UMEÅ UNIVERSITY

SUPRAMAXIMAL HIGH-INTENSITY INTERVAL TRAINING FOR OLDER ADULTS

MOTIVATION, APPLICABILITY, PHYSIOLOGICAL AND COGNITIVE EFFECTS

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"All we have to decide is what to do with the time that is given to us."

– J.R.R. Tolkien

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Abstract

Background: Regular physical exercise can counteract age-related physiological and cognitive decline, reduce the risk of disease, and improve quality of life. Even so, a considerable proportion of older adults are insufficiently physically active. Supramaximal high-intensity interval training (HIT) is a potential time-efficient, effective, and appealing alternative to longer duration moderate-intensity training (MIT). Research also indicates promising effects from supramaximal HIT for older adults, but the interpretation of these results is limited to a few small studies, highlighting a need for larger, high-quality randomized controlled trials (RCT) for this population. The aims of this thesis were to investigate motivational aspects of physical exercise, and controlled supramaximal HIT in particular; and to examine the applicability and effects of controlled supramaximal HIT in comparison to aerobic MIT, among older adults not engaged in regular physical exercise.

Methods: This thesis comprises four research papers, totaling 117 participants (64-79 years old, 56% women). *Paper I* used cross-sectional data from 49 participants to investigate a neurobiological link between dopamine and exercise-related motivation. *Papers II-IV* used data from the Umeå HIT Study, an RCT with 68 participants, to examine applicability and effects from 3 months of twice-weekly controlled supramaximal HIT (10×6-sec intervals, 20 minutes in total) compared to MIT (3×8-min intervals, 40 minutes in total). Both groups exercised on stationary bicycles in a group setting. All participants in the Umeå HIT study received medical clearance before the training started. *Paper II* described the applicability of controlled supramaximal HIT and its effect on exercise-related motivation. *Paper III* examined the effects on physiological and cognitive functions, such as cardiorespiratory fitness and global cognitive function. *Paper IV* used data from 42 participants on structural and functional magnetic resonance imaging (MRI) to investigate the effects of the exercise on the hippocampus and episodic memory.

Results: *Paper I* indicated a positive association between self-reported exercise motivation and dopamine D2-receptor availability in the frontal parts of the brain. *Paper II* showed that non-exercising, but otherwise relatively healthy older adults were able to exercise at supramaximal training intensities without compromising their physical and mental well-being during the training, or their exercise motivation. The participation was high, and no serious adverse events occurred. Notably, the participants performing supramaximal HIT reported more positive and fewer negative exercise-related events compared to the participants performing MIT. The results from *Paper III* showed that three months of controlled supramaximal HIT resulted in similar but also additional effects compared to MIT, despite the total training time being halved. Both groups improved fitness and cardiovascular function, and in favor of supramaximal HIT there was an improvement in muscular function. Neither group showed an effect on global cognitive function, but a potential improvement in working memory was observed in favor of supramaximal HIT. While the effects on episodic memory were mixed, *Paper IV* observed associations between change in cardiorespiratory fitness and change in hippocampus function for the CA4/DG subfield during pattern completion, which in turn was associated with episodic memory improvements in pattern completion.

Conclusion: Overall, this thesis supports controlled supramaximal HIT as an effective and appealing training method for older adults, which can make meaningful contributions to their independence in daily life activities. Although the connection between motivation, dopamine, and aging requires further research, an interesting observation in this thesis was that, contrary to previous concerns, controlled supramaximal HIT had no negative impact on the participants' motivation. Controlled supramaximal HIT can be a meaningful addition to the exercise programs commonly available for older adults, as providing more tailored and individualized training may contribute to promoting physical exercise for health and well-being. The cognitive effects of supramaximal HIT were mixed, and future studies should aim for longer interventions and more pronounced physiological changes. Further, research should evaluate controlled supramaximal HIT in a broader population, including individuals with chronic conditions and diseases, and explore how this form of exercise can be effectively implemented in everyday settings.

Sammanfattning på svenska

Att vara regelbundet fysiskt aktiv kan vara ett effektivt sätt att förbättra och bibehålla fysiologiska och kognitiva funktioner som är viktiga för att upprätthålla självständighet och välbefinnande i sin vardag. Vidare är fysisk inaktivitet en av de stora riskfaktorerna kopplade till flertalet sjukdomar, däribland en ökad risk för demens. Med en åldrande befolkning och stigande siffror gällande fysisk inaktivitet behövs fler effektiva och anpassade träningsmetoder som främjar en ökad fysisk aktivitet över tid och högre upp i åldrarna. Supramaximal högintensiv intervallträning (HIT) är ett tidseffektivt och tilltalande alternativ till träning på måttlig intensitet. Forskning pekar på lovande resultat även för äldre, men resultaten är begränsade till få små studier. Det finns ett behov av större randomiserade kontrollerade studier av högre kvalité. Dessutom har oro uttryckts angående säkerhet och tolerans för supramaximal HIT bland äldre och otränade, vilket ifrågasatt träningsformens lämplighet. Syftet med denna avhandling var att undersöka genomförbarhet och effekter av ett supramaximalt HIT-program anpassat för äldre personer, samt aspekter av motivation kopplat till fysisk träning.

Denna avhandling består av fyra delarbeten och inkluderar totalt 117 äldre personer som vid tiden för inkludering inte deltog i regelbunden fysisk träning. *Delarbete I* använde tvärsnittsdata från 49 deltagare för att undersöka en neurobiologisk koppling mellan dopamin och motivation till träning. *Delarbete II-IV* använde data från Umeå HIT-studien, en randomiserad kontrollerad träningsstudie med 68 deltagare, för att undersöka genomförbarheten och effekterna av tre månaders kontrollerad supramaximal HIT (tio 6-sekunders intervaller, totalt 20 minuter), jämfört med konditionsträning på måttlig intensitet (tre 8-minutersintervaller, totalt 40 minuter). Alla Umeå HIT-deltagare genomgick en medicinsk bedömning innan träningen påbörjades. Båda grupperna genomförde träningen två gånger i veckan på stationära cyklar i grupp. *Delarbete II* använde data insamlad under träningspassen för att beskriva genomförbarheten av kontrollerad supramaximal HIT, samt data från före och efter träningsperioden för att utvärdera träningens effekt på motivation. *Delarbete III* fortsatte att undersöka träningens effekter på olika fysiologiska och kognitiva mått såsom kondition och global kognition. *Delarbete IV* använde data från 42 av deltagarna i HIT-studien som även genomgick strukturell och funktionell hjärnavbildning med magnetkamera (MRI) för att undersöka

effekter av träningen på Hippocampus – ett område i hjärnan som är viktigt för bildandet av nya minnen och återkallning av lagrade minnen.

Resultaten i denna avhandling visar att tre månaders kontrollerad supramaximal HIT ger likvärdiga förbättringar som träning på måttlig intensitet, men också ytterligare effekter, trots en halverad total träningstid. Båda grupperna förbättrade kondition och kardiovaskulär funktion, medan supramaximal HIT dessutom ledde till en förbättrad benstyrka. Ingen av träningsmetoderna visade effekt på global kognitiv funktion, men en potentiell förbättring i arbetsminne observerades till fördel för supramaximal HIT. Även om effekterna på episodiskt minne var blandade, tyder resultaten från den sista delstudien på att förbättrad prestation i episodiskt minne efter träning kan bero på funktionella förändringar i Hippocampus till följd av förbättrad kondition. Resultaten visar även att äldre personer, som innan träningsperioden inte deltog i regelbunden träning, klarade av att träna på supramaximal intensitet utan att äventyra sitt fysiska eller psykiska välbefinnande under perioden. Träningsnärvaron var hög och jämförbar med gruppen som tränade på måttlig intensitet. Inga allvarliga biverkningar inträffade, och deltagarna i supramaximal HIT rapporterade färre tillfälliga biverkningar (exempelvis träningsvärk), samt fler positiva träningsrelaterade upplevelser. Deras motivation till träning påverkades inte heller negativt under träningsperioden. Resultaten från det första delarbetet visade på en association mellan motivation och receptortillgängligheten för dopamin i de främre delarna av hjärnan.

Sammantaget stöder denna avhandling att kontrollerad supramaximal HIT kan vara en effektiv och tilltalande träningsmetod för äldre, och kan bidra meningsfullt till deras självständighet och vardagliga liv. Även om sambandet mellan motivation, dopamin och åldrande kräver vidare forskning, var en intressant observation att kontrollerad supramaximal HIT inte hade någon negativ inverkan på deltagarnas motivation, i motsats till tidigare farhågor. Träningsformen kompletterar de träningsprogram som vanligtvis erbjuds äldre personer, och att erbjuda mer skräddarsydd och individanpassad träning kan främja fysisk aktivitet för både hälsa och välbefinnande. De kognitiva effekterna av supramaximal HIT var blandade, och framtida studier bör fokusera på längre interventioner med fler upprepade mätningar och mer uttalade fysiologiska förändringar för att undersöka sambandet mellan kognition, träning och träningsintensitet. Vidare bör forskningen också utvärdera kontrollerad supramaximal HIT i en bredare population, inklusive individer med kroniska tillstånd och sjukdomar, samt undersöka hur denna träningsform effektivt kan implementeras i vardagliga sammanhang.

Abbreviations

BOLD – Blood-Oxygen-Level-Dependent

BPND – Non-Displaceable Binding Potential

BREQ-2 – Behavioural Regulation in Exercise Questionnaire-2

CRF – Cardiorespiratory Fitness

D2R – Dopamine D2-family of receptors (D2, D3, D4)

DG – Dentate Gyrus

FS – Feeling scale

HIT – High-Intensity Interval Training

HRR – Heart Rate Reserve

LMM – Linear Mixed-Effects Models

MAP – Maximum Aerobic Power (w)

MIT – Moderate-Intensity Training

MPO6 – maximal Mean Power Output for 6 seconds (w)

MRI – Magnetic Resonance Imaging

PET – Positron Emission Tomography

PHIBRA Study - Physical Influences on Brain in Aging Study

PPO – Peak Power Output

RAI – Relative Autonomy Index

RCT – Randomized Controlled Trial

ROI – Region of Interest

RPE – Rate of Perceived Exertion

RPM – Revolutions per Minute

SDT – Self-Determination Theory

TPO – Target Power Output

Umeå HIT Study –Umeå Hight-Intensity Interval Training Study

VO2max – Maximal rate of Oxygen Consumption

VO2peak – Peak rate of Oxygen Consumption

Definitions

Adherence (intensity)	To what degree the participant was able to achieve the prescribed exercise interval intensity
Attendance (session)	To what degree the participant attended the exercise session
HIT	High-intensity interval training (HIT) is defined as short and repeated work intervals at an intensity close to (80%–100%), or above (>100%) the external intensity (i.e., power in watts) that elicits maximum oxygen uptake ($\dot{V}O_2max$), interspersed with periods of recovery[1]
Older adults	The older adults referred to in this thesis are generally adults aged 65 years or older
Physical Activity	Any bodily movement produced by skeletal muscles that results in energy expenditure[2]
Physical Exercise	A subset of physical activity that is planned, structured, and repetitive, with a goal to improve or physical fitness[2]
Supramaximal HIT	Supramaximal high-intensity interval training (HIT) refers to short and repeated work intervals a an external training intensity higher (i.e., supra) than that which elicits maximal oxygen uptake[1,3], but not necessarily being a maximal all-out effort

Original papers

This thesis is based on the following four papers. The thesis will refer to these papers by their Roman numerals (I-IV). The original paper I and paper II are reproduced under the CC BY 4.0 license, and paper III under the CC BY-NC 4.0 License.

I. Simonsson E, Stiernman LJ, Lundquist A, Rosendahl E, Hedlund M, Lindelöf N, Boraxbekk CJ. Dopamine D2/3-receptor availability and its association with autonomous motivation to exercise in older adults: An exploratory [11C]-raclopride study. Front Hum Neurosci. 2022 Nov 11;16:997131. doi: 10.3389/fnhum.2022.997131

II. *Frykholm E, *Simonsson E, Levik Sandström S, Hedlund M, Holmberg H, Johansson B, Lindelöf N, Boraxbekk CJ, Rosendahl E. Applicability of a supramaximal high-intensity interval training program for older adults previously not engaged in regular exercise; analyses of secondary outcomes from the Umeå HIT Study. Psychol Sport Exerc. 2024 Jul;73:102647. doi: 10.1016/j.psychsport.2024.102647

III. Simonsson E, Levik Sandström S, Hedlund M, Holmberg H, Johansson B, Lindelöf N, Boraxbekk CJ, Rosendahl E. Effects of Controlled Supramaximal High-Intensity Interval Training on Cardiorespiratory Fitness and Global Cognitive Function in Older Adults: The Umeå HIT Study-A Randomized Controlled Trial. J Gerontol A Biol Sci Med Sci. 2023 Aug 27;78(9):1581-1590. doi: 10.1093/gerona/glad070

IV. Simonsson E, [Co-authors], Boraxbekk C-J. Functional changes in hippocampus activity during pattern completion are related to improved fitness and performance improvements (Manuscript)

* These authors share first authorship.

Introduction

Aging is an inevitable and universal process that impacts all individuals throughout their lives, with most people today being fortunate enough to experience old age. While acknowledging that no universal threshold exists for the term “older adults”, this thesis generally refers to adults aged 65 years or older. In 2020, the global population of individuals aged 65 and older exceeded 700 million, a figure projected to double by 2050, which will raise the proportion of older adults from 9% to 16%[4]. In Sweden, the proportion of older adults is already higher than 20% and is expected to increase to 25% by 2070[5]. This rise in life expectancy, along with the demographic shift towards an aging population, presents both opportunities and challenges for individuals and society. For older adults to maintain independence and a high quality of life, it is important to sustain both physiological and cognitive functions while delaying the onset of disease and disability. One way to support this is through regular physical exercise[6,7].

This thesis delves into the multifaceted aspects of aging and physical exercise, and sits within the fields of sports medicine, psychology, cognitive neuroscience, physiotherapy, and gerontology. The goal was to provide insights into the role of physical exercise in promoting healthy aging, focusing on potential barriers, benefits, and experiences associated with exercise among older adults, particularly with regards to the exercise form supramaximal high-intensity interval training (HIT). Hopefully, this thesis will contribute to the development of more effective training strategies for enhancing health in older age.

Ageing and Physical Exercise

Ageing and older age is accompanied by gradual changes in multiple bodily systems accompanied by decreasing capacities. These age-related changes are often non-linear and vary widely among individuals, but they tend to accelerate as people age[8,9]. While part of the aging process is inevitable, influenced by time and genetics, it can also be accelerated by lifestyle and environmental factors. However, these factors can be mitigated or prevented[10]. Sustaining cardiorespiratory and muscular capacities is important for supporting overall functional performance and reducing the risk of frailty and disability. Equally important is maintenance of cognitive functions that are closely tied to the ability to live independently[7,11].

A widely used indicator of overall health and disease risk is Cardiorespiratory fitness (CRF). While the influence of other factors, such as genetics, should not be overlooked[12], multiple studies have shown an inverse relationship between CRF and conditions such as hypertension, cardiovascular disease, and all-cause mortality[13–15]. CRF is typically measured as maximal aerobic capacity, also known as maximal oxygen uptake (VO_2max). On average, VO_2max declines by about 1% per year starting at age 30, with an accelerated decline of 1.5-2% per year from around the age of 60[9,16,17]. The decline in VO_2max is partly due to an inevitable decrease in maximal heart rate with age, but the decline in maximal cardiac output can be mitigated by a physically active lifestyle or accelerated by a sedentary lifestyle[18,19]. Low CRF not only increases the risk of disease and death but also results in a greater physiological strain from daily activities usually considered low or moderate intensity, such as walking up the stairs or vacuum-cleaning.

Just like CRF, muscular functions undergo age-related changes, including reduced strength, slower muscle recruitment, and impaired balance[20,21]. Such changes increase the risk of falls[22,23]. Physical exercise can reduce the risk of falls, and contribute to improving, or at least maintaining muscle function, balance, and functional capabilities in daily activities[24,25].

In the brain, noticeable structural and functional changes occur as we age[26–28], impacting cognitive functions and memory[8,29]. One of the more age-sensitive cognitive domains is episodic memory, which is associated with a more pronounced decline from around the age of 60[8]. Episodic memory refers to memories of events that are connected to a context of time and place[30], and age-related decline in episodic memory has been linked to structural and functional changes in the hippocampus[31–33]. This brain region manages information by distinguishing and completing patterns[34], processes essential for successful memory formation and memory recall. Maintained hippocampal integrity has been linked to better memory aging[32,35], and deficits in pattern completion processing are thought to underly the more general deficits in cognitive aging and age-related decline in episodic memory[36]. Notably, the hippocampus appears to be one of the more plastic brain regions responsive to exercise-induced changes[37,38]. Some studies have found that increases in cardiorespiratory fitness from aerobic exercise at moderate intensity are associated with increased or maintained hippocampal volume[39,40], with potentially added benefits from higher intensities for episodic memory[41]. However, while research indicates benefits for both overall and specific cognitive abilities, the effects are relatively small, and our causal understanding of the neural mechanisms behind CRF-induced brain changes and their effects on cognition is limited[42–45].

The evidence of benefits from regular physical exercise in aging is comprehensive[46–49], and exercise can serve as a multifaceted approach for targeting several modifiable risk factors associated with common non-communicable diseases, such as cardiovascular disease and dementia[11,13,50]. Furthermore, physical exercise not only enhances physical functions and functional performance but, under the right conditions, can also be enjoyable, and has the potential to boost self-confidence, sense of capability, and psychological well-being[51–53]. Despite these compelling evidence, accompanied with global and national guidelines for physical activity and exercise[54,55], the number of older adults adhering to the physical activity guidelines is concerningly low. Recent numbers suggest that only about 14% of older adults world-wide meet the guidelines[56]. Sweden was ranked as one of the most active countries in Europe, yet only 35.5% of adults aged 18 years or older meet the guidelines, a number that decrease with age[57]. The guidelines include 150 to 300 minutes of aerobic exercise at moderate-intensity, or 75-150 minutes of vigorous (high) intensity, or an equivalent combination of moderate-to-high intensity during the week[54,55]. Notably, aerobic exercise at a higher intensity is included in the recommendations also for older adults, and even small amounts of intense physical activity are associated with lower mortality risk[58]. Still, the range of exercise programs targeted towards older adults often focus on low- and medium-intensity training, and older adults seem to rarely challenge themselves with brief and intense bouts of activities.

To effectively promote physical exercise among older adults, it is important to understand the motivation for – as well as barriers to – regular exercise. Common reasons to not exercise are perceived lack of time and competing priorities[52,53,59], which can be tied to motivation and misconceptions regarding exercise having to be extensive and time-consuming to make any difference. However, higher training intensity offers a time-efficient alternative[60,61]. Further on, this thesis will focus on motivational aspects of physical exercise, and high-intensity training specifically adapted for older adults.

High-Intensity Interval Training (HIT)

Physical exercise generally refers to physical activity that is planned, structured, and repetitive[2]. With principles of overload and specificity, exercise programs are often structured around components such as frequency, intensity, time, and type to induce different physiological improvements. A primary aim with aerobic training is to improve cardiorespiratory fitness, such as increasing the maximal aerobic capacity ($\dot{V}O_2$max). There is more than one approach to improve $\dot{V}O_2$max, and training sessions are modified in duration and intensity to induce different stimulus on the bodily systems involved. The duration of a training session and a work interval is often related to the level of intensity to be performed (Figure 1). In general, lower intensities can be performed for longer continuous work bouts, as in aerobic training at moderate intensities, while higher intensities can be sustained only for shorter durations as in high-intensity interval training (HIT). The intensity of a training session or work interval generally relates to the level of physical effort performed in relation to a physiological anchor, and prescribed as a percentage of the maximal capacity of that anchor. In aerobic training at moderate intensity, it is common to prescribe the intensity as a percentage of maximal heart rate or maximal aerobic capacity (maximal rate of oxygen consumption, $\dot{V}O_2$max). When exercising at external intensities above the maximal aerobic capacity, as in some HIT sessions, other physiological anchors may be of more relevance, such as the maximal ability to generate force quickly (i.e., peak power output, PPO)[62,63]. While there are multiple options for determining and prescribing training intensity[62], and the terminology and boundaries for different intensities vary across the literature[64]. This thesis will mainly distinguish between moderate-, high-, and supramaximal training intensities (Figure 1), and relate these intensities to external intensity (power in watts), objective internal intensity (HR and $\dot{V}O_2$), and subjective internal intensity (rate of perceived exertion, RPE).

To maximize the time-efficient benefits of aerobic training, a proposed key factor is to increase the intensity beyond moderate training intensities, as in HIT[65]. While aerobic moderate-intensity training (MIT) generally refers to longer continuous work bouts (minutes to hours) at intensities below the anaerobic threshold, HIT is broadly defined as short (seconds to minutes), repeated work intervals at an intensity above the anaerobic threshold and interspersed with periods of recovery[1]. The term HIT often includes training intensities both close to (80%–100%) and above (>100%) the external intensity (i.e., power in watts) that elicits $\dot{V}O_2$max (maximal aerobic power, MAP). However, for supramaximal HIT (in some literature referred to as sprint interval training[64]), the focus is solely on short-duration intervals (≤ 30 seconds) at work intensities above (i.e., supra) that which elicits $\dot{V}O_2$max[3,65].

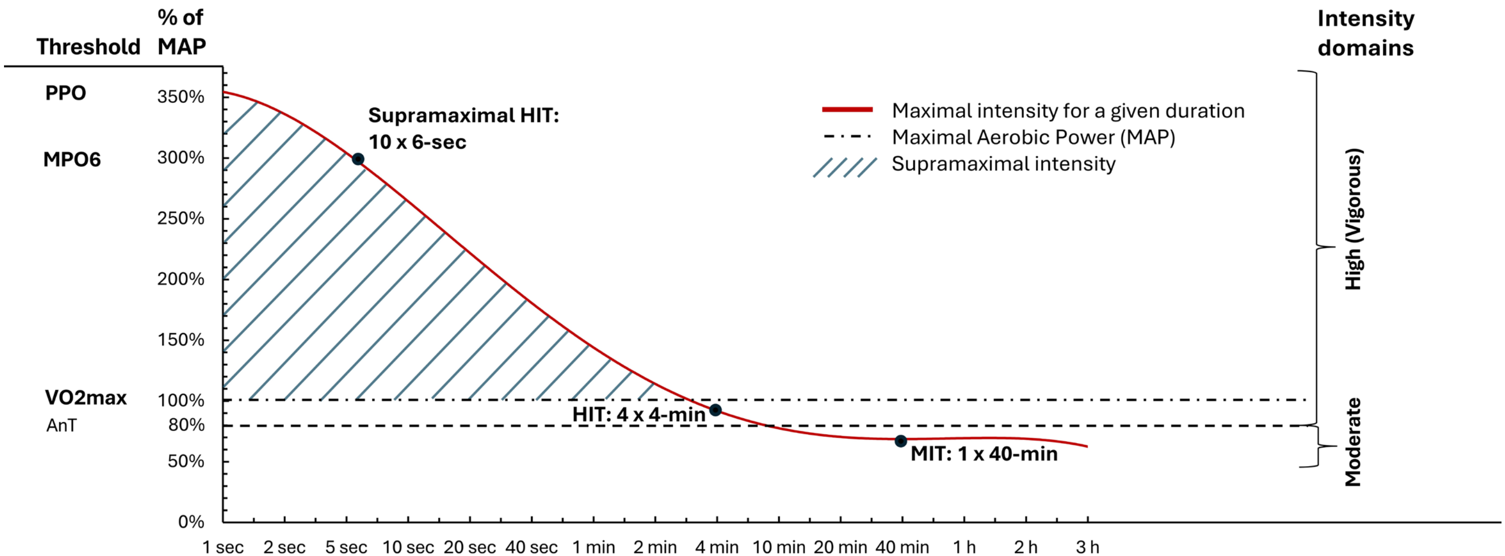


Figure 1. An illustration of the maximal intensity-duration relationship (solid red line) as a percentage of maximal aerobic power (MAP, dot-dashed line), along with examples of three training protocols with different numbers of intervals, intensities, and durations. The solid red line represents the maximal mean power output for given durations as a percentage of MAP (i.e., the external training intensity that elicits VO_2max). In this thesis, supramaximal training intensities refers to external training intensities above MAP (dot-dashed line); high-intensity training is referred to training intensities between the anaerobic threshold (AnT) and the MAP; and moderate-intensity training refers to intensities below AnT. Supramaximal HIT (10 x 6-s) is the type of training protocol investigated in this thesis and is performed at an external training intensity above MAP (dot-dashed line). HIT (4 x 4-min) is a more common form of HIT performed at an external intensity below MAP. MIT (1 x 40-min) is performed for longer durations and at an external intensity below AnT. Abbreviations: MAP = maximal aerobic power; PPO = peak power output; MPO6 = maximal mean power output for 6 seconds; VO_2max = maximum rate of oxygen consumption; AnT = Anaerobic threshold; HIT = high-intensity interval training; MIT = moderate-intensity training.

Supramaximal HIT

The short-duration intervals in supramaximal HIT can be performed at external target intensities reaching up to five times the intensity output during MIT (Figure 1). Despite a lower time commitment, higher training intensities can produce greater metabolic stress on bodily systems. For example, supramaximal HIT can efficiently improve peripheral factors that influence VO_2max, such as increasing the number of capillaries that supply oxygen and nutrients to muscles and improve the efficiency of mitochondrial energy production[65,66]. Supramaximal HIT can also improve cardiovascular and metabolic health markers such as blood pressure and insulin sensitivity[67–70], and studies comparing effects of supramaximal HIT and MIT have shown similar and superior improvements from supramaximal HIT in cardiorespiratory fitness and cardiometabolic functions[71–74].

Additionally, supramaximal HIT recruits more fast-twitch muscle fibers, which can lead to improvements in muscle function and strength[75–77]. Although research on the impact of supramaximal HIT on brain function and cognition is limited, it has the potential to enhance metabolic responses and key mediators such as IGF-1 and PGC-1α[78,79]. In turn, these factors may regulate neurotrophic factors important for brain health, such as BDNF, involved in neural growth and remodeling[80–82]. While aerobic capacity is strongly associated with reduced risk for cardiovascular disease and all-cause mortality[14,15], anaerobic and muscular functions are important for functional abilities involved in everyday tasks[24,83].

There are sound theoretical reasons to believe that the anaerobic aspects of supramaximal HIT may be particularly effective and important for older adults. As people age, aerobic capacity (VO_2max) tends to decline faster than anaerobic capacity and muscle strength[21,84–86]. This is due to a natural reduction in the heart's maximum rate, regardless of training. However, when training intensity is primarily related to the aerobic capacity, as in MIT, older adults may over time perform training at a progressively lower intensity relative to their anaerobic capacity and muscle strength. This potentially reduces the effects from the training, and over time augments decline in anaerobic capacity and muscle function due to insufficient activation of these capacities. Supramaximal HIT with very short intervals places more emphasis on muscle strength and anaerobic power, while also affecting aerobic capacity, making it a potentially important training method to study in older adults.

Previous studies of supramaximal HIT for older adults show promising results, such as improvements in both aerobic, anaerobic, and muscular functions[67,75,87]. Nonetheless, these studies have a series of limitations, including small sample sizes, use of inactive control groups, or even the absence of control conditions altogether, strict experimental protocols, and one-to-one supervision requirements. This limits the scope for interpreting the results, as well as reduces the potential for large-scale implementation. Especially for older adults, there is a need for large and high-quality randomized controlled trials (RCT)[3,71,88].

The few existing studies on Supramaximal HIT among older adults show promising numbers for attendance[67,89], however the applicability and safety of supramaximal HIT is still quite unexplored. In addition, concerns have been raised regarding the safety and tolerance of repeated all-out sprint intervals with uncontrolled target intensity among older and untrained individuals, questioning its appropriateness and applicability within this population[90,91]. On one side, there are doubts regarding older adults' ability to reach intensities high enough to gain the desired benefits, while conversely there are concerns about the adverse effects of excessively high intensity for the population in question[90–92]. It has been argued that supramaximal HIT programs are too excessive, and that accompanied high perceived exertion, negative responses in affective state, and minor adverse events, may result in exercise intolerance and low attendance[92,93]. For example, with all-out efforts, an increased risk of overshooting exercise interval intensity[94] leading to physical discomfort and nausea[95], may potentially decrease attendance and adherence to the training program[92]. While the debate questions whether older and untrained individuals should engage in supramaximal HIT at all, it also highlights the importance of considering the potential motivational implications of negative affect and minor adverse events[93]. To conclude, much remains to be investigated regarding the applicability and effects of supramaximal HIT for older and untrained individuals.

Controlled Supramaximal HIT for Older Adults

A controlled supramaximal HIT-protocol for older adults has been developed with emphasis put on the previously mentioned concerns and with the aim of being both safe, applicable, and enjoyable[96]. This protocol involves ten six-second intervals to be performed at a controlled external training intensity in watts, interspersed with recovery. The protocol was developed for training on a stationary bicycle. Key features of this protocol include the use of standardized pedaling cadence and individual adjustment of resistance load. This enables controlled regulation of the desired target intensity to be performed during each interval and across training sessions, which may decrease the risk of both over- and undershooting the desired interval intensity[94], as well as reduce issues of delayed but excessive responses in heart rate and perceived exertion related to overshooting intensity[1]. The training intensity is based on each person's individual capacity for a six-second work and prescribed as the external target power output (TPO) in watts, and the progression of intensity across sessions follows a set of standardized criteria. This approach enables starting a training period at a supramaximal intensity but below one's maximal capacity, together with a standardized procedure to individually progress the training intensity over time. Another difference is that, compared to previous protocols performed with one-on-one supervision, this controlled supramaximal HIT protocol can be applied in a group setting with the participants themselves adjusting the resistance load.

This controlled supramaximal HIT protocol has been deemed feasible among a group of older adults already engaged in physical exercise[96], and a next step is to evaluate the applicability and effects of this protocol among older adults not engaged in regular physical exercise.

Exercise-Related Motivation

Motivation can generally be defined as a driving force affecting the direction and intensity of behavior initiation and behavior maintenance[97,98]. Within the context of exercise-related motivation, one of the major theoretical frameworks used is the Self-Determination Theory (SDT)[99,100]. The SDT is a macro theory emphasizing the differences in the quality of various types of motivation that drive behavior, ranging from being more controlled and externally driven, to more autonomous and self-determined (Figure 2)[101].

From a neurocognitive perspective, it has been proposed that the dopaminergic system plays a role in the facilitation of autonomous motivation[102]. Dopamine is a neurotransmitter central to the neurobiology of motivation that contributes to the reinforcement of behaviors, such as enhancing a positive experience[97]. It is involved in the initiation of physically effortful behaviors[103], and reduced dopamine D2 receptor (D2R) availability has been associated with lower levels of physical efforts[104,105].

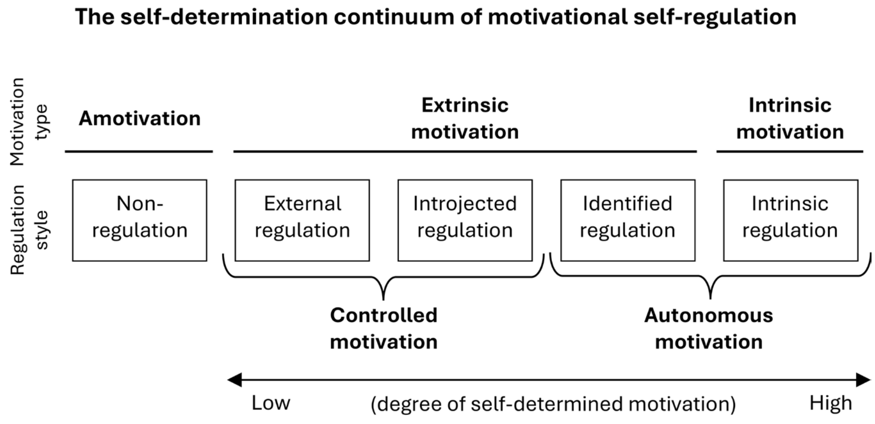


Figure 2. A simplified model of the self-determination continuum of motivation types and regulation styles from the Self-Determination Theory (SDT) [106] included in the Behavioural Regulation in Exercise Questionnaire-2 (BREQ-2, [107]). The SDT emphasizes the difference in quality among distinct types of motivation that regulates behaviors. Intrinsic motivation is the highest quality motivation driven by internal rewards, and engagement in the activity is enjoyable and fulfilling. In comparison, behaviors can be driven by more extrinsic forms of motivation, ranging from more controlled and external rewards towards more autonomous and self-determined. While controlled motivation involves external pressures or obligations, autonomous motivation involves a sense of volition, choice, and self-control[101].

Neuroimaging research on the intrinsic regulation of motivation has primarily focused on the striatum, a brain region particularly rich in dopamine D2 receptors (D2R). Striatal D2R availability has been linked to traits and internal reward processes related to the concept of autonomous motivation and positive affect[108–110]. While this suggests that striatal dopamine D2R availability is linked to an individual's regulation of autonomous motivation, there is also support for the involvement of extrastriatal regions during intrinsically motivating situations, including the frontal cortex, anterior insular cortex, and anterior cingulate cortex[98,111–114].

The suggested association between autonomous motivation and dopamine becomes particularly interesting in relation to known age-related changes in the dopaminergic system, such as decreased D2R availability[115,116]. Furthermore, there may be a diminishing effect of aging on D2R availability among those older adults who are able to maintain a higher level of physical activity[117]. While it is possible that age-related changes in the dopaminergic system may influence the extent of older adults' capacity for autonomous motivation to exercise, and autonomous motivation is important for exercise behaviors and maintained exercise behaviors over time[118,119], no study has directly examined the potential link between dopamine and self-reported autonomous motivation. In conclusion, there is still much to explore regarding the motivational aspects of physical exercise among older adults, such as the underlying mechanisms of autonomous motivation, as well as how high intensity training impacts autonomous motivation among older adults.

Rationale

Aging is an inevitable universal process that impacts all individuals throughout their lives, with a majority of people fortunate enough to experience old age. This increased life expectancy and a demographic shift towards an older population, bring opportunities as well as challenges for both the individual and society.

To maintain independence and quality of life, older adults need to preserve physical and cognitive function while delaying the onset of disease and disability. Regular physical exercise offers numerous health benefits for older adults and is associated with a decreased risk of common diseases, maintained physiological and cognitive abilities, and improved well-being. Still, a concerningly small number of older adults adhere to recommended levels of physical activity. To address this issue, we need a better understanding of older adults' exercise motivation and its underlying processes, as well as provide older adults with tailored forms of time-efficient and appealing exercise methods.

Supramaximal HIT is favored as a time-efficient and effective form of exercise. However, there is a need for more high-quality RCTs that delve into the applicability, safety, and effectiveness of supramaximal HIT for older and untrained adults to further support and facilitate physical exercise for health and well-being, as well as to benefit public health.

Purpose and Aims

The overarching purpose of this doctoral thesis was to investigate motivational aspects, applicability, and effects of physical exercise among older adults, and supramaximal high-intensity interval training (HIT) in particular. It aimed to address the applicability and effects of controlled supramaximal (HIT), in comparison to aerobic moderate-intensity training (MIT), among older adults not engaged in regular physical exercise.

The specific aims were:

1. **To explore the potential neurobiological association between dopamine and exercise-related motivation among older adults (Paper I), and to examine the effects of controlled supramaximal HIT compared to MIT on exercise-related motivation (Paper II).**

2. **To provide a comprehensive description of the applicability and safety of controlled supramaximal HIT, compared to MIT, in older adults not engaged in regular physical exercise. (Papers II-III).**

3. **To examine the effects of supramaximal HIT, compared to MIT, on physiological and cognitive health-related factors that commonly decline with age (Papers III-IV).**

Materials and Methods

Overview and Design

This thesis comprises four research papers. An overview of these papers, together with my overarching and paper-specific contributions, is given in Table 1.

The data in these four papers are utilized from two larger trials: The Umeå Hight-Intensity Interval Training (HIT) Study, and the Physical Influences on Brain in Aging (PHIBRA) Study. The PHIBRA Study was conducted in 2014-2015, and the Umeå HIT Study was conducted in 2018-2020. Both studies were situated in Umeå (Sweden), and targeted older adults not engaged in regular moderate-to-vigorous physical activity.

To examine the proposed link between autonomous motivation and D2R availability, Paper I used baseline data from the PHIBRA Study on self-reported motivation and D2R availability measured with positron emission tomography (PET). A full description of the PHIBRA Study RCT is beyond the scope of this thesis but provided in Jonasson et al. (2016)[40].

To examine the applicability and effects of controlled supramaximal HIT adapted for older adults, Papers II- IV used data from the Umeå HIT Study. The Umeå HIT Study is a randomized controlled superiority trial of parallel design aimed at examining the applicability and effects of controlled supramaximal HIT among untrained older adults. Participants were randomly assigned with a 1:1 allocation to 25 sessions of controlled supramaximal HIT or MIT (active comparison). The primary outcome measures are cardiorespiratory fitness and global cognitive function. The Umeå HIT Study is registered ClinicalTrials.gov (NCT03765385).

Ethics

The regional ethical Review Board in Umeå approved the PHIBRA study (2013-238-31M), and the Umeå HIT Study (2018-307-31 M, 2018-421-32 M). All participants provided written informed consent before data collection and intervention.

Table 1. Overview of the Papers and Outcomes included in this Thesis

Paper	**I**	**II**	**III**	**IV**
Trial data	PHIBRA Study	Umeå HIT Study		
Inclusion criteria	Age ≥ 64 years	Age ≥ 65 years		
	Not engaged in any type of regular MVPA over the past year			
Exclusion criteria	Neurological disease; Diabetes; DA-influencing medication; Any MRI or PET contraindication; MMSE ≤ 26	Exercise-induced symptoms of movement-related pain, heart, or lung conditions; Any significant cardiac or neurological disease contraindicative of high-intensity exercise; Untreated arterial hypertension (≥140/90 mmHg); Insulin treated diabetes; MMSE ≤ 26; previous participation in the PHIBRA study		
Paper-specific exclusion criteria	Major missing data for target variables	-	-	Any MRI contraindication; Missing data for the fMRI-task
Sample size, n	49	68	68	42
Intervention	-	Controlled supramaximal HIT or MIT		
Target variables	DA D2R availability; Exercise-related motivation	Applicability; Exercise-related motivation	CRF; cognitive function; blood pressure; muscle strength	Episodic memory; Hippocampus structure and function; CRF
Statistical analyses	Semi-partial correlation	Linear Mixed-Effects Models		
Covariates	ROI volume	Age; Sex	Age; Sex; *Education	Age; Sex; Education
My contributions (based on the CRediT author statement)	First and corresponding author; Conceptualization; Formal analyses; Data curation; Visualization; Writing original draft and editing	Shared first author; Formal analyses; Visualization; Writing original draft	First and corresponding author; Formal analyses; Visualization; Writing original draft	First author and corresponding author; Formal analyses; Visualization; Writing original draft
		Investigation (part of participant recruitment and screening, administration of data collection, data collection of cognitive outcomes and MRI, supervisor of the exercise intervention); Data curation (data entry and metadata management); Funding acquisition (partial funding for Paper III and IV)		

Abbreviations: HIT, high-intensity interval training; MVPA, moderate-to-vigorous physical activity; DA, dopamine; MRI, magnetic resonance imaging; PET, positron emission tomography; MMSE, mini-mental state examination; DA D2R, Dopamine D2 receptor; CRF, Cardiorespiratory fitness; ROI, region of interest; CRediT, Contributor Roles Taxonomy.
*Education was used as a covariate only for cognitive outcomes.

Participants and Procedures

The participants included in this thesis had a mean (SD) age of 69 (2.9) years, 14 (3.7) years of education, and 56% were women. Table 2 provides an overview of participant characteristics for each of the four papers. All participants were recruited via local newspaper advertisement. Eligible were older adults not engaged in any type of regular moderate-to-vigorous physical activity for the past year and did not meet any of the exclusion criteria. Both trial and paper-specific inclusion and exclusion criteria are stated in Table 1. Participant flow of the Umeå HIT Study (Papers II-IV) is depicted in Figure 3.

Table 2. Paper-Specific Participant Baseline Characteristics

	Paper I (n = 49)	**Papers II-III** (n = 68)	**Paper IV** (n = 42)
Trial cohort	PHIBRA Study	Umeå HIT Study	
Demographics			
Women, n (%)	28 (57)	38 (56)	23 (57)
Age, years	68.7 (2.7)	69.7 (3.0)	69.7 (3.0)
Education, years	13.8 (4.2)	14.4 (3.3)	14.5 (3.1)
Anthropometrics			
Body mass, kg	75.2 (12.3)	76.5 (14.4)	75.3 (13.5)
BMI	26.5 (3.5)	26.2 (3.9)	25.7 (3.2)
Cardiorespiratory fitness			
VO_2peak, L/min	1.5 (0.3)	1.7 (0.4)	1.8 (0.4)
VO_2peak, mL/kg/min	20.4 (3.7)	22.9 (4.9)	23.8 (5.2)
Motivation to exercise			
RAI-score	6.7 (7.1)	8.0 (5.8)	8.4 (5.0)
No previous exercise experience, n (%)	-	15 (22)	8 (19)

Numbers are presented as mean (SD) unless stated otherwise.
Abbreviation: HIT, high-intensity interval training; BMI, body mass index, VO_2peak, peak oxygen uptake from standardized cycle ergometer tests; RAI, relative autonomy index score from the BREQ-2 questionnaire.

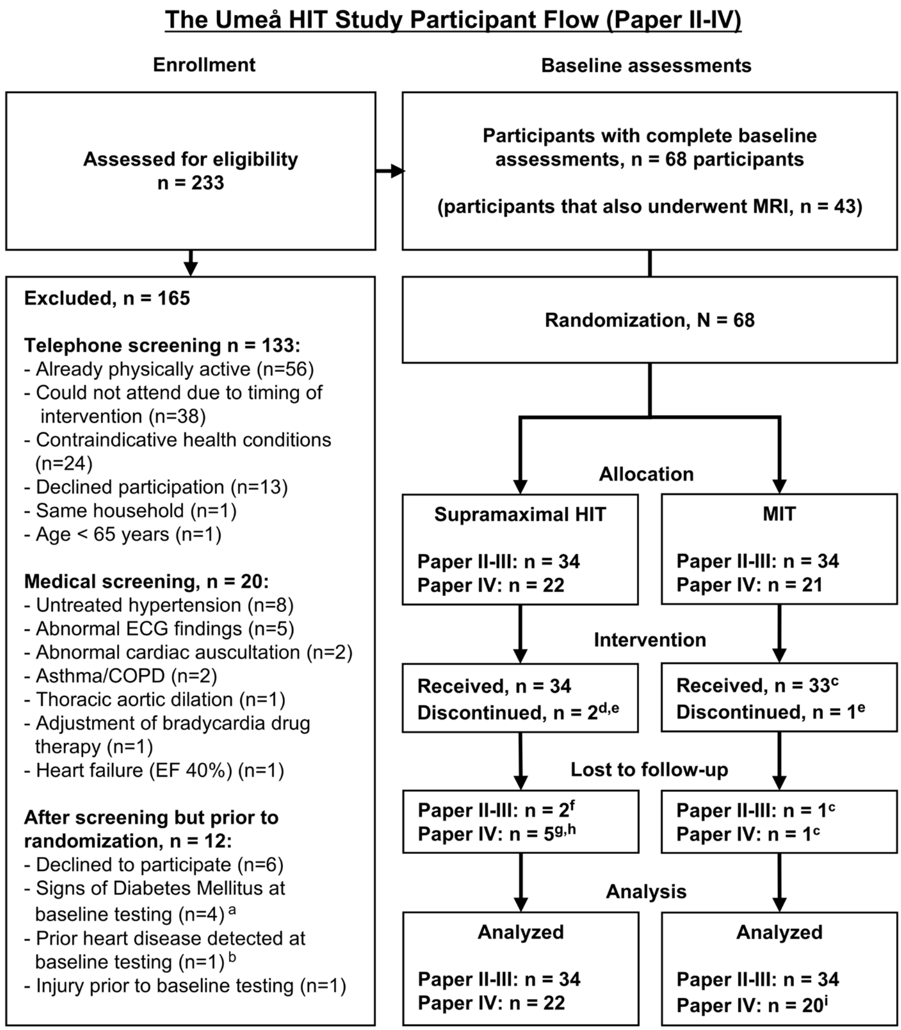


Figure 3. CONSORT flow diagram of the Umeå HIT Study (Papers II-IV). [a]Unexpected signs of diabetes mellitus at baseline testing in need of further medical evaluation. [b]Unexpected heart disease history emerging at baseline familiarization visit. [c]Withdrew from the study during the intervention and was lost to follow-up without attending any training sessions. [d]Discontinued the intervention at the doctor's request (a precaution due to re-diagnosed thrombophlebitis), but continued participation in follow-up. [e]Discontinued the intervention at own request, but continued participation in follow-up. [f]Two withdrawals from study, one of which was during the intervention, and one after the intervention but prior to follow-up. [g]Four participants were lost to MRI follow-up due to illness and re-scheduling issues. [h]One participant was excluded from MRI follow-up due to superficial metal fragments discovered at baseline. [i]One participant in MIT was excluded from MRI analyses due to a technical error with the in-scanner functional MRI task. Abbreviations: HIT = high-intensity interval training; COPD = chronic obstructive pulmonary disease; ECG = electrocardiogram; EF = ejection fraction; MRI = magnetic resonances imaging.

In the Umeå HIT Study enrolment (Papers II-IV), an initial telephone screening of applicants was performed by a physiotherapist or an exercise physiologist. Eligible applicants received further in-depth oral and written information about the study and were scheduled for a physical meeting at the Clinical Research Centre in Umeå, Sweden. At this meeting, the applicant provided their written informed consent, performed the Mini Mental State Examination (MMSE-SR) to rule out cognitive impairment, and underwent a medical examination (including a 12-lead electrocardiography) by an experienced cardiologist to rule out significant cardiac disease contraindicative of high-intensity exercise. Additional medical clearance during baseline assessments included another 12-lead electrocardiography recording during the cardiorespiratory fitness assessment, examined by the same cardiologist to rule out exercise-induced arrythmia; and if the capillary blood sample for the oral glucose tolerance test showed signs of untreated diabetes in need for further medical evaluation resulted (kP-Glucose ≥ 12.2 mmol/L).

The Umeå HIT Study enrolment period spanned from December 2018 to September 2019 and resulted in four waves, totaling 68 participants (Figure 3). Out of the 68 participants, 78% had some form of medical diagnosis; 56% were diagnosed with high but controlled blood pressure; 69% were medicated; and 54% were on blood pressure-lowering medication. For more detailed participant characteristics, see Simonsson et al. (2023)[120].

For each wave of participants, the overall study procedure started with baseline assessments, followed by randomization, a 3-month long exercise intervention (i.e., 25 sessions of supramaximal HIT or MIT), and a 3-month follow-up assessment (i.e., immediately after the exercise intervention). The Umeå HIT Study baseline assessments were distributed over the three weeks prior to the exercise intervention. Detailed descriptions of each visit have been provided in Simonsson et al. (2023)[120] supplementary material. In short, the first visit was a familiarization session of upcoming laboratory-based physiological tests of cardiovascular fitness and muscular function, and a demonstration of the equipment to be used by the participants during seven days of home-based assessments. The laboratory-based tests were distributed over three to five days covering a wide range of functions (cardiovascular-, muscular-, cognitive-, and metabolic functions), and were performed at the Sports Science Lab, the Umeå Motion of Exercise Lab of Umeå University, and the Clinical Research Centre in the University Hospital of Umeå. Due to practical matters, the visit order and total number of visits varied to some extent between participants, with some participants performing the cognitive function assessment at the same visit but always prior to the cardiorespiratory fitness (VO_2peak) assessment. The visit with VO_2peak assessment was always prior to the visit with muscular function assessment, and with at least 72 hours of rest in between. A subsample of participants (Figure 3), without any contraindications for the MRI protocol (e.g., claustrophobia, metal implants or visual impairments that could not be corrected by MRI-compatible glasses), had an additional visit of structural and functional MRI assessment at the University Hospital of Umeå. Apart from the familiarization visit, the same procedure was used during baseline and follow-up assessments. A 9-month follow-up (i.e., nine months from baseline assessments) was planned, but due to the covid-19 pandemic majority of that follow-up was cancelled for the last two participant waves. Hence, this thesis only includes data collected from baseline, intervention, and 3-month follow-up assessments. The last wave of participants completed their 3-month follow-up in February 2020. See Figure 3 for the overall as paper-specific (II-IV) participant flow.

Randomization (Papers II-IV)

For each of the four waves of participants, randomization was performed after complete baseline assessments with a 1:1 allocation ratio to controlled supramaximal HIT or MIT. To ensure good balance between groups, the randomization was stratified by age (65-69 years, or ≥ 70 years) and sex (male/female). A researcher not involved in the Umeå HIT Study used Research Randomizer (http://www.randomizer.org/) to generate the lists of random numbers. For each wave of participants, the exercise intervention started within one week from randomization.

Blinding and Bias (Papers II-IV)

Blinding is an essential method to increase internal validity by preventing biases that can affect participation and outcomes, such as performance and detection bias[121]. However, the possibility to fully blind participants and exercise supervisors during exercise trials is naturally limited[71].

To minimize performance bias among the participants in the Umeå HIT Study, the participants were informed about the general study purpose (e.g., to compare effects of bicycle cardio of different duration and intensity), but only received detailed information about their allocated exercise protocols and blinded to the study's superiority design.

To minimize performance and detection bias during assessments, participants were randomized only after completed baseline assessments. During follow-up assessments, the participants were repeatedly instructed to not reveal any details regarding their group allocation to the assessors. All outcome assessors were blind to group allocation, except E.S., who supervised all exercise sessions for both supramaximal HIT and MIT. E.S. also administered the cognitive tests during the 3-month follow-up MRI assessment. In case of overlapping participant schedules, E.S. always administered the outside scanner introduction and practice rounds, while a cognitive neuroscience student administered the in-scanner tasks. In Paper III, the primary outcomes of the Umeå HIT Study were initially analyzed by a statistician blinded to group allocation, using a masked data set. The code key was generated and distributed by a researcher not involved in the study.

Sample Size (Paper III)

The sample size for the Umeå HIT Study was based on power analyses for the two primary outcomes cardiorespiratory fitness (VO_2peak) and global cognitive function (composite score).

The power calculation for VO_2peak was based on an estimated between-group difference in change of 3.5 mL/kg/min (SD = 4.0). The assumed difference of 3.5 mL/kg/min has been associated with a 15% risk reduction in cardiovascular disease, and is considered a clinically meaningful change[14]. The SD of 4.0 was an approximation derived from findings in the PHIBRA study[40], and a large intervention study among subjects with coronary artery disease[122]. This analysis revealed a need for 42 participants.

The power calculation for global cognitive function was based on estimated within-group changes for a global cognitive composite score in the supramaximal HIT (mean = 0.288, SD = 0.312) and MIT (mean = 0.0657, SD=0.246) groups. The numbers are based on data from the PHIBRA study, which compared the effects 6-months of aerobic exercise at moderate intensity with an active control group of toning and stretching[40]. This analysis revealed a need for 52 participants.

Overall, these analyses, while also accounting for a 15% dropout rate during the intervention period and an extra margin for missing data, revealed a need for 70 participants.

Interventions

This section describes the training protocols for controlled supramaximal HIT and MIT (active control) used in the Umeå HIT Study (Papers II-IV). The parts that are the same regardless of protocol are described first, followed by protocol-specific details for supramaximal HIT and MIT under each respective subheading.

Both groups exercised twice weekly for 25 sessions at a local training center in groups of eight to ten participants, on indoor bicycles (Tomahawk IC7, Indoor Cycling Group, Nürnberg, Germany), with at least 72 hours of recovery between sessions. Limiting the exercise frequency to two sessions per week was based on findings implying that some older adults may require more than three days to achieve full recovery after a HIT session[123,124].

The training was computer guided with an interval timer. Two supervisors (educated in sports medicine or physiotherapy) were always present to prepare the equipment, monitor the training, and collect training related data such as attendance, adherence to interval intensity, positive and negative events, escalation and de-escalation criteria (see Figure 4). More detailed information on the exercise settings and data sampling during exercise sessions are provided in Simonsson et al. (2023)[120] supplementary material.

The first two sessions were introductory sessions for the participants to familiarize themselves with the equipment and designated training protocol. From session three, the full training protocol and procedure to progress the interval intensity were applied (Figure 4).

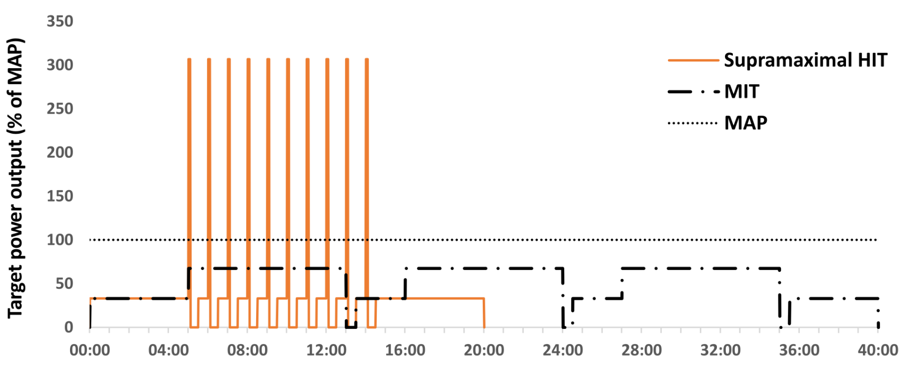
The exercise intensity was individually prescribed as the external target power output (TPO) in absolute watts, regulated by a standardized pedaling cadence and individual adjustment of the brake resistance level on the bike. The stipulated TPO for warm-up, between-interval active recovery, and cool-down corresponded to 33% of the participant's maximum aerobic power (MAP; the watts produced when reaching VO_2peak during the baseline cycle ergometer ramp test), with a set pedaling cadence of 60 revolutions per minute (RPM). For the MIT group, the stipulated interval TPO was also prescribed in % of MAP. In supramaximal HIT, the stipulated TPO was instead anchored to anaerobic power[63] and prescribed in % of the participant's estimated maximal 6-s mean power output (MPO6). The maximal MPO6 was estimated at baseline from a modified version of the submaximal Borg Cycle Strength Test, by multiplying the participants power output (watts) at the last stage of the test with 1.75[96].

To ensure a safe training intensity progression according to the participant's own ability, a set of standardized escalation and de-escalation criteria was used (Figure 4). The de-escalation criteria were applied already from the first session. To decrease the interval intensity for the next session either the participant explicitly asked to decrease intensity, or only one de-escalation criteria needed to be fulfilled. To increase the interval intensity for the next session all escalation criteria had to be fulfilled, of which one criterion was the participant themselves being ready to increase intensity. Each escalation/de-escalation step was equally large in absolute terms in watts during the entire intervention (i.e., 4% of MPO6 for supramaximal HIT and 4% of MAP for MIT). This approach results in the relative intensity increase becoming smaller over time as the participant gets closer to their maximal capacity.

To increase compliance with the exercise protocols, participants were allowed to dismount the bicycle during the passive recovery period to reduce physical discomfort. Further, the training supervisors observed whether the pedaling cadence and produced power output corresponded to the stipulated TPO for each participant once per session. If necessary, additional instructions were provided to guide the participant to find the stipulated TPO.

Controlled Supramaximal HIT

The supramaximal HIT protocol used in the Umeå HIT Study was developed by Hedlund et al. (2019)[96]. Each training session totaled 20 minutes and consisted of 10 x 6-second intervals interspersed with a 54-second recovery (24 seconds of passive recovery followed by 30 seconds of active recovery) (Figure 4). During the last five seconds of active recovery, participants were instructed to increase their pedaling cadence from 60 to 85 RPM and prepare to adjust the brake resistance level for the upcoming interval. The stipulated interval TPO for the first three sessions corresponded to 60% of MPO6. The progression of intensity began after the third session and was implemented in absolute steps of 4% of baseline MPO6. If a participant rated their RPE ≥ 18 at any time during the training session, they completed the rest of the session at 33% of MAP and the interval TPO was de-escalated one step at the following session.



Exercise setup	Supramaximal HIT	MIT
Total duration	20 minutes	40 minutes
Number of intervals x duration	10 x 6 seconds	3 x 8 minutes
Standardized pedaling cadence		
Warm-up, active recovery and cool-down	60 RPM	60 RPM
Intervals	85 RPM	60 RPM
Stipulated interval TPO		
Warm-up, active recovery and cool-down	33% of MAP	33% of MAP
Intervals (session 1-3)	60% of MPO^6	40% of MAP
TPO escalation criteria (from 3rd session)		
Maintained cadence during last interval	85 RPM	60 RPM
Rated perceived exertion (RPE)	RPE ≤ 16	RPE ≤ 14
Peak HR during last interval	≤ 95% HRR	≤ 70% HRR
Possible to do an additional (11th) interval	YES	-
Participant ready to escalate load	YES	YES
TPO de-escalation criteria		
Maintain cadence during the last interval	RPM < 85	RPM < 60
Rated perceived exertion (RPE)	RPE ≥ 18	RPE ≥ 16
Peak HR during last interval	> 95% HRR	> 70% HRR
Possible to do an additional (11th) interval	NO	-
Participant ready to escalate load	Wants to de-escalate	Wants to de-escalate
Between-session regulation of interval TPO		
Escalation/de-escalation (one step)	4% of MPO^6	4% of MAP

Figure 4. Exercise protocol characteristics of controlled supramaximal HIT and MIT from Simonsson et al. (2023) [120] under the CC BY-NC 4.0 license. The plotted lines represent the group means values of target power output, expressed as a percentage of MAP, at the end of the training period for supramaximal HIT (solid line) and MIT (dot-dashed line). The full protocols were applied from session three and onwards. The escalation/de-escalation step was equally large in absolute terms (watts) during the entire intervention. All escalation criteria had to be fulfilled to increase intensity 1 step for the next session, whereas decrease of intensity only required fulfillment of 1 de-escalation criterion or the participant explicitly asking to decrease intensity. In cases when all escalation criteria were met except RPE, and the rated RPE was 17 for HIT, and 15 for MIT, the exercise intensity was maintained for the next session. Abbreviations: HIT = high-intensity interval training; HRR = heart rate reserve; MIT = moderate-intensity training; MAP = maximum aerobic power at baseline; MPO6 = maximum mean power output for 6 seconds estimated at baseline; Peak HR = peak heart rate (10-second mean during last interval for HIT, average of 60 seconds of the last interval for MIT); RPE = rating of perceived exertion on the Borg (6–20) scale; RPM = revolutions per minute; TPO = target power output.

Moderate-Intensity Training

The active control MIT protocol totaled 40 minutes and consisted of 3 x 8-minute intervals interspersed with a 3-minute recovery period (30 seconds of passive recovery followed by 150 seconds of active recovery) (Figure 4). The stipulated interval TPO for the first three sessions corresponded to 40% of MAP. The progression of intensity began after the third session and was implemented in absolute steps of 4% of baseline MAP. If a participant rated their RPE ≥ 16 at any time during the training session, the interval TPO was immediately de-escalated with one step and maintained for the next session. The MIT protocol was divided into three longer bouts (instead of a continuous constant load) to prevent exercise-related negative events, boredom and drop-out[125], and to make it similar to exercise protocols used at public training facilities.

Outcomes and Assessments

An overview of the outcomes included in this thesis and the distribution across the four papers is shown in Table 1. The primary outcomes of the Umeå HIT Study (cardiorespiratory fitness and global cognitive function) are included in Paper III. All other outcomes are secondary outcomes.

Exercise-Related Motivation

Exercise-related motivation was assessed with the Swedish version of the Behavioural Regulation in Exercise Questionnaire-2 (BREQ-2)[107]. This questionnaire, based on the self-determination theory by Ryan and Deci[106], measures different quality types of motivation for exercise along a continuum from controlled to autonomous forms of regulation. Each item in this questionnaire loads onto one out of five regulation styles of motivation (amotivation, external motivation, introjected motivation, identified motivation and intrinsic motivation).

While later versions of the BREQ exists, the BREQ-2 has shown a good five-factor model fit[126,127], and the Swedish version of BREQ-2 has been validated with high reliability among young, middle-aged, and older adults[128,129].

To examine the proposed link between autonomous motivation and D2R availability (Paper I), a mean composite score for autonomous motivation was computed from the identified and intrinsic factor scores. The score ranges from 0 to 4, with a higher score indicating more autonomous motivation[130].

To examine the effects of supramaximal HIT on exercise-related motivation (Paper II), a Relative Autonomy Index (RAI) score was computed by summing weighted factor scores for all five factors. The score ranges from -24 to 20, with a higher score indicating more autonomous motivation[107,131].

Dopamine D2R Availability

Dopamine D2 receptor (D2R) availability within the brain was assessed as the non-displaceable binding potential (BP_{ND}) of the [11C]-raclopride-ligand from positron emission tomography (PET).

PET is a functional imaging technique that uses radioactive tracers to visualize changes in bodily metabolic processes. The biological process under investigation will affect which tracer to use and inject into the body, and the PET scanner measures the concentration of radioactivity from the tracer and its decay over time, typically in units of Bq/ml. The [11C]-raclopride-ligand is a tracer that binds specifically to the dopamine D2/3-receptor family[132]. The concentration of this tracer will be higher in brain regions rich of D2-receptors such as the striatum, compared to regions low in D2-receptors. Given that the tracer circulates also in brain plasma and tissue with non-specific binding, a reference tissue method is employed to calculate the non-displaceable binding potential (BP_{ND})[133,134]. The BP_{ND} is calculated as a ratio between the concentration of [11C]-raclopride tracer in the brain region of interest (specific and non-displaceable binding) and a reference region (non-specific and displaceable binding). The cerebellum was chosen as the reference tissue, under the assumption that it shares similar characteristics with the striatum, apart from the striatum being rich in D2-receptors.

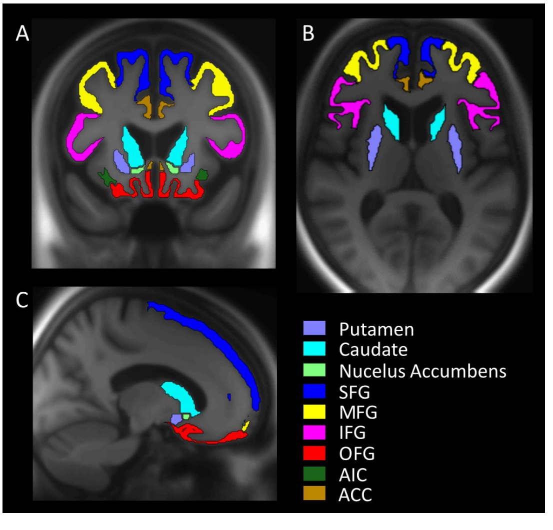


Figure 5. Visualization of the grey matter segmentation for each region of interest used to assess dopamine D2R availability in paper I, from Simonsson et al. (2022) [135] *under the CC BY 4.0 license. (A) Coronal plane, (B) horizontal plane, and (C) sagittal plane. Abbreviations: SFG = superior frontal gyrus; MFG = middle frontal gyrus; IFG = inferior frontal gyrus; OFG = orbitofrontal gyrus; AIC = anterior insular cortex; ACC = anterior cingular cortex.*

The [11C]-raclopride BP_{ND} was extracted separately for each a priori defined brain region of interest (Figure 5): three striatal subregions (nucleus accumbens, caudate nucleus and putamen), the anterior insular cortex, anterior cingulate cortex, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, and orbitofrontal cortex. The extrastriatal regions were based on previous findings of good test-retest reliability for the [11C]-raclopride ligand within the PHIBRA Study control group[136], and their suggested involvement in motivational processes[102,137].

Applicability of Supramaximal HIT

Applicability was described in terms of exercise session attendance, participant-reported exercise-related events, interval intensity adherence, intensity progression, perceived effort, and affective state, all of which were assessed across sessions.

Exercise-related events

Exercise-related events were documented at the beginning and end of each session with a direct open-ended question to each participant, asking them for any positive or negative experience related to the exercise. The participants themselves defined the experience as positive or negative.

All positive and negative events were categorized based on symptom descriptions, and reported as total counts, medians (min; max), and the three most common types of events (Paper II).

In addition, all negative events were managed as adverse events and assessed whether considered a serious adverse event (SAE). This assessment was performed by two reviewers (a medical doctor and a sports medicine researcher) not involved in the Umeå HIT study. An SAE was defined as an event resulting in death; risk of death; hospitalization; disability or permanent damage; or requiring an intervention to prevent permanent impairment, damage, or other medical events. The SAE assessment was first conducted by each reviewer independently, after which they discussed each case until reaching a mutual conclusion. The reviewers also assessed whether each case of discontinuation from the exercise intervention and study withdrawal was related to the intervention, and if so, whether the case was considered an SAE.

Interval intensity

The stipulated interval intensity and its progression is presented as individual and group medians in watts, with the corresponding % of

MPO6 and MAP for supramaximal HIT, and % of MAP for MIT. The median (min; max) number of escalation steps are presented together with the three most common criteria for not escalating the intensity. The participants adherence to the prescribed intensity is presented as the median (min; max) % of participants at the correct intensity across training sessions.

Specific for this thesis, I also present the overall median interval intensity and stipulated total workload (kJ) across all 25 training sessions (determined from each participant's median), and for the last training session.

Perceived exertion and Affective state

Participant-rated perceived exertion was assessed with the 15-point Borg Rating of Perceived Exertion scale[138], ranging from 6 (no exertion at all) to 20 (maximal exertion). With the same scale the participants also rated their session average perceived exertion (session RPE). The affective state was assessed with the 11-point Feeling Scale (FS)[139], ranging from –5 (very bad) to +5 (very good). The interval specific RPE and FS was assessed at six and three time points, respectively, during each session. In supramaximal HIT, the ratings were collected immediately after a completed interval, with the question framed towards the sensation during the end of the completed interval. In MIT, the ratings were assessed at mid- and end of intervals. Session RPE and post-session FS was assessed after completed cool-down. The interval specific median (min; max) RPE and FS ratings are presented for session 3 (the first complete training session), 13, and 23. Session 23 was chosen for an even spread of example sessions.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed as the relative VO_2peak (mL/kg/min) from a standardized ramp-test performed on an electronically braked cycle ergometer (Monark 839E Monark Exercise AB, Vansbro, Sweden). The test started with a three-minute constant load at 30 watts for women and 40 watts for men, followed by a ramp protocol with a continuous workload increase of 10 and 15 watts per minute for women and men, respectively. Expired air was analyzed continuously during the test with a mixing chamber-based ergo-spirometry system (AMIS 2001 Innovision A/S, Odense, Denmark) and registered as means of 30-second intervals. Test termination criteria were 1) volitional exhaustion, 2) inability to maintain a cadence of 60 rpm despite encouragement, 3) HR and/or VO_2 reaches a plateau despite increased intensity, 4) RPE exceeding 17, 5) test leader judging the participant as too exhausted, 6) any perceived chest pain exceeding 0 on the CR10-scale[138], 7) drop of systolic blood pressure of 15 mmHg or more, or systolic blood pressure above 250 mmHg. Detailed descriptions of the test criteria assessments are found in Simonsson et al. (2023)[120] supplementary material.

A similar setup was used for the VO_2peak assessment used in Paper I, and a detailed description is found in Jonasson et al. (2016)[40].

Cardiovascular Function

Cardiovascular function was assessed as average systolic and diastolic blood pressure (mmHg), based on six days of home-based measurements with a validated automatic upper arm blood pressure monitor (Omron M2[140,141]). Each day the participant performed three consecutive registrations in the morning (before breakfast and medication), and in the evening (before medication). Only participants with at least 30 valid measurements were assigned an average[142].

Muscular Function

Muscular function was assessed as the maximal isometric knee extensor strength (normalized joint torque in N·m/kg) averaged across both legs. This was measured with a load cell (Lutron FG-5100, Lutron Electronic Enterprise Co., Ltd., Taipei, Taiwan) positioned in a Biodex dynamometer chair (Biodex System Pro X, Biodex Medical Systems, Shirley, New York, NY). The participant was seated with restraining straps over the chest, pelvis, and ankles. The arms were crossed at the chest, the back in contact with the backrest and knees in a 90 degrees flexion. After submaximal practice, the participant performed two maximal trials for each leg with two minutes of rest between trials. For each leg, the maximal torque (N·m) was calculated from the highest obtained force (N) of the two trials multiplied by the moment arm (m), then averaged across both legs and divided by weight (kg).

Global- and Domain-Specific Cognitive Functions

Global- and domain-specific cognitive functions (paper III) were assessed during one visit with a test battery comprised of 11 cognitive tests administered in the following order: 1) Digit symbol[143], 2) Free recall[144], 3) Automated Operation Span[145], 4) Word recognition (encoding)[146], 5) Backward digit span[143], 6) Stroop[147], 7) n-back[148], 8) Word recognition (retrieval), 9) Trail Making Test (TMT) 2,3 and 4[149], 10) Paired associates[150], 11) Form boards[151]. A detailed description of each test has been provided in Simonsson et al. (2023)[120] supplementary material.

To capture a broad range of cognitive abilities and to reduce potential floor and ceiling effects[152], the global and domain-specific composites were computed from the test battery above. The global and domain-specific composites were based on cognitive tests and models from previous studies[40,153,154]. For each test and time point, participant raw scores were z-transformed, using the whole-sample baseline mean and standard deviation (SD). Then, the z-transformed scores were averaged to form unit-weighted composite scores for global- and domain-specific cognition (Paper III). A higher composite score indicates better cognitive function. Domain-specific composites include episodic memory, processing speed, working memory, executive function, and visuospatial ability.

Episodic Memory and Pattern Completion

Episodic memory was assessed in four different tests. Three of the tests were administered during the same visit (free recall, word recognition, and paired associates). The fourth test was administered during the MRI visit with concomitant functional MRI acquisition of the hippocampus (Paper IV).

The in-scanner episodic memory test was a partial cued memory retrieval task tapping into processes of pattern completion[155]. Pattern completion enables the brain to reconstruct a memory based on partial input by facilitating accurate recognition and recall of familiar information and is critical for effective encoding and retrieval of stored memories. A detailed description of this in-scanner task can be found in Nyberg et al. (2020)[155]. In short, it is a partial cued recall task consisting of modified versions of previously presented and encoded faces from a face-name task (Figure 6A). The modified faces were either fragmented, or morphed with a new face and the participant was given three answer options to choose from (a correct old name, an incorrect old name, and "new face") (Figure 6B). The participants responded to each item with a button press on a scanner-compatible response pad and was instructed to guess if being unsure. For this pattern completion task, response was defined as correct when the participant responded with the old name related to the original but modified face.

In paper IV, for all four episodic memory tasks, the dependent outcome measure was the number of correct responses.

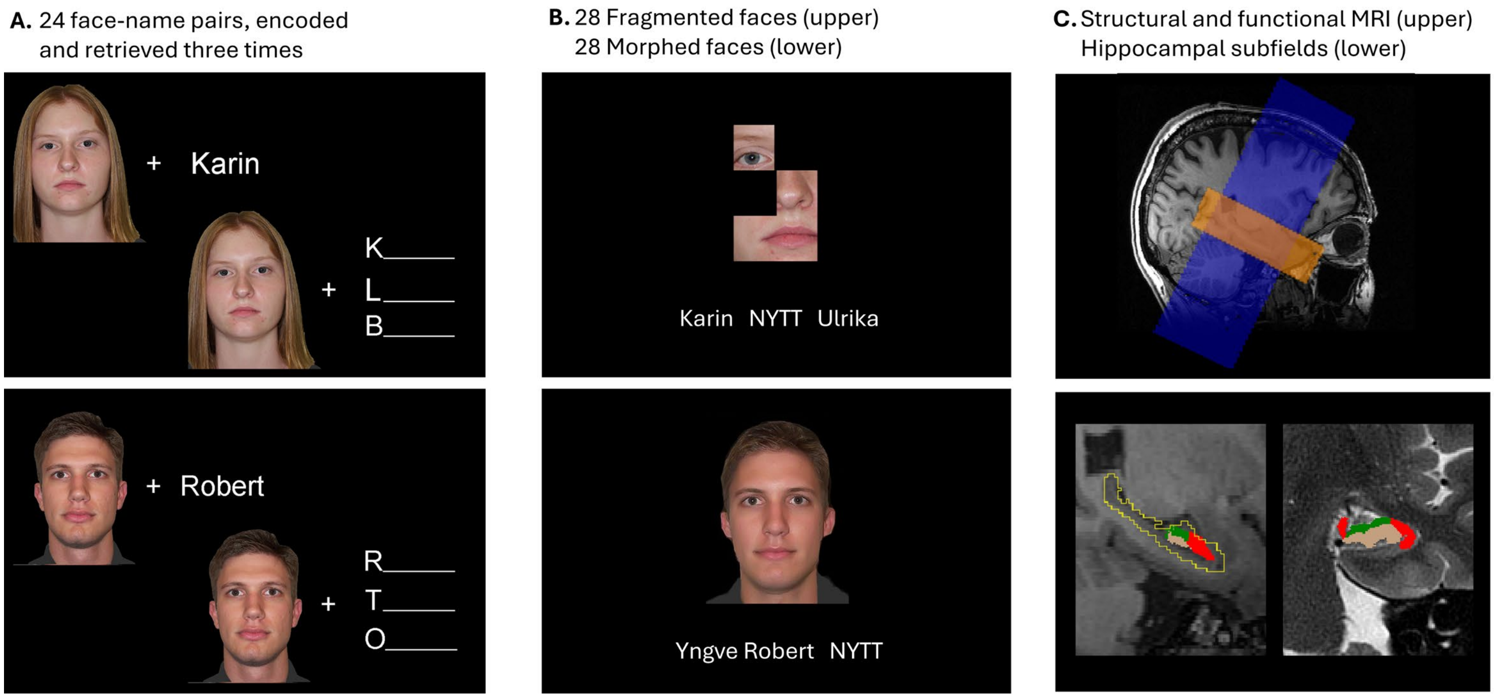


Figure 6. Overview of the episodic memory test of pattern completion and the magnetic resonance imaging (MRI) sequences included in Paper IV. Image examples of the (A) face-name task that was performed outside the scanner, and the (B) fragmented and morphed face cues that was used in the in-scanner pattern completion task. (C) The MRI scans included a whole-brain structural T1W-image (grey), a high-resolution structural T2W-image (blue contour), and high-resolution functional volumes (orange) of the hippocampus. Hippocampal subfield segmentation of CA1 (red), CA2/3 (green), and CA4/DG (beige) was performed with the HippocampalSubfields module in FreeSurfer 7.2.

Hippocampus

Hippocampal structure and function were assessed with structural and functional MRI (Paper IV). The dependent outcome measure for hippocampus structure was volume (mm^3), while hippocampus function was examined with the blood-oxygen-level-dependent (BOLD) signal during the in-scanner pattern completion task. For both hippocampus structure and function, the regions of interest were the left and right hippocampus, and three hippocampal subfields CA1, CA2/3 and CA4/DG.

MRI is an imaging technique using electromagnetic fields at varying strengths and frequencies to produce anatomical images of different biological tissues, such as grey and white matter in the brain. The MRI-sequences vary depending on which tissue that is of interest. T1- and T2-weighted sequences are commonly used to produce structural images of the brain. For the assessment of hippocampus structure, and hippocampal subfields, a whole-brain T1-weighted sequences was used together with a high-resolution T2-weighted sequence specifically overlaying the hippocampus (Figure 6C).

Hippocampal segmentation (e.g., to determine the size and place of the hippocampal structures) was performed in FreeSurfer 7.2. FreeSurfer is a software package used for analysis and visualization of structural and functional MRI data, with automated and semi-automated packages for segmentation of cortical and subcortical brain structures. In paper IV, the HippocampalSubfields module, with both the T1- and high-resolution T2-weighted images as input, was used to extract the hippocampal regions of interest (whole hippocampus, and CA1, CA2/3 and CA4/DG subfields). To account for individual differences in brain size, all regions were corrected for intracranial volume estimate from the FreeSurfer segmentation, using the residual method[156,157].

In functional MRI, the aim is to assess the physiological variation in brain activity, and how it changes over time. A T2*-weighted sequence can provide us with information about factors related to changes in the magnetic field homogeneity, such as the change in the ratio of oxygenated and deoxygenated hemoglobin in the brain (BOLD-signal). By measuring the local changes in the BOLD-signal, we can infer changes to brain activity in specific brain regions. For task fMRI, a participant completes a cognitive test, such as a pattern-completion task, in the scanner, with changes in the BOLD signal being measured, allowing for inferences about changes in brain activity.

Statistical methods

All primary analyses in this thesis were conducted in R[158] and RStudio[159], using the tidyverse[160] package. The MASS[161] and ppcor[162] packages were used for the partial and semi-partial correlations. The lme4[163], emmeans[164], and effectsize[165] packages were used for the linear-mixed effects models (LMM). Table 1 provides an overview of the primary statistical methods and covariates for each paper in this thesis.

Semi-Partial Correlation

In Paper I, the associations between D2R availability and self-reported autonomous motivation to exercise was explored with semi-partial correlations on the autonomous motivation composite score and the [^{11}C]-raclopride BP_{ND} for each ROI, controlling for ROI volume (mm^3) on BP_{ND} to account for partial volume effects. The use of parametric statistics on Likert data have previously been suggested valid[166], and criteria of normal distribution was met. A positive direction was assumed and therefore a 1-tailed significance testing and $\alpha = 0.05$ was used. The false discovery rate (FDR)[167] was used to correct for multiple comparisons. Based on the exploratory purpose of Paper I, a $q = 0.1$ was used.

<u>Sensitivity analysis</u>

Post hoc sensitivity analyses included semi-partial correlations partial correlations also controlling for age and sex, and partial correlations not controlling for ROI volume. These analyses were run with and without the two outliers in change detected during examination of longitudinal data (SD ≥ 2.5 in BP_{ND} change).

<u>Post hoc analysis</u>

In a previous study, an association between baseline striatal D2R availability and VO_2peak was confirmed[168]. To examine if there was an association also between exercise-related motivation and VO_2peak, a post hoc correlation was added.

To address the potential issue of low power in paper I, an additional correlation was included specifically for this thesis, pooling the baseline data on autonomous exercise-related motivation and VO_2peak from the PHIBRA sample with the Umeå HIT Study sample.

Linear Mixed-Effects Models

In papers II-IV, to evaluate effects, a linear mixed-effects model was applied to examine the between-group difference in change, within-group change, and the overall change of time regardless of group. For each outcome, group (supramaximal HIT and MIT), time (baseline and follow-up outcome values), and a group × time interaction was used. All analyses were *a priori* adjusted for age and sex as fixed effects, and individual as random effect. In addition, all analyses with cognitive outcomes were adjusted for education (years) as a fixed effect. Unadjusted analyses did not significantly change the results.

In this thesis, all LMM-results are reported as linear mixed-effects model estimated mean change and difference in mean change, with 95% confidence interval (95% CI), and a 95% CI excluding zero was chosen as the primary indication of statistical significance. Effect sizes (ES) were calculated from the model estimates of mean change divided by the unadjusted pooled SD. Percent change were calculated from the LMM-estimates.

In paper IV, the false discovery rate (FDR)[167] was used to correct for multiple comparisons, with a $q = 0.05$.

Sensitivity analysis

In Papier III, a sensitivity analysis for cardiorespiratory fitness (VO_2peak) was performed. This was based on the recommended age-adjusted end-criteria for reaching VO_2max[169]. This involved removing individuals that did not reach a respiratory exchange ratio (RER) ≥ 1.0, and post-lactate of ≥ 3.5 mmol/l for women and 4.0 mmol/l for men. This was achieved in sixty-seven cases at baseline and fifty-seven cases at 3-month follow-up. In total, fifty-six cases fulfilled the criteria during both baseline and 3-month follow-up.

Linear Regression

In paper IV, linear regressions were used to explore the associations between changes in cardiorespiratory fitness, episodic memory, and hippocampal structure and function. Delta values were computed by subtracting the baseline value from the follow-up value. First, regressions were performed with episodic memory performance as the dependent variable. Second, for the hippocampal subfields significantly associated with episodic memory performance, regressions were performed with each hippocampal subfield as the dependent variable and the change in cardiorespiratory fitness as the independent variable. A significance level of $\alpha = 0.05$ was used.

Intention-to-Treat Principle

In papers II-IV, in accordance with intention-to-treat principles, all available data from baseline and follow-up were analyzed (without imputation of missing data) according to the participants' original group allocation, regardless of session attendance and intensity adherence to the intervention[170]. Result tables of LMM-analyses display the number of available data points for each outcome and time point (baseline/follow-up).

Results

Exercise-Related Motivation

Motivation and Dopamine D2R Availability

In Paper I, the participants' mean (SD) unit-weighted composite score of exercise-related autonomous motivation was 2.21 (±0.91), on a scale ranging from 0 to 4. There were no statistically significant associations between exercise-related autonomous motivation and the D2R availability (BP_{ND}) within the striatal subregions; nucleus accumbens ($r = -0.021$, $p = 0.557$), caudate ($r = 0.037$, $p = 0.400$), and putamen ($r = 0.023$, $p = 0.438$).

For the exploratory analyses of extrastriatal regions, a statistically significant positive association was observed for the superior frontal gyrus ($r = 0.289$, $p = 0.023$), and for the middle frontal gyrus ($r = 0.330$, $p = 0.011$), meaning that a higher score in autonomous motivation was associated with higher D2R availability in these brain regions. No associations were observed for the inferior frontal gyrus ($r = 0.129$, $p = 0.190$), orbitofrontal cortex ($r = 0.145$, $p = 0.162$), anterior cingulate cortex ($r = 0.010$, $p = 0.474$), or anterior insular cortex ($r = 0.159$, $p = 0.140$).

These results remained essentially the same in post hoc sensitivity analyses controlling for age and sex; not controlling for ROI volume on D2R availability; or removing of outliers in BP_{ND} change (≥ 2.5 SD, n = 2) that were detected during examination of longitudinal data (PI, supplementary).

Motivation and VO_2peak

A post hoc correlation of the PHIBRA participants' baseline autonomous motivation and baseline VO_2peak (mL/kg/min) did not reach statistical significance [$r(47) = 0.194$, $p = 0.181$]. For the pooled data set using both PHIBRA and Umeå HIT data, the positive association between participants autonomous motivation and VO_2peak (mL/kg/min) reached statistical significance [$r(114) = 0.312$, $p = 0.001$]. Replacing the autonomous motivation score (used in paper I) with the RAI score (used in paper II) did not change the significance of this association [$r(112) = 0.330$, $p > 0.001$].

Motivation and Supramaximal HIT

From baseline to follow-up, there was no significant between-group difference in change for the RAI score (mean difference = 0.69, 95% CI [-2.39; 1.02]). There was however an overall significant increase over time regardless of group (mean change = 1.54, 95% CI [0.69; 2.40]).

Applicability of Supramaximal HIT

In total, 63 out of 68 participants completed the exercise intervention in the Umeå HIT Study: 31 out of 34 (91%) participants in supramaximal HIT, and 32 out of 34 (94%) participants in MIT. In supramaximal HIT, two participants discontinued the intervention voluntarily, and one participant discontinued at doctor's request. The latter was a precautionary measure due to thrombophlebitis being re-diagnosed by primary health care, but not considered related to the intervention. The one participant in MIT who discontinued the exercise intervention did so voluntarily following a musculoskeletal adverse event related to the intervention (back pain arising from trying to adjust the bicycle handlebar that had gotten stuck). For more detailed participant flow, see Figure 3.

Attendance

The participants in the supramaximal HIT group attended 748 out of 850 (88%) training sessions, with a median (min; max) participant attendance rate of 92% (44; 100%). The Corresponding numbers for the MIT group was 749 (88%) attended sessions, and a participant attendance rate of 92% (0; 100%). Regardless of group, the three most common reasons for not attending the training sessions were planned and pre-announced absence (56% in supramaximal HIT, 54% in MIT), absence due to illness (28% in supramaximal HIT, 24% in MIT), or withdrawal from the study (7% in supramaximal HIT, 17% in MIT).

Exercise-Related Events

During the 748 attended training sessions in supramaximal HIT, the participants' expressed a total of 52 negative and 112 positive exercise-related events. In MIT, the corresponding numbers for 749 attended sessions were 94 negative and 74 positive events (Table 3). Overall, across both groups, 36% of all negative events, and 60% of all positive events were expressed in supramaximal HIT.

The three most common types of negative events were musculoskeletal pain or soreness of temporary nature (n = 102, 38% in supramaximal HIT); equipment-related issues (n = 16, 19% in supramaximal HIT) mainly regarding uncomfortable saddles; and psychological/general vitality decrements (n = 8, 12% in supramaximal HIT) such as “feeling more tired than usual”. There were no serious adverse events in any of the groups.

The three most common types of positive events were psychological/general vitality improvements (n = 52, 71% in HIT) such as “feeling more energetic” and “being happier”; musculoskeletal events of muscle soreness and stronger muscles (n = 42, 55% in supramaximal HIT); and session-induced affects (n = 36, 64% in supramaximal HIT) such as “looking forward to the training” and “the training was fun”.

Interval Intensity

The participants’ progression in stipulated interval intensity across sessions are depicted in Figure 7A, and Table 3 presents detailed numbers on the stipulated median (min; max) intensity in supramaximal HIT and MIT for the first, last and median session.

In supramaximal HIT, the stipulated median (min; max) interval intensity across all 25 training sessions, as determined from each participant’s median, was 327 W (150; 560 W). This corresponded to 92% (68; 100%) of estimated baseline MPO6, and 251% (153; 390%) of baseline MAP, and a median total work (including warm-up, active interval recovery and cool-down) of 62 kJ (34; 102kJ). Across the training sessions, the median number of progression steps was 12 (6; 19). The three most common criteria for not progressing the intensity for the next session were the participant themselves not feeling ready to progress (n = 140, 52%); having an RPE rating ≥ 17 (n = 40, 15%); and/or not being able to maintain the prescribed cadence during the last interval (n = 39, 14%).

In MIT, the stipulated median (min; max) interval intensity was 74 W (46; 127 W), corresponding to 63% (45; 85%) of baseline MAP and a total work (including warm-up, active interval recovery and cool-down) of 143 kJ (94; 237 kJ). Across the training sessions, the median number of intensity progression steps were 6 (1; 13). The three most common criteria for not progressing the intensity for the next session were the participant having a heart rate ≥ 70% of heart rate reserve at the end of the last interval (n = 196, 50%); having an RPE rating ≥ 15 (n = 101, 26%); and/or not feeling ready to progress (n = 91, 23%).

Across training sessions, the observer-rated participant median (min; max) adherence to the prescribed interval intensity was 89.1% (55.6; 100%) in the supramaximal HIT group, and 100% (94.7; 100%) in the MIT group.

Table 3. Overview of Attendance, Exercise-Related Events and Training Intensity

	Supramaximal HIT	MIT
Session attendance		
Overall, n (%)	748 (88)	749 (88)
Participant, median (min; max)	23 (11; 25)	23 (0; 25)
Exercise-related events		
Total, n	164	168
Positive, n (%)	112 (68)	74 (44)
Negative, n (%)	52 (32)	94 (56)
Interval intensity		
First session, median (min; max)		
- in watts (W)	231 (125; 336)	51 (33; 87)
- in % of MPO6	60	-
- in% of MAP	169 (125; 266)	40
Last session, median (min; max)		
- in watts (W)	422 (192; 627)	79 (44; 135)
- in % of MPO6	112 (88; 136)	-
- in% of MAP	323 (196; 442)	71 (40; 90)
- total work (kJ)	67 (45; 110)	154 (99; 250)
Median session, median (min; max)		
- in watts (W)	327 (150; 560)	74 (46; 127)
- in % of MPO6	92 (68; 100)	-
- in% of MAP	251 (153; 390)	63 (45; 85)
- total work (kJ)	62 (34; 102)	143 (94; 237)

Abbreviations: HIT = high-intensity interval training; MIT = moderate-intensity training; MPO6 = maximum mean power output for 6 seconds estimated at baseline; MAP = maximum aerobic power at baseline.

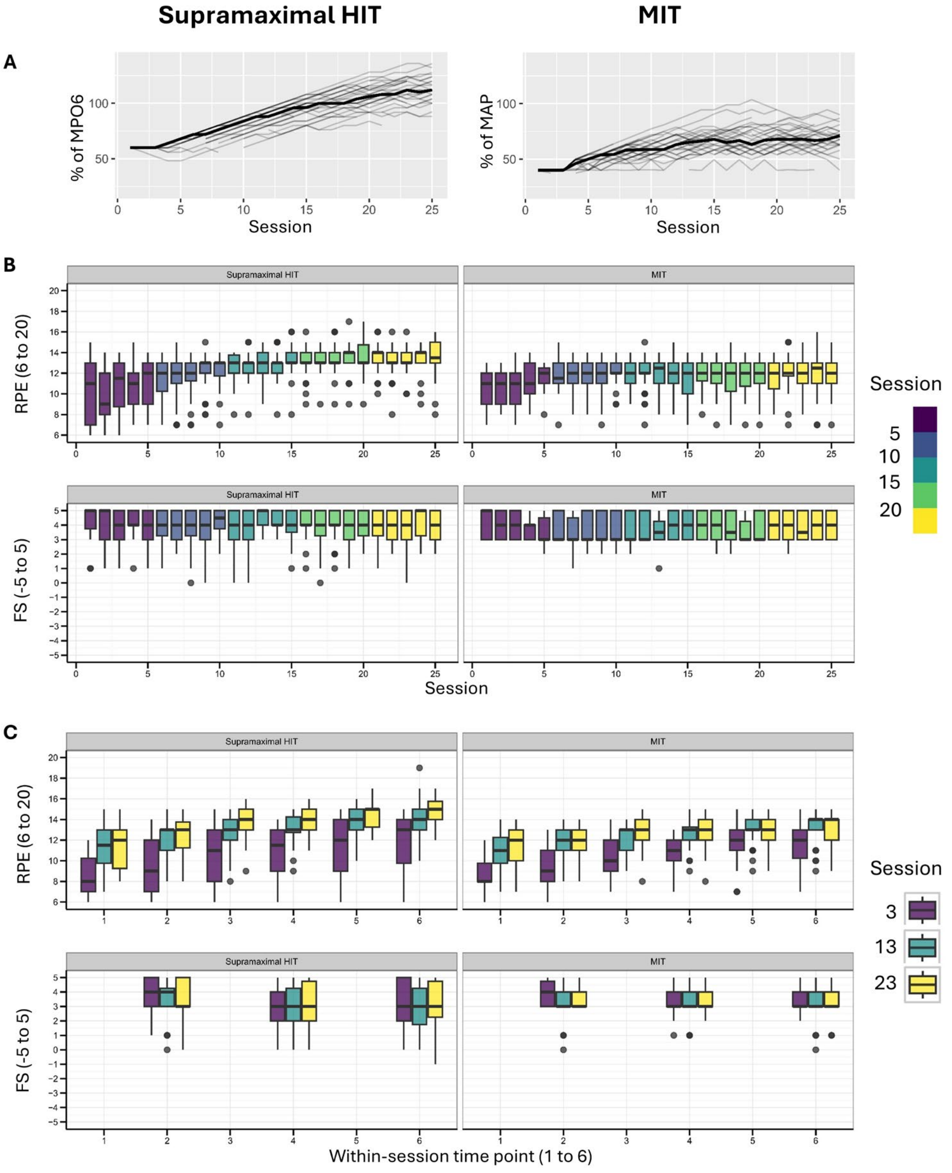


Figure 7. Training intensity, RPE, and FS across sessions for supramaximal HIT (left) and MIT (right), adapted from Frykholm et al. (2024)[171]. (A) Training intensity across sessions in supramaximal HIT relative to estimated maximal 6-s mean power output (MPO6) and in MIT relative to maximal aerobic power (MAP). Bold line represents the median, each thin line represents an individual. (B) Session RPE and post-session FS across all 25 sessions. (C) Interval-specific RPE and FS ratings for session 3, 13, and 23. For each session, RPE was collected at 6 time points, and FS was collected a 3 time points. Boxplots in (B) and (C) visualizing the median, two hinges and two whiskers, and all outlying points individually. Abbreviations: HIT = high-intensity interval training; MIT = moderate-intensity training; RPE = rating of perceived exertion; FS = feeling scale; Session RPE = session average rating of perceived exertion.

Perceived Exertion and Affective State

The change in participant ratings of session RPE and post-session FS across all 25 sessions is depicted in Figure 7B, while change in interval specific ratings of RPE and FS for training session three, thirteen and twenty-three is depicted in Figure 7C.

In the supramaximal HIT group, at session 23 and time point 6 (the last interval), the median (min; max) RPE rating was 15 (12; 17), and the median FS rating was 3 (-1; 5). During the same session, the median session RPE rating was 13 (10;16), and the median post-session FS rating was 4 (0; 5). In the MIT group, the corresponding ratings for session 23 and time point 6 were a median RPE of 14 (9; 15) and a median FS of 3 (1; 5). The median session RPE rating was 12 (8; 15), and the median post-session FS rating was 3.5 (3; 5).

Effects of Supramaximal HIT

Detailed results from linear mixed-effects model are provided in Table 4 (physiological changes), Table 5 (cognitive changes) and Table 6 (hippocampal changes).

Cardiorespiratory Fitness

Both groups significantly improved their VO_2peak, with no significant between-group difference in change (mean difference 0.05 mL/kg/min, 95% CI [−1.17; 1.25]). Overall, regardless of group, there was a significant mean increase in VO_2peak of 1.38 mL/kg/min (95% CI, [0.77; 1.98]).

<u>Sensitivity Analyses</u>

During the VO_2peak assessments, six participants failed to reach the age-adjusted end-criterion RER ≥ 1.0 for both measurement occasions (Edvardsen, 2014), and 40 out of 68 failed to reach the stricter and more common RER criterion of 1.1. For the ad hoc analysis with age-adjusted criteria (RER ≥ 1.0) the overall mean VO_2peak still increased significantly (n = 56, 1.63 mL/kg/min, 95% CI [1.04; 2.23]), with no between-group difference in change (mean difference 0.26 mL/kg/min, 95% CI [−0.94; 1.45]). For the post hoc analysis with stricter criteria (RER ≥ 1.1), the overall mean VO_2peak still increased significantly (n = 28, 2.18 mL/kg/min, 95% CI [1.18; 3.18]), with no between-group difference in change (mean difference 0.95 mL/kg/min, 95% CI [-1.02; 2.92]).

Table 4. Within-Group Change and Between-Group Differences in Physiological Change from Baseline to 3-Month Follow-Up

	Within-Group Change						Between-Group Difference in Change			
	Supramaximal HIT			MIT			Interaction (Group x Time)			
	No.[a]	Mean	[95% CI]	No.[a]	Mean	[95% CI]	Mean	[95% CI]	p	ES
Cardiorespiratory fitness										
$\dot{V}O_2$peak (mL/kg/min)	34/30	1.40	[0.52; 2.29]	34/32	1.36	[0.5; 2.22]	0.05	[-1.17; 1.25]	0.940	0.02
Sensitivity analysis RER ≥ 1.0	27/27	1.77	[0.89; 2.65]	29/29	1.51	[0.66; 2.36]	0.26	[-0.94; 1.45]	0.677	0.11
Sensitivity analysis RER ≥ 1.1	14/14	2.65	[1.19; 4.12]	14/14	1.70	[0.24; 3.17]	0.95	[-1.02; 2.92]	0.356	0.36
Cardiovascular function										
Systolic blood pressure (mmHg)	30/27	-1.95	[-4.47; 0.58]	29/27	-2.21	[-4.71; 0.29]	0.26	[-2.63; 3.16]	0.860	0.05
Diastolic blood pressure (mmHg)	30/27	-1.54	[-3.33; 0.25]	29/27	-1.02	[-2.79; 0.75]	-0.53	[-2.58; 1.52]	0.621	-0.12
Muscular function										
Isometric muscle strength (N·m/kg)	34/31	0.07	[0.02; 0.12]	34/31	0.00	[-0.05; 0.04]	0.07	[0; 0.14]	0.045	0.52

Notes. Estimates of mean change from linear mixed-effects models adjusted for fixed (age, and sex) and random (individual) effects, together with 95% CI. Effect Size (ES) was calculated from the model estimates of between-group difference in mean change and the unadjusted pooled standard deviation. Abbreviations: HIT = High-intensity interval training; MIT = Moderate-intensity interval training; $\dot{V}O_2$peak = Peak oxygen uptake; RER = Respiratory Exchange Ratio.

[a] No. (number) of available participant data at baseline/follow-up.

Cardiovascular Function

There were no significant between-group differences in change for systolic (mean difference 0.26 mmHg, 95% CI [-2.63; 3.16]) or diastolic (mean difference -0.53 mmHg, 95% CI [-2.58; 1.52]) blood pressure. There was however regardless of group, an overall significant decrease in systolic (−2.09 mmHg, 95% CI [−3.54; −0.64]) and diastolic (−1.27 mmHg, 95% CI [−2.31; −0.25]) blood pressure.

Muscular Function

In favor of supramaximal HIT, compared to MIT, there was a significant between-group differences in change in maximal isometric knee extensor muscle strength (mean difference 0.07 N·m/kg, 95% CI [0.003; 0.137]).

Cognitive Function

<u>Global Cognition and Cognitive Domains</u>

For global cognition, there was no significant between-group difference in change in the global composite score (mean difference 0.11, 95% CI [−0.03; 0.24]), and no change over time regardless of group (mean 0.02, 95% CI [−0.05; 0.09]).

For domain-specific cognitive functions, there was a significant between-group difference in change for working memory (mean difference 0.32, 95% CI, [0.01; 0.64]), in favor of supramaximal HIT. No other cognitive domain showed significant between-group difference in change. Regardless of group, there was an overall significant positive change in visuospatial ability (0.26, 95% CI [0.08; 0.44]), and an overall significant negative change in episodic memory (−0.15, 95% CI [−0.28; −0.02]).

Episodic Memory

The overall negative effect in the episodic memory composite was reflected in a significant negative change for word recognition (mean -1.7, 95% CI [-2.5; -0.8]), but not for the tests of free recall (mean 0.1, 95% CI [-0.4; 0.7]) or paired associates (mean -0.2, 95% CI [-0.9; 0.6]).

In the MRI-subsample (n = 42), the overall negative change in word recognition (mean -1.16, 95% CI [-2.17; -0.15]) remained significant, but not the change in episodic memory composite (mean -0.02, 95% CI [-0.20; 0.14]).

Table 5. Within-Group Change and Between-Group Differences in Cognitive Change from Baseline to 3-Month Follow-Up

	Within-Group Change						Between-Group Difference in Change			
	Supramaximal HIT			MIT			Interaction (Group x Time)			
	No.[a]	Mean	[95% CI]	No.[a]	Mean	[95% CI]	Mean	[95% CI]	p	ES
Cognitive function										
Global Cognition (composite)	34/30	0.07	[-0.03; 0.17]	34/29	-0.04	[-0.14; 0.06]	0.11	[-0.03; 0.24]	0.134	0.40
Executive function (composite)	34/30	-0.09	[-0.25; 0.08]	34/30	0.14	[-0.03; 0.3]	-0.22	[-0.45; 0]	0.062	-0.50
Processing speed (composite)	34/30	0.24	[0.05; 0.43]	34/32	-0.02	[-0.2; 0.17]	0.26	[0; 0.52]	0.057	0.49
Working memory (composite)	34/30	0.20	[-0.03; 0.43]	34/32	-0.12	[-0.34; 0.11]	0.32	[0.01; 0.64]	0.052	0.50
Episodic memory (composite)	34/30	-0.03	[-0.23; 0.16]	34/31	-0.26	[-0.45; -0.07]	0.23	[-0.04; 0.49]	0.097	0.43
Free recall (raw score)	34/30	0.28	[-0.52; 1.08]	34/31	-0.01	[-0.8; 0.78]	0.30	[-0.8; 1.39]	0.598	0.13
Word recognition (raw score)	34/30	-0.84	[-2.03; 0.34]	34/31	-2.51	[-3.68; -1.34]	1.67	[0.04; 3.29] [b]	0.049	0.50
Paired associates (raw score)	34/30	-0.03	[-1.12; 1.05]	34/31	-0.32	[-1.39; 0.75]	0.29	[-1.21; 1.78]	0.708	0.10
Visuospatial ability (composite)	34/30	0.33	[0.06; 0.59]	34/32	0.20	[-0.06; 0.46]	0.13	[-0.23; 0.49]	0.491	0.18
In-canner EM performance										
Pattern completion (raw score)	22/17	3.7	[1.1; 6.2]	20/19	2.3	[-0.2; 4.7]	1.4	[-1.97; 4.81]	0.423	0.26

Notes. Estimates of mean change from linear mixed-effects models adjusted for fixed (age, sex, and education) and random (individual) effects, together with 95% CI. Effect Size (ES) was calculated from the model estimates of between-group difference in mean change and the unadjusted pooled standard deviation. Abbreviations: HIT = High-intensity interval training; MIT = Moderate-intensity interval training.
[a] No. (number) of available participant data at baseline/follow-up.
[b] Did not survive FDR-correction of multiple comparisons (based on three episodic memory tests).

Table 6. Within-Group Change and Between-Group Differences in Hippocampal Structure and Function from Baseline to 3-Month Follow-Up

	Within-Group Change						Between-Group Difference in Change			
	Supramaximal HIT			MIT			Interaction (Group x Time)			
	No.[a]	Mean	[95% CI]	No.[a]	Mean	[95% CI]	Mean	[95% CI]	p	ES
HC structure (mm^3)										
Whole Hippocampus	22/17	-45.38	[-106.7; 15.9]	20/19	-9.51	[-67.5; 48.5]	-35.9	[-116.5; 46.1]	0.394	-0.29
CA1	22/17	-0.22	[-14.8; 14.4]	20/19	1.69	[-12.2; 15.5]	-1.9	[-21.19; 17.6]	0.848	-0.06
CA2/3	22/17	-7.25	[-13.6; -0.96][b]	20/19	-0.82	[-6.8; 5.1]	-6.4	[-14.7; 2.0]	0.141	-0.50
CA4/DG	22/17	-0.06	[-13.8; 13.7]	20/19	3.49	[-9.6; 16.6]	-3.6	[-21.68; 14.89]	0.706	-0.13
HC structure (ratio of HC)										
CA1	22/17	0.12	[-0.03; 0.27]	20/19	0.05	[-0.09; 0.2]	0.07	[-0.13; 0.27]	0.501	0.23
CA2/3	22/17	-0.08	[-0.18; 0.02]	20/19	-0.004	[-0.1; 0.09]	-0.07	[-0.21; 0.06]	0.280	-0.37
CA4/DG	22/17	0.09	[-0.04; 0.23]	20/19	0.07	[-0.06; 0.2]	0.02	[-0.16; 0.2]	0.822	0.08
HC function (BOLD)										
Whole Hippocampus	22/17	-0.02	[-0.1; 0.06]	20/19	-0.08	[-0.16; -0.002][b]	0.06	[-0.05; 0.17]	0.296	0.35
CA1	22/17	0.00	[-0.12; 0.12]	20/19	-0.07	[-0.19; 0.05]	0.07	[-0.1; 0.25]	0.448	0.26
CA2/3	22/17	-0.07	[-0.19; 0.05]	20/19	-0.13	[-0.24; -0.01][b]	0.05	[-0.1; 0.22]	0.511	0.22
CA4/DG	22/17	0.06	[-0.07; 0.19]	20/19	-0.05	[-0.17; 0.07]	0.11	[-0.06; 0.28]	0.230	0.40

Notes. Estimates of mean change from linear mixed-effects models adjusted for fixed (age, sex, and education) and random (individual) effects, together with 95% CI. Effect Size (ES) was calculated from the model estimates of between-group difference in mean change and the unadjusted pooled standard deviation. Abbreviations: HIT = High-intensity interval training; MIT = Moderate-intensity interval training; EM = Episodic memory, HC = Hippocampus, BOLD = Blood-Oxygen-Level-Dependent.

[a] No. (number) of available participant data at baseline/follow-up.

[b] Did not survive FDR-correction of multiple comparisons (based on three subfields).

Hippocampus and Pattern Completion

For the in-scanner episodic memory test of pattern completion, there was no significant between-group difference in change between supramaximal HIT and MIT (mean difference 1.4, 95% CI [-2.0; 4.8]), but an overall improvement in the number of correctly recalled faces (mean 2.9, 95% CI [1.2; 4.7]).

Hippocampus Volume

For bilateral hippocampus volume (mm3), a small but significant decrease in CA2/3]) was observed for the supramaximal HIT group only (mean -7.25, 95% CI [-13.55; -0.96]), but not significantly different from MIT (mean difference -6.43, 95% CI, [-14.72; 1.96]). The observed decrease in CA2/3 for supramaximal HIT occurred primarily in the left CA2/3 (mean -6.51, 95% CI [-11.44; -1.57]), and this negative change was significantly different from MIT (mean difference -8.98, 95% CI [-15.46; -2.36) (Paper IV, Supplementary Table 1). Additional analyses of the proportional change in hippocampal subfield volumes, as a percentage of the whole hippocampus, was performed to examine if any change had occurred in the relationship between each subfield in relation to the whole hippocampus. For supplementary lateral analyses, regardless of group, there was an overall increase in the right CA4/DG (mean 0.16, 95% CI [0.03; 0.27]), with no difference between groups (Paper IV, Supplementary Table 1). The observed effects were small and did not remain significant after multiple comparison corrections.

Hippocampus Function

For correct answers during the in-scanner pattern completion task, there was an overall small but significant decrease in BOLD signal in the CA2/3 (mean -0.10, [-0.18; -0.02]), with no significant difference in change between supramaximal HIT and MIT (mean difference 0.05, 95% CI, [-0.1; 0.22]). For unilateral analyses, there were a significant decrease for the left hippocampus (mean -0.10, 95% CI, [-0.2; -0.004]) and the left CA2/3 (mean -0.22, 95% CI [-0.43; -0.01]) for the MIT group, though not significantly different from supramaximal HIT (Paper IV, Supplementary Table 1).

Change-Change Associations

To better understand the underlying neural mechanisms of change to episodic memory performance, additional linear regressions were conducted to examine possible change-change associations between VO2peak, hippocampal volume and function, and episodic memory performance. A selection of plots is shown in Figure 8.

There were no significant associations between change in VO2peak (mL/kg/min) and change in episodic memory performance, either for the composite score ($F(1,58) = 2.61$, $p = .111$) or for the in-scanner task of episodic memory ($F(1,33) = 0.02$, $p = .883$).

For volumetric changes in the hippocampus, the only significant association was observed for change in the right hippocampus with change in the in-scanner episodic memory task ($F(1,34) = 5.09$, $p = .031$), such that an increase volume was associated increase in performance. Though not significant, this was mainly reflected in the change in the right CA4/DG ($F(1,34) = 3.65$, $p = .064$).

For the change in BOLD signal during pattern completion, in relation to the in-scanner episodic memory task of pattern completion, significant associations were observed for the BOLD signal change in the left hippocampus ($F(1,34) = 4.66$, $p = .038$), and for the BOLD-signal change in the left CA4/DG ($F(1,34) = 5.19$, $p = .029$), such that an increase in BOLD signal was associated with increased performance.

Further, the change in VO2 (mL/kg/min) was not significantly associated with volume changes in the right hippocampus ($F(1,34) = 1.12$, $p = .297$) or the right CA4/DG ($F(1,34) = 1.76$, $p = .193$). For change in VO2 and hippocampal function (BOLD), the association between VO2 and whole left hippocampus was not statistically significant ($F(1,33) = 2.93$, $p = .096$), however there was a positive association between change in VO2 and signal change in the left CA4/DG ($F(1,33) = 4.56$, $p = .040$).

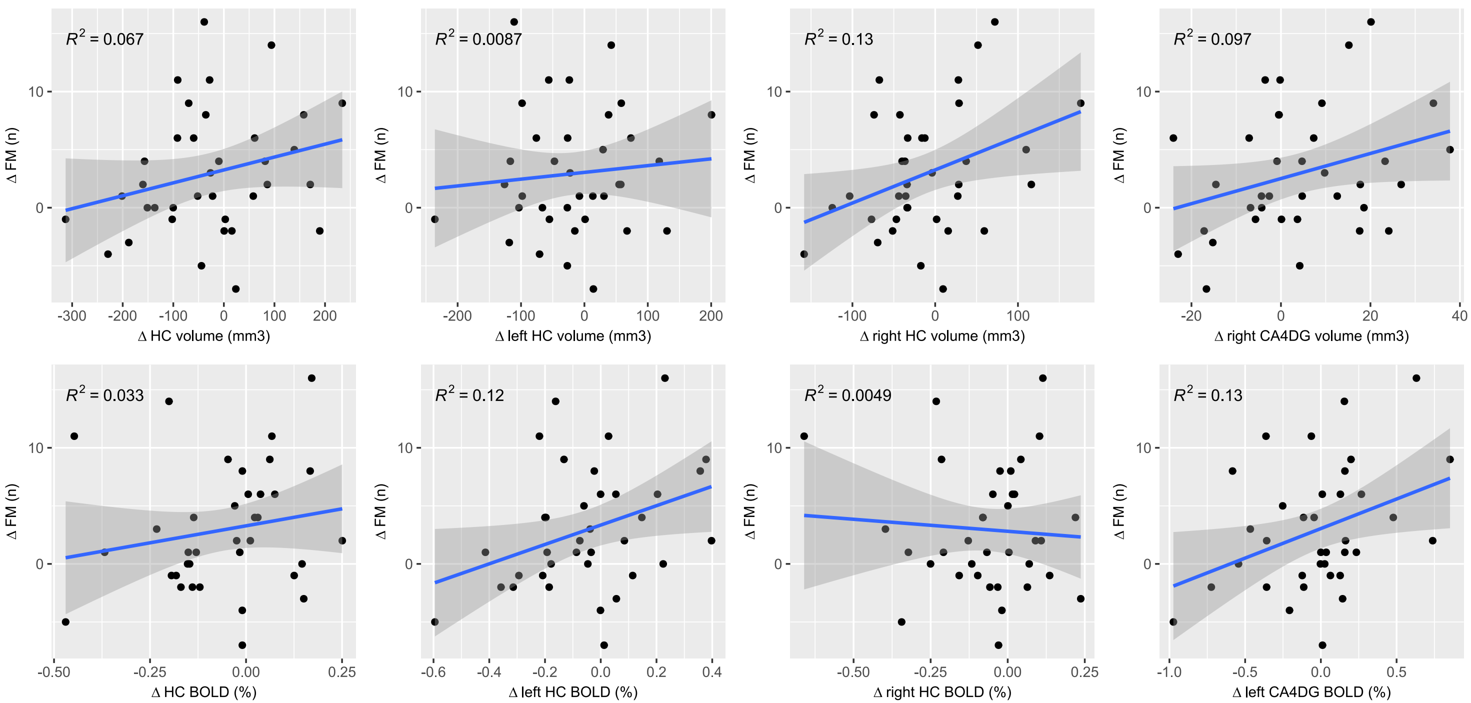


Figure 8. Linear regressions of change-change associations between the in-scanner episodic memory performance (ΔFM) on the y-axis, and changes in hippocampal structure (volume) or hippocampal function (BOLD) on the x-axis.

Discussion

This doctoral thesis demonstrates that three months of twice-weekly controlled supramaximal HIT among older adults showed similar and superior effects when compared to MIT, despite the total training time being halved. Older and untrained adults were capable of exercising at supramaximal training intensities on stationary bicycles in a supervised group-setting. Furthermore, the training could be performed without compromising their physiological and psychological well-being, or their motivation to exercise.

- <u>Motivation</u>: A link between striatal dopamine receptor availability and self-reported motivation to exercise could not be confirmed. Instead, the exploratory findings suggest an association with frontal brain regions. A higher cardiorespiratory fitness was related to higher autonomous motivation for the pooled dataset. Regarding the impact of controlled supramaximal HIT, no negative effect was observed on motivation. Instead, an overall small but positive effect was observed regardless of the training group.

- <u>Applicability</u>: All participants in the supramaximal HIT could adhere to and progress the training intensity over time. The overall attendance for supramaximal HIT was high and comparable to moderate-intensity training (MIT). Affective valence during and after the training sessions were similar in both groups, but with a larger variation in the supramaximal HIT group. No serious adverse events occurred, and notably, the participants in supramaximal HIT reported fewer minor adverse events, and more positive exercise-related events, compared to MIT.

- <u>Effects</u>: Both training groups improved cardiorespiratory fitness and cardiovascular function, with supramaximal HIT also inducing a small but superior improvement in lower-limb muscle strength. For supramaximal HIT, these effects were achieved with only half the training time required for MIT. None of the training modalities showed an effect on global cognitive function, but a domain-specific improvement in working memory was found, favoring supramaximal HIT. While the effects on episodic memory performance were mixed, associations were observed between cardiorespiratory fitness and hippocampus function in the CA4/DG subfield, which in turn was associated with improvements in task performance for pattern completion.

Exercise-Related Motivation

Dopamine D2R Availability

While the proposed link between striatal D2R availability and autonomous motivation[102] could not be confirmed, exploratory findings showed small but positive associations within frontal brain regions among older adults. These results tentatively suggest that frontal D2R availability may be involved in the autonomous regulation of exercise-related behaviors. Based on that individuals with higher levels of autonomous motivation tend to be more successful in maintaining regular physical exercise[119], the integrity of the dopaminergic system may play a role in this self-determined engagement in physical exercise. For example, while some individuals may have better biological prerequisites for more autonomous forms of motivation, others might need more external support. As D2R availability declines with age[115,116], an age-related biological constraint may further influence the motivation and regulation of engaging in physically effortful behaviors[104]. As we become older, external support may become increasingly important to encourage and maintain regular physical exercise, and particularly high-intensity exercise. The type of controlled supramaximal HIT examined in this thesis, with explicit guidance on intensity, duration, execution, and progression, may provide the additional support that some older adults need to engage in high-intensity training. The potential influence of aging on D2R availability and autonomous motivation to exercise must, however, be confirmed by future studies. The following discussion addresses some methodological aspects to consider.

First, the use of resting-state data for striatal D2R availability may present limitations, since the brain region striatum is involved in acute reward processing of both intrinsic (autonomous) and extrinsic (controlled) nature[172]. To more accurately capture the striatum's role in the more autonomous and self-determined forms of motivation, a different study design may be necessary. For example, combining a PET-assessment of striatal D2R availability with an active task, such as imagery or memory recall of autonomously motivating situations[112], could provide additional information about fluctuations in D2R availability in relation to autonomously motivating conditions.

Second, it could be argued the assessment of autonomous motivation should have been on a global rather than exercise-specific context[102]. However, previous studies, that also used resting-state D2R availability, have observed positive associations between striatal D2R availability and factors closely related to autonomous motivation and physical exercise.

For example, higher striatal D2R availability has been associated with higher flow (i.e., enjoyment and effortless task attention) among middle-aged adults[109], a greater engagement in high-intensity exercise among older adults[173], and higher cardiorespiratory fitness among older adults[168]. Notably, the latter observation was made within the same study population (the PHIBRA study) as used in this thesis. Further, exercise-related autonomous motivation assessed with the BREQ-2 questionnaire have repeatedly been associated with physical exercise behaviors[119]. For example, higher autonomous motivation among middle-aged and older adults have been related to more regular engagement in physical exercise, exercise at higher intensities, and higher cardiorespiratory fitness[126,174,175]. The latter was confirmed also in this thesis, at least for the pooled data set, showing a moderately strong association between the participants' exercise-related autonomous motivation and cardiorespiratory fitness at baseline. Even if a larger sample or a more heterogenous group of older adults may have been favorable for exploring the association between striatal D2R and autonomous motivation, the positive associations found for the exploratory analyses of the superior and middle frontal regions in this thesis were comparable in strength to the association between striatal D2R and VO_2peak reported by Jonasson et al. (2019)[168].

Third, analyses of dopamine D2R availability in the superior and middle frontal regions, estimated from [11C]-raclopride BPND, should be interpreted with caution and ideally replicated using a ligand with higher sensitivity for extrastriatal D2R[176]. Even so, these frontal regions have been linked to different intrinsically motivating states in fMRI-studies[112,177], which support the notion of an association between frontal D2R availability and autonomous motivation. While this should be confirmed by future studies, the findings in this thesis suggest that autonomous motivation, as assessed by the BREQ-2, may be more closely linked to frontal dopamine-dependent processes important for planning and initiation of future exercise-related behaviors[137,178].

Supramaximal HIT

The change in self-reported motivation after controlled supramaximal HIT and MIT in this thesis was similar to a study comparing HIT and MIT among pre-diabetic adults[179]. Notably, long-term follow-up assessments from that study indicated that while participants who engaged in MIT sustained their motivation levels after the supervised intervention ended, those in the HIT group experienced a decline. This may suggest a greater need for continued support during the transition from supervised to unsupervised HIT, compared to MIT. It would be interesting to investigate whether a similar trend in autonomous motivation is evident among older adults who undertake controlled supramaximal HIT, as well as whether maintained exercise relates to maintained autonomous motivation.

With regards to the impact of high and supramaximal exercise intensity on motivation among older and untrained individuals, three months of controlled supramaximal HIT did not negatively impact the participants exercise-related motivation. In opposite, there was a small but non-significant improvement in autonomous motivation within the supramaximal HIT group, not significantly different from the increase in the MIT group. This finding contradicts the previous concerns regarding a harmful impact on motivation from high- and supramaximal training intensities among older and untrained individuals[90–92]. There may instead be a positive relationship, at least when the intensity is achieved in a controlled manner during all intervals.

Applicability of Supramaximal HIT

To address the raised concerns regarding the applicability and safety of supramaximal training intensities for older and untrained adults[90,91], an important component of the supramaximal HIT program evaluated in this thesis was the use of a watt-controlled target intensity across all intervals within a session[96], instead of using all-out sprints[87]. Already from session one, the median external training intensity in the supramaximal HIT group was more than four times higher than in the MIT group and corresponded to 169% of the participants' maximal aerobic power. At the last session, the external training intensity had increased to more than five times higher than in the MIT group and corresponded to 250% of the participants' maximal aerobic power, and 112% of their estimated maximal MPO6 at baseline. The observer-evaluated adherence rate to the prescribed interval intensity across sessions was lower in supramaximal HIT, compared to MIT (89% vs 100%), but similar to other HIT studies with longer intervals[180,181]. These results suggest that the participants, notably some of whom had no previous experience with structured physical exercise, were capable of exercising at supramaximal training intensities. Furthermore, the participants who undertook controlled supramaximal HIT successfully adhered to a supramaximal training intensity over time, which was sufficient to induce VO_2peak improvements similar to moderate-intensity training (MIT).

The high attendance rate in supramaximal HIT was comparable to other RCTs of supervised HIT using more common, longer-duration intervals (1 to 4 minutes) among both older[181,182] and younger adults[183]. While the meta-analysis by Santos et al. (2023)[183] reported an average dropout rate of 13% among HIT-participants aged between 18-65, in this thesis, less than 10% of the older adults that participated in supramaximal HIT discontinued the exercise intervention. The high attendance and low dropout rates observed in this thesis may be the result of successfully adapting the supramaximal HIT protocol to be safe and applicable among the target population. However, a three-month exercise intervention is relatively short, and it would be worthwhile to explore more long-term attendance to this form of controlled supramaximal HIT.

There may of course be other contributing factors to high attendance, such as use of supervision and group setting. Among HIT interventions, supervised HIT generally results in higher attendance rates than unsupervised HIT[181,183]. A feasibility study using the same type of controlled supramaximal HIT as in this thesis, but conducted among regularly exercising older adults, revealed valuable insights about contributing factors[96]. Interviews revealed that participants valued performing this type of training in a group setting. They were inspired to engage in supramaximal HIT alongside other older adults and became more self-confident about their capability of exerting themselves to a larger degree[96]. Performing supramaximal HIT in a supervised group setting may help address important barriers and motivators, such as facilitating competence and capability, providing a social context, and fostering a sense of relatedness[53].

Consistent with other studies altering the number and duration of sprint intervals to reduce perceived exertion and negative affect[184,185], the change in affective valence during the controlled supramaximal HIT remained stable and mostly positive. The median ratings of affect were similar across supramaximal HIT and MIT in this thesis; however, there was more variation and a few isolated ratings of negative affect in supramaximal HIT. While not examined in this thesis, possibly, individual differences in the dopaminergic system may modulate trait preferences for high-intensity training[173,186], and result in a greater influence on affect and enjoyment from high-intensity compared to moderate-intensity training[187]. For instance, it would be interesting to explore whether the participants in this thesis who experienced higher positive affect during supramaximal HIT also reported more positive and fewer negative exercise-related events, and whether this was related to changes in motivation.

The systematic effort to record and report also minor adverse events showed that participation in supramaximal HIT, when compared with MIT, did not increase the number of adverse events. In opposite, participants in supramaximal HIT reported fewer negative exercise-related events than in MIT, and none were serious. The most common type of minor adverse event was musculoskeletal pain or soreness of temporary nature, and only 38% of these occurred in the supramaximal HIT group. These findings are important for the interpretation of the applicability and safety of supramaximal HIT. According to Ekkekakis et al. (2023)[93], minor adverse events are common during high-intensity interval training (HIT) and can reduce participants' motivation and willingness to continue with HIT. However, the authors also point out that the lack of detailed reporting on these minor adverse events makes it difficult to fully understand their impact and the broader implications of HIT. For example, a recent umbrella review including 14 randomized controlled HIT trials totaling 429 middle-aged and older adults reported only four adverse events, all of which resulted in intervention discontinuation[180]. This is a large contrast to the observations in this thesis, where the participants in supramaximal HIT reported a total of 52 minor adverse events. While this number of minor adverse events may seem concerning, it should be noted that we recorded all events that the participants themselves considered negative, and none of these minor adverse events led to intervention discontinuation. Additionally, the participants in supramaximal high-intensity training (HIT) reported 112 positive exercise-related events, and their motivation to exercise was not negatively affected. Notably, participants in supramaximal HIT reported not only fewer negative exercise-related events but also more positive exercise-related events compared to participants in MIT. To summarize, three months of twice-weekly controlled supramaximal HIT could be safely implemented among older adults who were not engaged in regular exercise at the time. However, whether these findings extend beyond this type of controlled supramaximal HIT needs to be confirmed by future studies.

Effects of Supramaximal HIT

Physiological Effects

To improve cardiorespiratory fitness ($\dot{V}O_2max$), three months of twice weekly controlled supramaximal HIT was not superior to MIT but induced a similar increase with only half the training time. The lack of superior effects from supramaximal HIT on maximal oxygen uptake is not entirely unexpected and aligns with previous research not matching the total workload between HIT and MIT[71,188]. In this thesis, not only was the duration of a supramaximal HIT session halved in comparison to a MIT session, but the total workload (kJ) for the median session in supramaximal HIT was even less than half the amount of work in MIT.

Given that cardiorespiratory fitness shows an accelerated annual decline of 1.5-2% among older adults[16,17], the observed improvements in this thesis correspond to approximately three to five years of reversed age-expected decline. An improvement of 3.5 mL/kg/min has been associated with a 15% reduced risk for cardiovascular disease and an 11-13% reduced risk for all-cause mortality[14,15]. Changes in cardiorespiratory fitness show an inverse relationship with all-cause mortality risk[189], with even a 1 mL/kg/min difference in $\dot{V}O_2max$ being considered clinically meaningful[190]. This further highlights the significance of the 1.38 mL/kg/min increase observed in this thesis.

This increase is also similar to that observed for six months of home-based HIT among older adults[191], but falls within the lower range when compared to more common sprint interval training[192], and was smaller than the 8% increase that Adamson et al. (2014)[87] observed after only six weeks with 6-second all-out sprint intervals. The latter was however a small study with only six participants receiving the training. In contrast, a meta-analysis comparing the effects of HIT (including SIT) and MIT among middle-aged and older adults reported and average increase of 2.26 mL/kg/min from HIT and 1.34 mL/kg/min for MIT. In this thesis, the improvements in cardiorespiratory fitness may have become larger with stricter $\dot{V}O_2max$ criteria[169], or an additional constant load verification phase performed after the graded $\dot{V}O_2peak$ test[193]. While the sensitivity analyses using stricter criteria did not significantly change the results, there was a tendency towards a larger overall effect (increasing from 5.9% to 7.8%), and the within-group change in supramaximal HIT (2.65 mL/kg/min) became more comparable to other HIT-studies[194].

Another methodological aspect is the intensity progression. All participants in supramaximal HIT progressed in intensity, with the median session reaching 90% of their maximal MPO6. However, individual intensities ranged from 68% to 100% of MPO6, suggesting that a steeper progression or longer intervention might have been necessary for some to train more close to their maximal capacity[195]. While some participants in supramaximal HIT might have tolerated a steeper progression, there is a challenging trade-off between achieving the optimal dose-response relationship and what is reasonably achievable over time. The most common reason for not increasing intensity in the subsequent session was that participants did not feel ready to progress. This suggests that a longer training period might be preferable to a more rapid progression among older and untrained adults.

The overall small but significant reduction in blood pressure may be explained by the participants' average blood pressure being within a normal range already at baseline[196]. While larger reductions in blood pressure are associated with greater risk reductions of different cardiac events, even small reductions (≥ 2 mm Hg) are considered clinically relevant on a population level[197]. A meta-analysis by Edwards et al. (2015)[196] showed that aerobic exercise in general provides clinically meaningful blood pressure lowering effects, but the findings for HIT were mixed. For sub-group analyses of HIT, separated into 4 x 4-minutes and all-out sprint intervals, an effect was observed only for maximal all-out sprint intervals. For example, the study by Adamson et al. (2019)[67], utilizing 10 x 6-second all-out intervals among hypertensive individuals presented promising effects on blood pressure. The controlled supramaximal HIT evaluated in this thesis is similar to all-out sprint intervals in terms of duration and external intensity. However, there may be differences between all-out and watt-controlled intervals in reaching maximal power output[198], and the acute cardiovascular response during watt-controlled intervals may be lower[199]. Thus, it would be interesting to further evaluate the effects from controlled supramaximal HIT among participants with clinically high blood pressure.

The observed improvement in lower-limb muscle strength for supramaximal HIT, while significantly different from MIT, was small compared to 12 weeks of resistance training[200], but similar to that observed in a HIT study using 10 x 1-minute intervals among older adults[201]. While heavy resistance training may yield larger and long-term effects on muscle strength[202], the observed 4% increase from supramaximal HIT in this thesis corresponds to approximately 1 to 1.5 years of anticipated decline in muscle strength for men and women, respectively[20]. Additional results from the Umeå HIT Study, indicates that controlled supramaximal HIT was comparable to MIT for improving leg power, balance, and physical function[203]. Furthermore, while both groups improved their anaerobic cycling performance, this improvement was larger in the supramaximal HIT group. Overall, while controlled supramaximal HIT may not serve as a substitute for resistance training, these findings support controlled supramaximal HIT as a viable alternative to traditional aerobic training, with the added potential for anaerobic and muscular improvements that are important for our ability to perform everyday tasks as we age[24,83].

Cognitive Effects

The lack of significant improvements in global cognition in this thesis may be attributable to the study sample. There is ongoing debate regarding the small effects and lack of causal evidence for exercise-induced improvements in cognition, especially among a cognitively healthy population[204–206]. All participants in this thesis were classified as cognitively healthy based on an MMSE score of 27 or higher, which is the commonly used threshold for people aged 65 to 69 years with a higher education[207].

Further, the lack of difference in change between supramaximal HIT and MIT, despite the differing intensities and durations, may suggest that physiological changes are more important than intensity per se when trying to understand exercise-induced cognitive changes. Other studies have failed to observe significant differences in cognitive change between different types of aerobic exercise, but demonstrating that a 1 MET (3.5 mL/kg/min) increase in VO_2peak is associated with better global cognition[208], and that change in VO_2peak is positively associated with change in global cognition and episodic memory[182]. Compared to this thesis, both studies showed larger improvements in cardiorespiratory fitness, and support the notion that exercise-induced physiological changes may mediate the relationship between physical exercise and cognitive improvements[81,209]. While the exercise intervention in this thesis may have been insufficient to produce physiological changes large enough to translate into broader cognitive improvements, it did find a potential domain-specific improvement in working memory favoring the supramaximal HIT group, as well as mixed effects for episodic memory.

An increase in VO2peak is likely not the sole driver of cognitive enhancement, but an indicator of significant metabolic impact that induces remodeling factors[31]. Aerobic and resistance training may affect cognitive functions through slightly different metabolic pathways involved in the growth and reorganization of neurons and blood vessels, with aerobic and resistance training supporting neural growth and reorganization via increased levels of BDNF and IGF-1, respectively[209]. The small but superior effect of supramaximal HIT on working memory may be explained by the combined effects of improved VO_2peak and muscle strength, as it has previously been shown in a meta-analysis that resistance training have a domain-specific effect on working memory[45].

The overall negative change observed in the episodic memory composite appeared to be driven by a decline in one test, with a significantly larger decrease in the MIT group. Meanwhile, there was an overall positive change for the in-scanner task. While within-group improvements in pattern completion performance reached statistical significance only for supramaximal HIT, this change was not significantly different from MIT. Therefore, learning effects unrelated to the exercise intervention cannot be completely ruled out, and this limits the kind of conclusions drawn from the results.

At the neural level of episodic memory, volumetric changes in the hippocampus were observed for the CA2/3 subfield. Similar to the Generation 100[210], there was a possible lateralization of decreased volume to the left hippocampus, mainly for the supramaximal HIT group. These results are in contrast to other studies observing increases, or at least a reduced decline, in hippocampus volume after one year of aerobic or multicomponent exercise[39,211]. Notably, this thesis observed an increase of the right CA4/DG in proportion to total hippocampus volume, which suggest that exercise-induced reorganization of the hippocampus may occur before more evident structural effects can be observed. The volumetric change in the right hippocampus was linked to improved performance in the in-scanner pattern completion task. Although not statistically significant, this may have been driven by increased right CA4/DG volume, which would align with studies demonstrating the DG as a site for adult hippocampal neurogenesis[212–214]. Additionally, a positive association between exercise-induced changes in the DG/CA3 and pattern separation performance have been observed after 12 weeks of exercise in sedentary young adults[215]. However, unlike Nauer et al. (2020)[215], there were no significant associations between changes in cardiorespiratory fitness and hippocampal volumes in this thesis, possibly due to a smaller change in cardiorespiratory fitness.

Furthermore, for hippocampus function, there was an overall decrease in BOLD signal within CA2/3, with a possible lateralization to a decreased signal in the left CA2/3 primarily in MIT. Similarly, a decrease in left hippocampus BOLD signal during a pattern separation task have been observed after 60 days of bed rest combined with plyometric training, compared to bedrest only[216]. While that study did not observe any changes in task performance and consequently concluded that the decrease in BOLD signal reflected higher neuronal efficiency[216], this thesis observed an increase in task performance. Nevertheless, performance improvement was not associated with the signal decrease in CA2/3. Performance change in pattern completion was, however, positively associated with BOLD signal change in the left hippocampus and the left CA4/DG subfield. These associations are in line with studies showing that high-performers in episodic memory often exhibit a stronger BOLD signal, compared to low-performers[32,155]. The BOLD signal change in the left CA4/DG was positively associated with change in cardiorespiratory fitness. Although the effects on hippocampal structures and functions were small, and did not survive corrections for multiple comparison, the findings lend support to the notion that enhanced cardiorespiratory fitness may be linked to improved performance through exercise-induced changes in hippocampal function[81,209]. Additionally, the effects of functional changes on memory performance may occur before potential effects from volumetric changes. However, this should ideally be confirmed in future studies using longer time spans, ensuring greater physiological effects, and more than two measurement points.

There are also other aspects that may influence the effect of exercise on cognition. For example, it has been suggested that there is a need of some concurrent cognitive demand to successfully incorporate exercise-induced neurogenesis and plasticity, such that beneficial effects from physical exercise may be enhanced when combined with cognitive training[217,218]. Furthermore, research has indicated that physical exercise may be less effective among women than men[44]. While out of scope for this thesis, differences in genotype and sex may affect the relationship between exercise and cognition, in such that these differences may vary across different types of exercise as well as different cognitive domains examined[219–221].

<u>Interpreting Changes in Hippocampal Subfield Volumes</u>

The non-significant changes in hippocampus volume corresponded to -0.4%, -0.5% and -0.3% for bilateral, left and right volumes, respectively. These changes are within previously reported numbers of 0.8-2.0% yearly age-expected decline[26]. In contrast to previous studies examining the effects of exercise on hippocampus volume, Erickson et al. (2011)[39] observed a 2% increase for both left and right hippocampus after 1 year of aerobic exercise at moderate intensity; and while Jonasson et al. (2016)[40] observed a non-significant bilateral decrease of about -0.4% after 6 months of moderate-intensity training; Demnitz et al. (2022)[211] observed a 2.3% and 4% decrease in the left and right hippocampus, respectively, after 1 year of multicomponent exercise; while Pani et al., (2021)[210] reported a 1.1% yearly decline rate during five years of HIT. The significant decrease for supramaximal HIT in CA2/3 and left CA2/3 corresponded to -1.8% and -3.8%, respectively. While the decrease in

CA2/3 for supramaximal HIT may seem large, few longitudinal studies exist to compare and interpret this change with. Cross-sectional data have suggested yearly bilateral decline of 1.4% in CA2/3 among older adults, though concomitant with 1.5% for the whole hippocampus[222]. In this thesis, the supramaximal HIT group had an 0.8% decrease in total hippocampus volume. Further, there are limitations to consider regarding the automated methods used for extracting hippocampal subfield volumes. Since the CA2/3 is one of the smaller subregions (<300 mm^3) in the hippocampus it may be more prone to measurement errors[223]. Ultimately, more longitudinal data is needed before we can draw more certain conclusions regarding the volumetric changes in hippocampal subfields.

Methodological Considerations

Overall, the Umeå HIT Study included in this thesis has many methodological strengths. High quality RCTs that use concealed randomization, blinded outcome assessors, and intention-to-treat analysis have repeatedly been requested within the research of HIT and supramaximal HIT[71,180]. The Umeå HIT Study is a large RCT compared to other existing studies examining interval training at supramaximal intensities among older adults[67,75,87]. Further, pre-registration of the training protocol, including defined primary and secondary outcomes, helps prevent reporting bias, and reporting in accordance with the CONSORT guidelines and TIDieR template contributes to improved transparency and reproducibility[121,224].

However, biases are not unavoidable. For example, in exercise trials, it is difficult to blind the participants and exercise supervisors. This can affect how the participants are treated and how they perform during the study. To reduce the risk of performance bias, the participants did not receive information on the assumed superiority of supramaximal HIT compared to MIT, and only received detailed information about their allocated training group. To further reduce the risk of contamination, the participants in the supramaximal HIT and MIT exercised on different days, but in the same training environment. The potential bias from unblinded supervisors was limited by using computer-guided intervals, and standardized criteria to progress intensity over time. While I served as one of the exercise supervisors, and was therefore not blinded to group allocation, the statistical analyses of the primary outcomes were applied on a masked data set and conducted by a statistician blind to group allocation.

Another methodological strength of the RCT is the extensive assessment of applicability-related aspects during each of the 25 training sessions, such as exercise-related participant experiences, perceived exertion and affect. This allows for the evaluation of applicability beyond observer-rated adherence and attendance, and multiple assessment points provides a more nuanced understanding of change over time[225,226]. However, a limitation is that the responses of RPE and FS were asked by the training supervisors, and not blinded for the participants sitting close to each other during the training session. This could potentially introduce a bias from factors such as social desirability, with less dispersion and higher median responses compared to the feasibility study[96]. Preferably, it would have been better if the participants would have been able to give their answer more anonymously on a digital device. This could also have improved the timing of each assessment, which may be of importance when assessing components that may be rather dynamically affected by the variation in exercise intensity and its physiological changes[227]. Meanwhile, the BREQ-2 questionnaire was distributed in a different manner, with the participants answering the questions without the presence of supervisors or other participants, and the positive change in motivation supports the idea that the participants' affective state during the training sessions were mostly on the positive side.

A limitation for the Umeå HIT study is the 9-month follow-up (i.e., nine months from baseline assessments) that could not be conducted to the extent that was intended. Due to the COVID-19 pandemic, majority of assessments for the long-term follow-up were cancelled for the last two participant waves. Questionnaire data from 9-month follow up is available and could provide additional information on the differences and similarities between supramaximal HIT and MIT, however it may be difficult to disentangle the influence of the pandemic. This thesis only included data collected from baseline, intervention, and the 3-month follow-up assessments. While the extensive assessments within and across sessions provided a nuanced picture of participant experiences, such as changes in perceived exertion with increased intensity over time, the majority of outcomes used to evaluate the training effects included only two assessment points, limiting the ability to interpret trajectories of change[225,226].

As in the majority of RCTs, the participants in the Umeå HIT Study volunteered to partake in the study, and the implications of this thesis are to some extent limited to the population sample consisting of older adults aged between 64 to 79 years, not engaged in any regular physical exercise at study enrolments. Further, the participants in the Umeå HIT

Study underwent a thorough medical examination to rule out history of significant cardiac or neurological disease or other symptoms contraindicative of high-intensity exercise, i.e., non-exercising but otherwise relatively healthy. Out of the 156 applicants excluded at enrolment, about a third was due to contraindicative health conditions or the need for further medical evaluation. Future studies should evaluate the safety of controlled supramaximal HIT across a more heterogenous older population.

Ethical Considerations

When conducting a randomized controlled exercise trial, a key consideration is the choice of an active or inactive control group. In the Umeå HIT Study, an active control group performing moderate-intensity training (MIT) was chosen over an inactive control group. An inactive control group may have simplified the interpretation of some of the results in this thesis, such as whether the unexpected negative change in episodic memory was related to the training or potential learning effects. However, with the benefits of being physically active[11,46,48,50], it was considered unethical to withhold the potentially beneficial effects of physical exercise from the participants in the control group. Further, it can be considered a strength that the supramaximal HIT protocol was evaluated in relation to a type of aerobic training already proven beneficial.

With regards to safety, it is understandable that concerns have been raised about the safety of HIT and supramaximal training intensities, and, and that extra precautionary measures are requested. However, considering the heterogeneity of the group “older adults”, it is also unethical and ageist to portrait older adults as being unable or incapable of exercising above moderate intensities and exclude them from training methods with proven positive effects. Engaging in supramaximal training intensities can result in a work closer to both one’s aerobic and anaerobic maximum capacities. To exercise closer to both maximal capacities may become even more important as we age, and older adults may therefore have an even greater need for these type of training interventions[19,84,85]. Still, the potential benefits must outweigh the potential risks, and the Umeå HIT Study implemented measures to prevent harmful side effects in several stages of the study:

- All participants underwent a comprehensive medical examination, including a resting ECG performed by a cardiologist. Individuals with contraindicative health conditions for high-intensity training were excluded (i.e., a significant history of cardiac or neurological disease, or in need for further medical evaluation).

- Two supervisors educated in sports medicine or physiotherapy were present during all training sessions. There was an action plan in place for any potential injuries or illnesses during the training sessions, and the training facility had access to a defibrillator.

- The exercise frequency was limited to two sessions per week since previous research implies that some older adults may require more than three days to achieve full recovery after a HIT session [123,124].

- To further avoid excessive efforts, the exercise intensity was watt-controlled [96], and a set of standardized criteria was used to ensure a safe progression in training intensity according to the participant's individual ability. In order to keep the individual on the desired level of exertion, the intensity could either be increased, maintained, or decreased between sessions. The criteria considered both objective and subjective aspects. In addition to ensuring that heart rate and self-rated perceived exertion aligned with desired level of exertion (Figure 4), the participants also verified their readiness to increase the intensity for the next session.

Practical implications and future research

The findings in this thesis support a broader use of watt-controlled supramaximal HIT for older adults, as it can lead to significant improvements important for health and maintained independence in daily life. The older adults in this thesis were able to regularly engage in supramaximal training intensities. Contrary to concerns about supramaximal HIT for non-exercising older adults[91,92], this thesis found that participation was high over three months of supramaximal HIT, dropout rates were low, and no serious adverse events occurred. This type of watt-controlled supramaximal HIT may offer a more individualized high-intensity training for older adults and lower the threshold for older adults to participate in supramaximal HIT.

This study is one of the few that have involved older adults in supramaximal HIT. The training was conducted in groups on stationary bicycles in a local training center, and each participant was responsible for adjusting their own training load during the session. These features make watt-controlled supramaximal HIT more accessible, compared to the all-out sprint intervals typically studied in laboratory settings with one-on-one supervision. The use of methods to control intensity and reduce exertion and discomfort, and the possibility to perform the training in groups are practical aspects that support future large-scale implementation of this supramaximal HIT program. Still, some challenges remain.

The supramaximal HIT protocol evaluated in this thesis was adapted for mechanically braked, speed-dependent bikes, which are commonly found in fitness facilities. For these bikes, the resistance is less precise and depend on the rider's speed. For a participant to reach the prescribed intensity they need both to set the correct resistance and be able to maintain a steady pace (pedaling cadence). An ergometer bicycle that allows for a set wattage output regardless of pedaling frequency could simplify this procedure, however, at the moment this type of bicycle is less common in public training facilities. While bicycles are the most common method among high- and supramaximal intensity interventions[228], future research should identify and explore alternative modalities that can be performed more independently at home or outdoors. It will also be necessary to identify accessible assessment of baseline fitness and starting intensity, determine the key criteria for intensity progression, and examine to which extent the supervisor guidance can be minimized without compromising intensity adherence and long-term attendance[181,183].

Another challenge to large-scale implementation is whether all older adults should undergo medical screening before engaging in supramaximal training intensities, and how extensive this screening must be. Future studies should evaluate the safety and effects of controlled supramaximal HIT across a more heterogenous older population. While controlled supramaximal HIT could be safely implemented among non-exercising older adults that had received medical clearance, research on supramaximal HIT among clinical populations is needed[180]. For instance, research is needed on whether the gradual and tailored intensity progression used in this controlled supramaximal HIT can be safely implemented among older adults with chronic conditions and diseases. It would also be beneficial to examine both immediate and long-term risks in relation to the benefits of the supramaximal HIT to enable more thorough and accurate risk-benefit assessments. Some populations may even benefit more from controlled supramaximal HIT, compared to MIT. For example, among individuals with chronic obstructive pulmonary disease (COPD), controlled supramaximal HIT may induce a more optimal stimulus for training adaptations by circumventing the ventilatory limitations often associated with continuous aerobic exercise at moderate intensity[199]. It will be interesting to follow the ongoing RCT which aims to examine both feasibility and effects of controlled supramaximal HIT and MIT among people with and without COPD[229].

Interventions that compare different combinations of exercise modalities, or physical exercise in combination with cognitive tasks, may enhance the beneficial effects physical exercise[217]. While controlled supramaximal HIT may be a viable alternative to traditional aerobic training, it would also be interesting to see more interventions evaluating combined effects of aerobic training at different duration and intensity, as well as in combination with other training modalities, such as resistance and balance training[202,230].

Conclusion

This thesis demonstrates that three months of watt-controlled supramaximal HIT among non-exercising, medically cleared older adults was safe to perform and induced significant physiological changes, comparable or even superior to moderate-intensity training (MIT); changes that may make meaningful contributions to the independence and daily life activities of older adults. While the link between motivation, dopamine and aging needs further research, an interesting observation was that, contrary to previous concerns, controlled supramaximal HIT in a supervised group setting did not negatively impact the participants motivation to exercise. Possibly, the individually tailored approach may have provided the external guidance that some older adults need to engage in high-intensity exercise. Taken together, these findings support the inclusion of controlled supramaximal HIT as an appealing, time-efficient, and effective training method also for older adults. It is a meaningful addition to the exercise programs commonly available for older adults, as providing more tailored and individualized training may contribute to promoting physical exercise for health and well-being.

The impact of supramaximal HIT on cognitive functions were mixed. To better understand the relationship between cognition, exercise and intensities, future studies should aim for longer interventions and more pronounced physiological changes. Looking forward, research should also evaluate controlled supramaximal HIT across more diverse populations including those with chronic conditions and diseases, as well as focus on how to effectively implement controlled supramaximal HIT in real-world settings.

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