR (2012). Barriers to Physical Activity in East Harlem, New York. *J Obes* **2012**: 1–8.

Frazão DT, Farias Junior LF de, Dantas TCB, Krinski K, Elsangedy HM, Prestes J, *et al* (2016). Feeling of Pleasure to High-Intensity Interval Exercise Is Dependent of the Number of Work Bouts and Physical Activity Status. *PLoS One* **11**: e0152752.

Fritschi C, Quinn L (2010). Fatigue in patients with diabetes: a review. *J Psychosom Res* **69**: 33–41.

Frost JJ, Douglass KH, Mayberg HS, Dannals RF, Links JM, Wilson AA, *et al* (1989). Multicompartmental analysis of [^{11}C]-carfentanil binding to opiate receptors in humans measured by positron emission tomography. *J Cereb Blood Flow Metab* **9**: 398–409.

Gabilondo AM, Meana JJ, García-Sevilla JA (1995). Increased density of mu-opioid receptors in the postmortem brain of suicide victims. *Brain Res* **682**: 245–50.

Gambert SR, Garthwaite TL, Pontzer CH, Cook EE, Tristani FE, Duthie EH, *et al* (1981). Running elevates plasma beta-endorphin immunoreactivity and ACTH in untrained human subjects. *Proc Soc Exp Biol Med* **168**: 1–4.

Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee I-M, *et al* (2011). Quantity and Quality of Exercise for Developing and Maintaining Cardiorespiratory, Musculoskeletal, and Neuromotor Fitness in Apparently Healthy Adults. *Med Sci Sport Exerc* **43**: 1334–1359.

Gibala MJ, Little JP, Essen M Van, Wilkin GP, Burgomaster KA, Safdar A, *et al* (2006). Short-term sprint interval *versus* traditional endurance training: similar initial adaptations in human skeletal muscle and exercise performance. *J Physiol* **575**: 901–911.

Gibala MJ, Little JP, MacDonald MJ, Hawley JA (2012). Physiological adaptations to low-volume, high-intensity interval training in health and disease. *J Physiol* **590**: 1077–1084.

Giuliano C, Robbins TW, Nathan PJ, Bullmore ET, Everitt BJ (2012). Inhibition of Opioid Transmission at the μ-Opioid Receptor Prevents Both Food Seeking and Binge-Like Eating. *Neuropsychopharmacology* **37**: 2643–2652.

Glaister M (2005). Multiple sprint work : physiological responses, mechanisms of fatigue and the influence of aerobic fitness. *Sports Med* **35**: 757–77.

Gordon BR, McDowell CP, Lyons M, Herring MP (2017). The Effects of Resistance Exercise Training on Anxiety: A Meta-Analysis and Meta-Regression Analysis of Randomized Controlled Trials. *Sport Med* **47**: 2521–2532.

Gorelick DA, Kim YK, Bencherif B, Boyd SJ, Nelson R, Copersino M, *et al* (2005). Imaging Brain Mu-Opioid Receptors in Abstinent Cocaine Users: Time Course and Relation to Cocaine Craving. *Biol Psychiatry* **57**: 1573–1582.

Gosnell BA, Levine AS (2009). Reward systems and food intake: role of opioids. *Int J Obes* **33**: S54–S58.

Green N, Wertz T, LaPorta Z, Mora A, Serbas J, Astorino TA (2017). Comparison of Acute Physiological and Psychological Responses Between Moderate Intensity Continuous Exercise and three Regimes of High Intensity Training. *J Strength Cond Res*. Advance online publication. doi: 10.1519/JSC.0000000000002154

Greenwood BN, Foley TE, Le T V., Strong P V., Loughridge AB, Day HEW, *et al* (2011). Long-term voluntary wheel running is rewarding and produces plasticity in the mesolimbic reward pathway. *Behav Brain Res* **217**: 354–362.

Grossman A, Bouloux P, Price P, Drury PL, Lam KS, Turner T, *et al* (1984). The role of opioid peptides in the hormonal responses to acute exercise in man. *Clin Sci (Lond)* **67**: 483–91.

Gunn RN, Gunn SR, Cunningham VJ (2001). Positron Emission Tomography Compartmental Models. *J Cereb Blood Flow Metab* **21**: 635–652.

Gunn RN, Lammertsma AA, Hume SP, Cunningham VJ (1997). Parametric imaging of ligand-receptor binding in PET using a simplified reference region model. *Neuroimage* **6**: 279–87.

Haber SN, Knutson B (2010). The reward circuit: linking primate anatomy and human imaging. *Neuropsychopharmacology* **35**: 4–26.

Haile L, Gallagher M Jr, Robertson RJ (2015). Perceived exertion laboratory manual: From standard practice to contemporary application. New York, NY: Springer.

Hall EE, Ekkekakis P, Petruzzello SJ (2002). The affective beneficence of vigorous exercise revisited. *Br J Health Psychol* **7**: 47–66.

Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U (2012). Global physical activity levels: surveillance progress, pitfalls, and prospects. *Lancet* **380**: 247–57.

Hallgren MÅ, Moss ND, Gastin P (2010). Regular exercise participation mediates the affective response to acute bouts of vigorous exercise. *J Sports Sci Med* **9**: 629–37.

Harber VJ, Sutton JR (1985). Endorphins and exercise. *Sports Med* **1**: 154–71.

Hardcastle SJ, Ray H, Beale L, Hagger MS (2014). Why sprint interval training is inappropriate for a largely sedentary population. *Front Psychol* **5**: 1505.

Hargreaves M (2000). Skeletal Muscle Metabolism During Exercise In Humans. *Clin Exp Pharmacol Physiol* **27**: 225–228.

Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, *et al* (2007). Physical Activity and Public Health: Updated Recommendation for Adults From the American College of Sports Medicine and the American Heart Association. *Circulation* **116**: 1081–1093.

Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, *et al* (2012). Evidence-based intervention in physical activity: lessons from around the world. *Lancet* **380**: 272–81.

Heiskanen MA, Sjöros TJ, Heinonen IHA, Löyttyniemi E, Koivumäki M, Motiani KK, *et al* (2017). Sprint interval training decreases left-ventricular glucose uptake compared to moderate-intensity continuous training in subjects with type 2 diabetes or prediabetes. *Sci Rep* **7**: 10531.

Heiss W-D, Herholz K (2006). Brain receptor imaging. *J Nucl Med* **47**: 302–12.

Heisz JJ, Tejada MGM, Paolucci EM, Muir C, Ward B, Schiller J, *et al* (2016). Enjoyment for High-Intensity Interval Exercise Increases during the First Six Weeks of Training: Implications for Promoting Exercise Adherence in Sedentary Adults. *PLoS One* **11**: e0168534.

Heitkamp HC, Schmid K, Scheib K (1993). Beta-endorphin and adrenocorticotropic hormone production during marathon and incremental exercise. *Eur J Appl Physiol Occup Physiol* **66**: 269–74.

Hendee WR, Morgan CJ (1984). Magnetic Resonance Imaging Part I—Physical Principles. *West J Med* **141**: 491.

Henriksen G, Willoch F (2008). Imaging of opioid receptors in the central nervous system. *Brain* **131**: 1171–1196.

Hermann D, Hirth N, Reimold M, Batra A, Smolka MN, Hoffmann S, *et al* (2017). Low μ-Opioid Receptor Status in Alcohol Dependence Identified by Combined Positron Emission Tomography and Post-Mortem Brain Analysis. *Neuropsychopharmacology* **42**: 606–614.

Hirvonen J, Aalto S, Hagelberg N, Maksimow A, Ingman K, Oikonen V, *et al* (2009). Measurement of central mu-opioid receptor binding in vivo with PET and [^{11}C]carfentanil: a test-retest study in healthy subjects. *Eur J Nucl Med Mol Imaging* **36**: 275–86.

Hiura M, Sakata M, Ishii K, Toyohara J, Oda K, Nariai T, *et al* (2017). Central μ-Opioidergic System Activation Evoked by Heavy and Severe-Intensity Cycling Exercise in Humans: a Pilot Study Using Positron Emission Tomography with ^{11}C-Carfentanil. *Int J Sports Med* **38**: 19–26.

Hnasko TS, Sotak BN, Palmiter RD (2005). Morphine reward in dopamine-deficient mice. *Nature* **438**: 854–857.

Hoffman MD, Hoffman DR (2008). Exercisers achieve greater acute exercise-induced mood enhancement than nonexercisers. *Arch Phys Med Rehabil* **89**: 358–63.

Hopkins M, Gibbons C, Caudwell P, Webb D-L, Hellström PM, Näslund E, *et al* (2014). Fasting Leptin Is a Metabolic Determinant of Food Reward in Overweight and Obese Individuals during Chronic Aerobic Exercise Training. *Int J Endocrinol* **2014**: 1–8.

Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Walker SJ, *et al* (2015). It still hurts: altered endogenous opioid activity in the brain during social rejection and acceptance in major depressive disorder. *Mol Psychiatry* **20**: 193–200.

Hsu DT, Sanford BJ, Meyers KK, Love TM, Hazlett KE, Wang H, *et al* (2013). Response of the μ-opioid system to social rejection and acceptance. *Mol Psychiatry* **18**: 1211–7.

Huebschmann AG, Kohrt WM, Herlache L, Wolfe P, Daugherty S, Reusch JE, *et al* (2015). Type 2 diabetes exaggerates exercise effort and impairs exercise performance in older women. *BMJ open diabetes Res care* **3**: e000124.

Huettel SA, Song AW, McCarthy G (2014). Functional magnetic resonance imaging. Sunderland, MA: Sinauer Associates.

Hulens M, Vansant G, Claessens AL, Lysens R, Muls E (2003). Predictors of 6-minute walk test results in lean, obese and morbidly obese women. *Scand J Med Sci Sports* **13**: 98–105.

Hulens M, Vansant G, Lysens R, Claessens AL, Muls E (2001). Exercise capacity in lean versus obese women. *Scand J Med Sci Sports* **11**: 305–9.

Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, *et al* (2007). Consensus Nomenclature for *in vivo* Imaging of Reversibly Binding Radioligands. *J Cereb Blood Flow Metab* **27**: 1533–1539.

Inoue K, Okamoto M, Shibato J, Lee MC, Matsui T, Rakwal R, *et al* (2015). Long-Term Mild, rather than Intense, Exercise Enhances Adult Hippocampal Neurogenesis and Greatly Changes the Transcriptomic Profile of the Hippocampus. *PLoS One* **10**: e0128720.

Janal MN, Colt EW, Clark WC, Glusman M (1984). Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain* **19**: 13–25.

Järvekülg A, Viru A (2002). Opioid receptor blockade eliminates mood effects of aerobic gymnastics. *Int J Sports Med* **23**: 155–7.

Jelleyman C, Yates T, O'Donovan G, Gray LJ, King JA, Khunti K, *et al* (2015). The effects of high-intensity interval training on glucose regulation and insulin resistance: a meta-analysis. *Obes Rev* **16**: 942–961.

Johnston V (2003). The origin and function of pleasure. *Cogn Emot* **17**: 167–179.

Joutsa J, Karlsson HK, Majuri J, Nuutila P, Helin S, Kaasinen V, *et al* (2018). Binge eating disorder and morbid obesity are associated with lowered mu-opioid receptor availability in the brain. *Psychiatry Res Neuroimaging.* Advance online publication. doi:10.1016/j.pscychresns.2018.03.006

Jung ME, Bourne JE, Beauchamp MR, Robinson E, Little JP (2015). High-intensity interval training as an efficacious alternative to moderate-intensity continuous training for adults with prediabetes. *J Diabetes Res* **2015**: 191595.

Jung ME, Bourne JE, Little JP (2014). Where Does HIT Fit? An Examination of the Affective Response to High-Intensity Intervals in Comparison to Continuous Moderate- and Continuous Vigorous-Intensity Exercise in the Exercise Intensity-Affect Continuum. *PLoS One* **9**: e114541.

Kahneman D (1999). Objective happiness. *Well-being Found hedonic Psychol* 3–25.

Karlsson HK, Tuominen L, Tuulari JJ, Hirvonen J, Parkkola R, Helin S, *et al* (2015). Obesity Is Associated with Decreased μ-Opioid But Unaltered Dopamine D2 Receptor Availability in the Brain. *J Neurosci* **35**: 3959–3965.

Karlsson HK, Tuulari JJ, Tuominen L, Hirvonen J, Honka H, Parkkola R, *et al* (2016). Weight loss after bariatric surgery normalizes brain opioid receptors in morbid obesity. *Mol Psychiatry* **21**: 1057–62.

Karoly HC, Stevens CJ, Magnan RE, Harlaar N, Hutchison KE, Bryan AD (2012). Genetic Influences on Physiological and Subjective Responses to an Aerobic Exercise Session among Sedentary Adults. *J Cancer Epidemiol* **2012**: 1–12.

Katsuura Y, Heckmann JA, Taha SA (2011). mu-Opioid receptor stimulation in the nucleus accumbens elevates fatty tastant intake by increasing palatability and suppressing satiety signals. *Am J Physiol Regul Integr Comp Physiol* **301**: R244-54.

Kennedy SE, Koeppe RA, Young EA, Zubieta J-K (2006). Dysregulation of endogenous opioid emotion regulation circuitry in major depression in women. *Arch Gen Psychiatry* **63**: 1199–208.

Kilpatrick M, Kraemer R, Bartholomew J, Acevedo E, Jarreau D (2007). Affective responses to exercise are dependent on intensity rather than total work. *Med Sci Sports Exerc* **39**: 1417–22.

Kilpatrick MW, Greeley SJ, Collins LH (2015a). The Impact of Continuous and Interval Cycle Exercise on Affect and Enjoyment. *Res Q Exerc Sport* **86**: 244–51.

Kilpatrick MW, Martinez N, Little JP, Jung ME, Jones AM, Price NW, *et al* (2015b). Impact of High-Intensity Interval Duration on Perceived Exertion. *Med Sci Sport Exerc* **47**: 1038–1045.

Kim S-G, Ogawa S (2012). Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals. *J Cereb Blood Flow Metab* **32**: 1188–206.

King NA (1999). What processes are involved in the appetite response to moderate increases in exercise-induced energy expenditure? *Proc Nutr Soc* **58**: 107–113.

Kinnunen JV, Piitulainen H, Piirainen JM (2017). Neuromuscular adaptations to short-term high-intensity interval training in female ice hockey players. *J Strength Cond Res.* Advance online publication. doi: 10.1519/JSC.0000000000001881

Kiviniemi AM, Tulppo MP, Eskelinen JJ, Savolainen AM, Kapanen J, Heinonen IHA, *et al* (2014). Cardiac Autonomic Function and High-Intensity Interval Training in Middle-Age Men. *Med Sci Sport Exerc* **46**: 1960–1967.

Kiviniemi MT, Voss-Humke AM, Seifert AL (2007). How do I feel about the behavior? The interplay of affective associations with behaviors and cognitive beliefs as influences on physical activity behavior. *Health Psychol* **26**: 152–8.

Koehl M, Meerlo P, Gonzales D, Rontal A, Turek FW, Abrous DN (2008). Exercise-induced promotion of hippocampal cell proliferation requires beta-endorphin. *FASEB J* **22**: 2253–62.

Koglin L, Kayser B (2013). Control and sensation of breathing during cycling exercise in hypoxia under naloxone: a randomised controlled crossover trial. *Extrem Physiol Med* **2**: 1.

Kolt GS, Driver RP, Giles LC (2004). Why older Australians participate in exercise and sport. *J Aging Phys Act* **12**: 185–98.

Koltyn KF (2000). Analgesia following exercise: a review. *Sports Med* **29**: 85–98.

Koltyn KF (2002). Exercise-induced hypoalgesia and intensity of exercise. *Sports Med* **32**: 477–87.

Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C (2014). Mechanisms of Exercise-Induced Hypoalgesia. *J Pain* **15**: 1294–1304.

Korkiakangas EE, Alahuhta MA, Husman PM, Keinänen-Kiukaanniemi S, Taanila AM, Laitinen JH (2011). Motivators and barriers to exercise among adults with a high risk of type 2 diabetes - a qualitative study. *Scand J Caring Sci* **25**: 62–69.

Kraemer RR, Dzewaltowski DA, Blair MS, Rinehardt KF, Castracane VD (1990). Mood alteration from treadmill running and its relationship to beta-endorphin, corticotropin, and growth hormone. *J Sports Med Phys Fitness* **30**: 241–6.

Kvam S, Kleppe CL, Nordhus IH, Hovland A (2016). Exercise as a treatment for depression: A meta-analysis. *J Affect Disord* **202**: 67–86.

Kwan BM, Bryan A (2010). In-task and post-task affective response to exercise: Translating exercise intentions into behaviour. *Br J Health Psychol* **15**: 115–131.

Laan LN van der, Ridder DTD de, Viergever MA, Smeets PAM (2011). The first taste is always with the eyes: A meta-analysis on the neural correlates of processing visual food cues. *Neuroimage* **55**: 296–303.

Lammertsma AA, Hume SP (1996). Simplified Reference Tissue Model for PET Receptor Studies. *Neuroimage* **4**: 153–158.

Lamusuo S, Hirvonen J, Lindholm P, Martikainen IK, Hagelberg N, Parkkola R, *et al* (2017). Neurotransmitters behind pain relief with transcranial magnetic stimulation - positron emission tomography evidence for release of endogenous opioids. *Eur J Pain* **21**: 1505–1515.

Landmark T, Romundstad P, Borchgrevink PC, Kaasa S, Dale O (2011). Associations between recreational exercise and chronic pain in the general population: evidence from the HUNT 3 study. *Pain* **152**: 2241–7.

Landuyt LM Van, Ekkekakis P, Hall EE, Petruzzello SJ (2000). Throwing the mountains into the lake: On the perils of nomothetic conceptions of the exercise–affect relationship. *J Sport Exerc Psychol* **22**: 208–234.

Laursen PB, Jenkins DG (2002). The scientific basis for high-intensity interval training: optimising training programmes and maximising performance in highly trained endurance athletes. *Sports Med* **32**: 53–73.

Lawrence NS, Hinton EC, Parkinson JA, Lawrence AD (2012). Nucleus accumbens response to food cues predicts subsequent snack consumption in women and increased body mass index in those with reduced self-control. *Neuroimage* **63**: 415–422.

Lee HH, Emerson JA, Williams DM (2016). The Exercise-Affect-Adherence Pathway: An Evolutionary Perspective. *Front Psychol* **7**: 1285.

Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **380**: 219–29.

Leknes S, Tracey I (2008). A common neurobiology for pain and pleasure. *Nat Rev Neurosci* **9**: 314–20.

Levenstein S, Prantera C, Varvo V, Scribano ML, Berto E, Luzi C, *et al* (1993). Development of the Perceived Stress Questionnaire: a new tool for psychosomatic research. *J Psychosom Res* **37**: 19–32.

Liao Y, Shonkoff ET, Dunton GF (2015). The Acute Relationships Between Affect, Physical Feeling States, and Physical Activity in Daily Life: A Review of Current Evidence. *Front Psychol* **6**: 1975.

Liberzon I, Taylor SF, Phan KL, Britton JC, Fig LM, Bueller JA, *et al* (2007). Altered central μ-opioid receptor binding after psychological trauma. *Biol Psychiatry* **61**: 1030–8.

Liberzon I, Zubieta J-K, Fig LM, Phan KL, Koeppe RA, Taylor SF (2002). μ-Opioid receptors and limbic responses to aversive emotional stimuli. *Proc Natl Acad Sci* **99**: 7084–7089.

Little JP, Jung ME, Wright AE, Wright W, Manders RJF (2014). Effects of high-intensity interval exercise versus continuous moderate-intensity exercise on postprandial glycemic control assessed by continuous glucose monitoring in obese adults. *Appl Physiol Nutr Metab* **39**: 835–841.

Loseth GE, Ellingsen D-M, Leknes S (2014). State-dependent μ-opioid modulation of social motivation. *Front Behav Neurosci* **8**: 430.

Magnan RE, Kwan BM, Bryan AD (2013). Effects of current physical activity on affective response to exercise: physical and social-cognitive mechanisms. *Psychol Health* **28**: 418–33.

Mahler DA, Murray JA, Waterman LA, Ward J, Kraemer WJ, Zhang X, *et al* (2009). Endogenous opioids modify dyspnoea during treadmill exercise in patients with COPD. *Eur Respir J* **33**: 771–7.

Majuri J, Joutsa J, Johansson J, Voon V, Alakurtti K, Parkkola R, *et al* (2017). Dopamine and Opioid Neurotransmission in Behavioral Addictions: A Comparative PET Study in Pathological Gambling and Binge Eating. *Neuropsychopharmacology* **42**: 1169–1177.

Manninen S, Tuominen L, Dunbar RI, Karjalainen T, Hirvonen J, Arponen E, *et al* (2017). Social Laughter Triggers Endogenous Opioid Release in Humans. *J Neurosci* **37**: 6125–6131.

Markoff RA, Ryan P, Young T (1982). Endorphins and mood changes in long-distance running. *Med Sci Sports Exerc* **14**: 11–5.

Martinez N, Kilpatrick MW, Salomon K, Jung ME, Little JP (2015). Affective and Enjoyment Responses to High-Intensity Interval Training in Overweight-to-Obese and Insufficiently Active Adults. *J Sport Exerc Psychol* **37**: 138–49.

Matheson GJ (2018). We need to talk about reliability: Making better use of test retest studies for study design and interpretation. *bioRxiv* 274894. doi:10.1101/274894

Matta Mello Portugal E, Cevada T, Sobral Monteiro-Junior R, Teixeira Guimarães T, Cruz Rubini E da, Lattari E, *et al* (2013). Neuroscience of Exercise: From Neurobiology Mechanisms to Mental Health. *Neuropsychobiology* **68**: 1–14.

McDowell CP, Campbell MJ, Herring MP (2016). Sex-Related Differences in Mood Responses to Acute Aerobic Exercise. *Med Sci Sport Exerc* **48**: 1798–1802.

McNeil J, Cadieux S, Finlayson G, Blundell JE, Doucet É (2015). The effects of a single bout of aerobic or resistance exercise on food reward. *Appetite* **84**: 264–70.

McRobbie D, Moore E, Graves M, Prince M (2006). *MRI from Picture to Proton*. New York, NY: Cambridge University Press. doi:10.1017/CBO9780511545405

Meer F Van, Charbonnier L, Smeets PAM (2016). Food Decision-Making: Effects of Weight Status and Age. *Curr Diab Rep* **16**: 84.

Meeusen R, Piacentini MF, Meirleir K De (2001). Brain microdialysis in exercise research. *Sports Med* **31**: 965–83.

Mela DJ (2001). Determinants of Food Choice: Relationships with Obesity and Weight Control. *Obes Res* **9**: 249S–255S.

Melanson EL, Keadle SK, Donnelly JE, Braun B, King NA (2013). Resistance to exercise-induced weight loss: compensatory behavioral adaptations. *Med Sci Sports Exerc* **45**: 1600–9.

Mendez IA, Ostlund SB, Maidment NT, Murphy NP (2015). Involvement of Endogenous Enkephalins and β-Endorphin in Feeding and Diet-Induced Obesity. *Neuropsychopharmacology* **40**: 2103–12.

Merskey H, Bogduk N, International Association for the Study of Pain (1994). *Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of pain terms*. Seattle, WA: IASP Press.

Mezzani A, Hamm LF, Jones AM, McBride PE, Moholdt T, Stone JA, *et al* (2012). Aerobic exercise intensity assessment and prescription in cardiac rehabilitation: a joint position statement of the European Association for Cardiovascular Prevention and Rehabilitation, the American Association of Cardiovascular and Pulmonary Rehabilitat. *Eur J Prev Cardiol* **20**: 442–467.

Mick I, Myers J, Stokes PRA, Erritzoe D, Colasanti A, Bowden-Jones H, *et al* (2014). Amphetamine induced endogenous opioid release in the human brain detected with [^{11}C]carfentanil PET: replication in an independent cohort. *Int J Neuropsychopharmacol* **17**: 2069–74.

Milanović Z, Sporiš G, Weston M (2015). Effectiveness of High-Intensity Interval Training (HIT) and Continuous Endurance Training for VO2max Improvements: A Systematic Review and Meta-Analysis of Controlled Trials. *Sports Med* **45**: 1469–81.

Mior S (2001). Exercise in the treatment of chronic pain. *Clin J Pain* **17**: S77-85.

Morgan WP (1985). Affective beneficence of vigorous physical activity. *Med Sci Sports Exerc* **17**: 94–100.

Murdaugh DL, Cox JE, Cook EW, Weller RE (2012). fMRI reactivity to high-calorie food pictures predicts short- and long-term outcome in a weight-loss program. *Neuroimage* **59**: 2709–21.

Murto J, Kaikkonen R, Pentala-Nikulainen O, Koskela T, Virtala E, Härkänen T, *et al* (2017). Aikuisten terveys-, hyvinvointi- ja palvelututkimus ATH:n perustulokset 2010-2017. Available at www.thl.fi/ath

Mysels DJ, Sullivan MA (2010). The relationship between opioid and sugar intake: review of evidence and clinical applications. *J Opioid Manag* **6**: 445–52.

Naugle KM, Fillingim RB, Riley JL (2012). A meta-analytic review of the hypoalgesic effects of exercise. *J Pain* **13**: 1139–50.

Nogueiras R, Romero-Picó A, Vazquez MJ, Novelle MG, López M, Diéguez C (2012). The opioid system and food intake: homeostatic and hedonic mechanisms. *Obes Facts* **5**: 196–207.

Nokia MS, Lensu S, Ahtiainen JP, Johansson PP, Koch LG, Britton SL, *et al* (2016). Physical exercise increases adult hippocampal neurogenesis in male rats provided it is aerobic and sustained. *J Physiol* **594**: 1855–73.

Norton K, Norton L, Sadgrove D (2010). Position statement on physical activity and exercise intensity terminology. *J Sci Med Sport* **13**: 496–502.

Nummenmaa L, Hirvonen J, Hannukainen JC, Immonen H, Lindroos MM, Salminen P, *et al* (2012). Dorsal striatum and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. *PLoS One* **7**: e31089.

Nummenmaa L, Manninen S, Tuominen L, Hirvonen J, Kalliokoski KK, Nuutila P, *et al* (2015). Adult attachment style is associated with cerebral μ-opioid receptor availability in humans. *Hum Brain Mapp* **36**: 3621–8.

Nummenmaa L, Saanijoki T, Tuominen L, Hirvonen J, Tuulari JJ, Nuutila P, *et al* (2018a). μ-opioid receptor system mediates reward processing in humans. *Nat Commun* **9**: 1500.

Nummenmaa L, Tuominen L (2017). Opioid system and human emotions. *Br J Pharmacol.* Advance online publication. doi:10.1111/bph.13812

Nummenmaa L, Tuominen L, Dunbar R, Hirvonen J, Manninen S, Arponen E, *et al* (2016). Social touch modulates endogenous μ-opioid system activity in humans. *Neuroimage* **138**: 242–247.

Nummenmaa L, Tuominen L, Hirvonen J (2018b). Simultaneous PET-MRI Confirms That Cerebral Blood Flow Does Not Confound PET Neuroreceptor Activation Studies. *ACS Chem Neurosci.* **9**: 159-161

O'Connor PJ, Cook DB (1999). Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. *Exerc Sport Sci Rev* **27**: 119–66.

Oh H, Taylor AH (2012). Brisk walking reduces ad libitum snacking in regular chocolate eaters during a workplace simulation. *Appetite* **58**: 387–92.

Oliveira BRR, Slama FA, Deslandes AC, Furtado ES, Santos TM (2013). Continuous and high-intensity interval training: which promotes higher pleasure? *PLoS One* **8**: e79965.

Oliveira MSR de, Silva Fernandes MJ da, Scorza FA, Persike DS, Scorza CA, Ponte JB da, *et al* (2010). Acute and chronic exercise modulates the expression of MOR opioid receptors in the hippocampal formation of rats. *Brain Res Bull* **83**: 278–83.

Peciña S, Smith KS (2010). Hedonic and motivational roles of opioids in food reward: Implications for overeating disorders. *Pharmacol Biochem Behav* **97**: 34–46.

Penedo FJ, Dahn JR (2005). Exercise and well-being: a review of mental and physical health benefits associated with physical activity. *Curr Opin Psychiatry* **18**: 189–93.

Petraglia F, Bacchi Modena A, Comitini G, Scazzina D, Facchinetti F, Fiaschetti D, *et al* (1990). Plasma beta-endorphin and beta-lipotropin levels increase in well trained athletes after competition and non competitive exercise. *J Endocrinol Invest* **13**: 19–23.

Physical Activitity Guidelines Advisory Committee (2008). Physical Activity Guidelines Advisory Committee Report 2008. U.S. Department of Health and Human Services. Available at: https://health.gov/paguidelines/report/pdf/CommitteeReport.pdf

Prossin AR, Love TM, Koeppe RA, Zubieta J-K, Silk KR (2010). Dysregulation of Regional Endogenous Opioid Function in Borderline Personality Disorder. *Am J Psychiatry* **167**: 925–933.

Quelch DR, Katsouri L, Nutt DJ, Parker CA, Tyacke RJ (2014). Imaging endogenous opioid peptide release with [^{11}C]carfentanil and [^{3}H]diprenorphine: influence of agonist-induced internalization. *J Cereb Blood Flow Metab* **34**: 1604–12.

Raedeke TD (2007). The Relationship Between Enjoyment and Affective Responses to Exercise. *J Appl Sport Psychol* **19**: 105–115.

Rahkila P, Hakala E, Alén M, Salminen K, Laatikainen T (1988). Beta-endorphin and corticotropin release is dependent on a threshold intensity of running exercise in male endurance athletes. *Life Sci* **43**: 551–8.

Raichlen DA, Foster AD, Gerdeman GL, Seillier A, Giuffrida A (2012). Wired to run: exercise-induced endocannabinoid signaling in humans and cursorial mammals with implications for the 'runner's high'. *J Exp Biol* **215**: 1331–6.

Raichlen DA, Foster AD, Seillier A, Giuffrida A, Gerdeman GL (2013). Exercise-induced endocannabinoid signaling is modulated by intensity. *Eur J Appl Physiol* **113**: 869–875.

Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS (2015). The impact of high-intensity interval training versus moderate-intensity continuous training on vascular function: a systematic review and meta-analysis. *Sports Med* **45**: 679–92.

Ray CA, Carter JR (2007). Central modulation of exercise-induced muscle pain in humans. *J Physiol* **585**: 287–94.

Reed J, Ones DS (2006). The effect of acute aerobic exercise on positive activated affect: A meta-analysis. *Psychol Sport Exerc* **7**: 477–514.

Reichert FF, Barros AJD, Domingues MR, Hallal PC (2007). The Role of Perceived Personal Barriers to Engagement in Leisure-Time Physical Activity. *Am J Public Health* **97**: 515–519.

Rhodes RE, Kates A (2015). Can the Affective Response to Exercise Predict Future Motives and Physical Activity Behavior? A Systematic Review of Published Evidence. *Ann Behav Med* **49**: 715–731.

Robertson RJ, Noble BJ (1997). Perception of physical exertion: methods, mediators, and applications. *Exerc Sport Sci Rev* **25**: 407–52.

Robison LS, Swenson S, Hamilton J, Thanos PK (2018). Exercise Reduces Dopamine D1R and Increases D2R in Rats. *Med Sci Sport Exerc.* Advance online publication. doi:10.1249/MSS.0000000000001627

Rose EA, Parfitt G (2008). Can the Feeling Scale Be Used to Regulate Exercise Intensity? *Med Sci Sport Exerc* **40**: 1852–1860.

Rose EA, Parfitt G (2012). Exercise experience influences affective and motivational outcomes of prescribed and self-selected intensity exercise. *Scand J Med Sci Sports* **22**: 265–77.

Ruegsegger GN, Toedebusch RG, Will MJ, Booth FW (2015). Mu opioid receptor modulation in the nucleus accumbens lowers voluntary wheel running in rats bred for high running motivation. *Neuropharmacology* **97**: 171–181.

Russell JA (2003). Core affect and the psychological construction of emotion. *Psychol Rev* **110**: 145–72.

Saarimäki H, Gotsopoulos A, Jääskeläinen IP, Lampinen J, Vuilleumier P, Hari R, *et al* (2016). Discrete Neural Signatures of Basic Emotions. *Cereb Cortex* **26**: 2563–2573.

Salmon P (2001). Effects of physical exercise on anxiety, depression, and sensitivity to stress: A unifying theory. *Clin Psychol Rev* **21**: 33–61.

Sander CY, Mandeville JB, Wey H-Y, Catana C, Hooker JM, Rosen BR (2017). Effects of flow changes on radiotracer binding: Simultaneous measurement of neuroreceptor binding and cerebral blood flow modulation. *J Cereb Blood Flow Metab.* Advance online publication. doi:10.1177/0271678X17725418

Scherr J, Wolfarth B, Christle JW, Pressler A, Wagenpfeil S, Halle M (2013). Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol* **113**: 147–55.

Schubert MM, Sabapathy S, Leveritt M, Desbrow B (2014). Acute exercise and hormones related to appetite regulation: a meta-analysis. *Sports Med* **44**: 387–403.

Schwarz L, Kindermann W (1992). Changes in beta-endorphin levels in response to aerobic and anaerobic exercise. *Sport Med* **13**: 25–36.

Scott DJ, Stohler CS, Koeppe RA, Zubieta J-K (2007). Time-course of change in [^{11}C]carfentanil and [^{11}C]raclopride binding potential after a nonpharmacological challenge. *Synapse* **61**: 707–714.

Seeger LL (1989). Physical principles of magnetic resonance imaging. *Clin Orthop Relat Res* 7–16.

Sforzo GA, Seeger TF, Pert CB, Pert A, Dotson CO (1986). In vivo opioid receptor occupation in the rat brain following exercise. *Med Sci Sports Exerc* **18**: 380–4.

Sgherza AL, Axen K, Fain R, Hoffman RS, Dunbar CC, Haas F (2002). Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry. *J Appl Physiol* **93**: 2023–8.

Shaw KA, Gennat HC, O'Rourke P, Mar C Del (2006). Exercise for overweight or obesity. *Cochrane Database Syst Rev* 4: CD003817

Sit CHP, Kerr JH, Wong ITF (2008). Motives for and barriers to physical activity participation in middle-aged Chinese women. *Psychol Sport Exerc* **9**: 266–283.

Smeets PAM, Charbonnier L, Meer F van, Laan LN van der, Spetter MS (2012). Food-induced brain responses and eating behaviour. *Proc Nutr Soc* **71**: 511–520.

Smith-Ryan AE (2017). Enjoyment of high-intensity interval training in an overweight/obese cohort: a short report. *Clin Physiol Funct Imaging* **37**: 89–93.

Smith MA, Lyle MA (2006). Chronic exercise decreases sensitivity to mu opioids in female rats: correlation with exercise output. *Pharmacol Biochem Behav* **85**: 12–22.

Sparling PB, Giuffrida A, Piomelli D, Rosskopf L, Dietrich A (2003). Exercise activates the endocannabinoid system. *Neuroreport* **14**: 2209–11.

Spiga R, Cherek DR, Roache JD, Cowan KA (1990). The effects of codeine on human aggressive responding. *Int Clin Psychopharmacol* **5**: 195–204.

Steptoe A, Edwards S, Moses J, Mathews A (1989). The effects of exercise training on mood and perceived coping ability in anxious adults from the general population. *J Psychosom Res* **33**: 537–47.

Stoeckel LE, Weller RE, Cook EW, Twieg DB, Knowlton RC, Cox JE (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. *Neuroimage* **41**: 636–647.

Stork MJ, Banfield LE, Gibala MJ, Martin Ginis KA (2017). A scoping review of the psychological responses to interval exercise: is interval exercise a viable alternative to traditional exercise? *Health Psychol Rev* **11**: 324–344.

Stutts WC (2002). Physical activity determinants in adults. Perceived benefits, barriers, and self efficacy. *AAOHN J* **50**: 499–507.

Swift DL, Johannsen NM, Lavie CJ, Earnest CP, Church TS (2014). The Role of Exercise and Physical Activity in Weight Loss and Maintenance. *Prog Cardiovasc Dis* **56**: 441–447.

Thayer RE, Newman JR, McClain TM (1994). Self-regulation of mood: strategies for changing a bad mood, raising energy, and reducing tension. *J Pers Soc Psychol* **67**: 910–25.

Thomas DM, Bouchard C, Church T, Slentz C, Kraus WE, Redman LM, *et al* (2012). Why do individuals not lose more weight from an exercise intervention at a defined dose? An energy balance analysis. *Obes Rev* **13**: 835–847.

Thum JS, Parsons G, Whittle T, Astorino TA (2017). High-Intensity Interval Training Elicits Higher Enjoyment than Moderate Intensity Continuous Exercise. *PLoS One* **12**: e0166299.

Titeler M, Lyon RA, Kuhar MJ, Frost JF, Dannals RF, Leonhardt S, *et al* (1989). Mu opiate receptors are selectively labelled by [3H]carfentanil in human and rat brain. *Eur J Pharmacol* **167**: 221–8.

Townsend DW (2004). Physical principles and technology of clinical PET imaging. *Ann Acad Med Singapore* **33**: 133–45.

Townsend LK, Islam H, Dunn E, Eys M, Robertson-Wilson J, Hazell TJ (2017). Modified sprint interval training protocols. Part II. Psychological responses. *Appl Physiol Nutr Metab* **42**: 347–353.

Trezza V, Campolongo P, Vanderschuren LJMJ (2011). Evaluating the rewarding nature of social interactions in laboratory animals. *Dev Cogn Neurosci* **1**: 444–458.

Tryon WW, Goldberg JL, Morrison DF (1992). Activity decreases as percentage overweight increases. *Int J Obes Relat Metab Disord* **16**: 591–5.

Tsatsoulis A, Fountoulakis S (2006). The Protective Role of Exercise on Stress System Dysregulation and Comorbidities. *Ann N Y Acad Sci* **1083**: 196–213.

Tuominen L, Nummenmaa L, Keltikangas-Järvinen L, Raitakari O, Hietala J (2014). Mapping neurotransmitter networks with PET: an example on serotonin and opioid systems. *Hum Brain Mapp* **35**: 1875–84.

Tuominen L, Tuulari J, Karlsson H, Hirvonen J, Helin S, Salminen P, *et al* (2015). Aberrant mesolimbic dopamine–opiate interaction in obesity. *Neuroimage* **122**: 80–86.

Tuso P (2015). Strategies to Increase Physical Activity. *Perm J* **19**: 84–8.

Tuulari JJ, Tuominen L, Boer F de, Hirvonen J, Helin S, Nuutila P, *et al* (2017). Feeding releases endogenous opioids in humans. *J Neurosci* **37**: 8284–8291.

Tzourio-Mazoyer N, Landeau B, Papathanassiou D, Crivello F, Etard O, Delcroix N, *et al* (2002). Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *Neuroimage* **15**: 273–289.

Vasankari T, Kolu P, Kari J, Pehkonen J, Havas E, Tammelin T, *et al* (2018). Liikkumattomuuden lasku kasvaa – vähäisen fyysisen aktiivisuuden ja heikon fyysisen kunnon yhteiskunnalliset kustannukset. Available at: http://urn.fi/URN:ISBN:978-952-287-535-8.

Vella CA, Taylor K, Drummer D (2017). High-intensity interval and moderate-intensity continuous training elicit similar enjoyment and adherence levels in overweight and obese adults. *Eur J Sport Sci* **17**: 1203–1211.

Vollaard NBJ, Metcalfe RS (2017). Research into the Health Benefits of Sprint Interval Training Should Focus on Protocols with Fewer and Shorter Sprints. *Sport Med* **47**: 2443–2451.

Voss MW, Vivar C, Kramer AF, Praag H van (2013). Bridging animal and human models of exercise-induced brain plasticity. *Trends Cogn Sci* **17**: 525–544.

Wager TD, Scott DJ, Zubieta J-K (2007). Placebo effects on human mu-opioid activity during pain. *Proc Natl Acad Sci U S A* **104**: 11056–61.

Wahl P, Mathes S, Köhler K, Achtzehn S, Bloch W, Mester J (2013). Acute metabolic, hormonal, and psychological responses to different endurance training protocols. *Horm Metab Res* **45**: 827–33.

Wang GJ, Volkow ND, Fowler JS, Franceschi D, Logan J, Pappas NR, *et al* (2000). PET studies of the effects of aerobic exercise on human striatal dopamine release. *J Nucl Med* **41**: 1352–6.

Wansink B, Sobal J (2007). Mindless Eating. *Environ Behav* **39**: 106–123.

Warburton DER, Nicol CW, Bredin SSD (2006). Health benefits of physical activity: the evidence. *CMAJ* **174**: 801–9.

Watson D, Clark LA, Tellegen A (1988). Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* **54**: 1063–70.

Wenzel JM, Cheer JF (2017). Endocannabinoid Regulation of Reward and Reinforcement through Interaction with Dopamine and Endogenous Opioid Signaling. *Neuropsychopharmacology* **43**:103-115.

Weston KS, Wisløff U, Coombes JS (2014). High-intensity interval training in patients with lifestyle-induced cardiometabolic disease: a systematic review and meta-analysis. *Br J Sports Med* **48**: 1227–1234.

WHO (2017). Depression and Other Common Mental Disorders: Global Health Estimates. Geneva: World Health Organization. Available at: http://www.who.int/mental_health/management/depression/prevalence_global_health_estimates/en/

Wienke B, Jekauc D (2016). A Qualitative Analysis of Emotional Facilitators in Exercise. *Front Psychol* **7**: 1296.

Williams DM (2008). Exercise, affect, and adherence: an integrated model and a case for self-paced exercise. *J Sport Exerc Psychol* **30**: 471–96.

Williams DM, Dunsiger S, Ciccolo JT, Lewis BA, Albrecht AE, Marcus BH (2008). Acute Affective Response to a Moderate-intensity Exercise Stimulus Predicts Physical Activity Participation 6 and 12 Months Later. *Psychol Sport Exerc* **9**: 231–245.

Williams DM, Dunsiger S, Jennings EG, Marcus BH (2012). Does Affective Valence During and Immediately Following a 10-Min Walk Predict Concurrent and Future Physical Activity? *Ann Behav Med* **44**: 43–51.

Wilson MA, Junor L (2008). The Role of Amygdalar Mu-Opioid Receptors in Anxiety-Related Responses in Two Rat Models. *Neuropsychopharmacology* **33**: 2957–2968.

Wipfli BM, Rethorst CD, Landers DM (2008). The anxiolytic effects of exercise: a meta-analysis of randomized trials and dose-response analysis. *J Sport Exerc Psychol* **30**: 392–410.

Wisloff U, Stoylen A, Loennechen JP, Bruvold M, Rognmo O, Haram PM, *et al* (2007). Superior Cardiovascular Effect of Aerobic Interval Training Versus Moderate Continuous Training in Heart Failure Patients: A Randomized Study. *Circulation* **115**: 3086–3094.

Yeung RR (1996). The acute effects of exercise on mood state. *J Psychosom Res* **40**: 123–141.

Zschucke E, Renneberg B, Dimeo F, Wüstenberg T, Ströhle A (2015). The stress-buffering effect of acute exercise: Evidence for HPA axis negative feedback. *Psychoneuroendocrinology* **51**: 414–25.

Zubieta J-K (2001). Regional Mu Opioid Receptor Regulation of Sensory and Affective Dimensions of Pain. *Science (80-)* **293**: 311–315.

Zubieta J-K, Dannals RF, Frost JJ (1999). Gender and age influences on human brain mu-opioid receptor binding measured by PET. *Am J Psychiatry* **156**: 842–8.

Zubieta J-K, Ketter TA, Bueller JA, Xu Y, Kilbourn MR, Young EA, *et al* (2003). Regulation of human affective responses by anterior cingulate and limbic mu-opioid neurotransmission. *Arch Gen Psychiatry* **60**: 1145–53.

Zubieta J-K, Smith YR, Bueller JA, Xu Y, Kilbourn MR, Jewett DM, *et al* (2002). mu-opioid receptor-mediated antinociceptive responses differ in men and women. *J Neurosci* **22**: 5100–7.

Annales Universitatis Turkuensis

Turun yliopisto
University of Turku

ISBN 978-951-29-7282-1 (PRINT)
ISBN 978-951-29-7283-8 (PDF)
ISSN 0355-9483 (Print) | ISSN 2343-3213 (Online)

Painosalama Oy, Turku, Finland 2018