

Research paper

The iReAct study – A biopsychosocial analysis of the individual response to physical activity

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ABSTRACT

Background: Physical activity is a substantial promoter for health and well-being. Yet, while an increasing number of studies shows that the responsiveness to physical activity is highly individual, most studies focus this issue from only one perspective and neglect other contributing aspects. In reference to a biopsychosocial framework, the goal of our study is to examine how physically inactive individuals respond to two distinct standardized endurance trainings on various levels. Based on an assessment of activity- and health-related biographical experiences across the life course, our mixed-method study analyzes the responsiveness to physical activity in the form of a transdisciplinary approach, considering physiological, epigenetic, motivational, affective, and body image-related aspects.

Methods: Participants are randomly assigned to two different training programs (High Intensity Interval Training vs. Moderate Intensity Continuous Training) for six weeks. After this first training period, participants switch training modes according to a two-period sequential-training-intervention (STI) design and train for another six weeks. In order to analyse baseline characteristics as well as acute and adaptive biopsychosocial responses, three extensive mixed-methods diagnostic blocks take place at the beginning (t_0) of the study and after the first (t_1) and the second (t_2) training period resulting in a net follow-up time of 15 weeks. The study is divided into five modules in order to cover a wide array of perspectives.

Discussion: The study's transdisciplinary mixed-method design allows to interlace a multitude of subjective and objective data and therefore to draw an integrated picture of the biopsychosocial efficacy of two distinct physical activity programs. The results of our study can be expected to contribute to the development and design of individualised training programs for the promotion of physical activity.

Trial registration: The study was retrospectively registered in the German Clinical Trials Register on 12 June 2019 (DRKS00017446).

1. Introduction

Physical activity is considered one of the most relevant strategies for the promotion of biopsychosocial health. Regular physical activity not

only lowers the risk of cardiovascular diseases [1], type 2 diabetes [2,3], and cancer [4,5] and prolongs life expectancy [3] but also has positive effects on mental well-being and fosters the development of personal resources, the sense of achievement, and social networks [6,7].

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Consequently, the World Health Organization (WHO) recommends that “adults aged 18–64 years should do at least 150 min of moderate-intensity aerobic physical activity throughout the week, or do at least 75 min of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity” [8].

In recent years, there has been an increasing number of studies that show that people respond individually and in different ways to exercise, both physiologically and affectively. These results imply that stereotypical advice for health-promoting physical activity is inadequate. However, both a comprehensive framework for the investigation of individual effects of physical activity and empirical evidence supporting differential counselling are still missing.

The study presented here is designed as an interdisciplinary research network consisting of five modules. Based on an analysis of activity- and health-related biographies, we investigate individual physiological, affective, and cognitive responses to high-intensity interval training (HIIT) versus moderate intensity continuous training (MICT). In contrast to most of the foregoing studies, which have primarily been mono-disciplinary approaches (e.g. physiological, biomedical, or psychological) we aim to adopt, in a proof-of-principle approach, a holistic biopsychosocial perspective in order to account for individuality.

2. Theoretical framework

2.1. A transdisciplinary model of biopsychosocial response to physical activity

A fundamental assumption of our project is that the individual responsiveness to physical activity cannot be explained by mono-disciplinary paradigms only. Individual development over the life-course [9] is a result of an interaction of psychosocial, affective, and physiological factors that leads to the formation of distinctive patterns. Individual responsiveness to physical activity and its consequences for the human being therefore has to be analysed as a complex biopsychosocial entity.

Early biopsychosocial models have been criticized due to their lack of differentiation. In order to explain individual differences in physical activity behaviour and response, more differentiated transdisciplinary models are needed. A model by Bryan et al. [10] integrates different disciplinary approaches (incorporating molecular approaches, animal models, human laboratory models, and social psychological models), and therefore claims to enable “a better understanding of characteristics of individuals that are important in the adoption and maintenance of physical activity” [10 p20]. According to Bryan’s model, the acute physiological response depends not only on the actual exercise behaviour, but also on genetic factors, the subjective experience of exercise (such as the perceived exertion, changes in affect, changes in arousal, and pain), and the motivation to exercise (including the attitude towards/self-efficacy for exercise, the intentions to exercise, the intrinsic/extrinsic motivation, expectancies, goals, and the self-concept). However, Bryan’s model does not cover all factors that are relevant for the explanation of biopsychosocial responsiveness to physical activity. In our perspective, the subjective responsiveness is influenced by the individual’s biography (as the subjective core element of individuality) and by the image the individual has of his/her own body. As we will explain in the following, these influences are not limited to an affective dimension, but also have physiological effects.

In order to depict developmental processes of individuality, we developed a transdisciplinary process model that is built on the framework by Bryan et al. [10]. In our model, the biography bundles all subjective experiences with regard to physical activity and health. The actual subjective responsiveness to a physical activity stimulus is reflected in affective and motivational responses and the body image. Epigenetic factors and the physical condition have an impact on the physical response to exercise, while the subjective experiences of

physical activity are psychologically processed and in consequence influence body image and motivation. Adaption in the medium and long term depends on the repetition of training bouts and their biological, psychological and social processing. In turn, the changed state of epigenetic factors, physical condition, body image and motivation to exercise determines the future reconstruction of past experiences (the “future biography”) and therefore future physical activity behaviour (Fig. 1).

2.2. The individual biography as a core factor of the individual response to physical activity

In orientation to studies on the (un)willingness of people to be physically active, we assume that the individual responsiveness to physical activity is not solely genetically predetermined and unchanging, but develops and changes over the life course. According to these studies, factors such as gender, social networks, environmental influences, or social and cultural norms are key correlates of physical activity, besides genetic, evolutionary physiological, political and global factors [11,12]. Although the findings of these studies give reason to assume that context-related factors, such as neighbourhood, social support, or education, influence activity behaviour and its effects, the mechanisms of the individual response to physical activity still remain unclear.

In our opinion, a key mechanism lies in the way how individuals reconstruct past experiences in physical activity-related contexts. On the one hand, the way a person reconstructs his/her past experiences is decisive for his/her subjective individuality (or, in other words, the feeling of being different from others). What makes a person unique as an individual is encapsulated in the experiences that he/she has made over the life course. On the other hand, memory research shows that the meaning that individuals attach to past events are ever changing depending on their present circumstances [13]. This leads to the assumption that the *currently remembered* history is more predictive regarding future behaviour than what *actually happened* in the past. This holds particularly true as the individual biography contains reflections about the individual’s capacity to overcome “disruptive experiences” [14,15] such as illness, personal crises, stigmatisation, or discrimination experiences [16]. From this perspective, biographies have to be considered a core factor of the subjective individual response to physical activity.

Biographies are mental constructs that become available through narration. Processes of reflection allow access to past experiences and eventually shape biographies in the form of a ‘reflexive self-consciousness’, including concepts of past, present, and anticipated future [17]. Hence, the analysis of individual biographies reveals information on how and why a person acts in activity- and health-related settings. However, the role biographies play with regard to the individual response to physical activity has barely been studied by now.

2.3. Body image and responsiveness to physical activity

Biographies also determine how we see ourselves in general and our body in particular. Body representation is a multifaceted construct encompassing a conglomerate of perceptual versus conceptual representations which can be more or less explicit [18,19]. The image an individual has of his/her own body is an integration of physiological sensations from the body with cognitive, emotional, and motivational perceptions and self-reflections of one’s own body and physical health. These self-reflections root in the past and are therefore an integral part of the individual’s life story.

Many studies report that physically active persons tend to be more satisfied with their body and also more sensitive towards physiological signals from the body [e.g. Ref. [20]]. Additionally, reduced abilities to form conscious representation of internal physiological signals have been theorized to predispose healthy individuals for greater body image

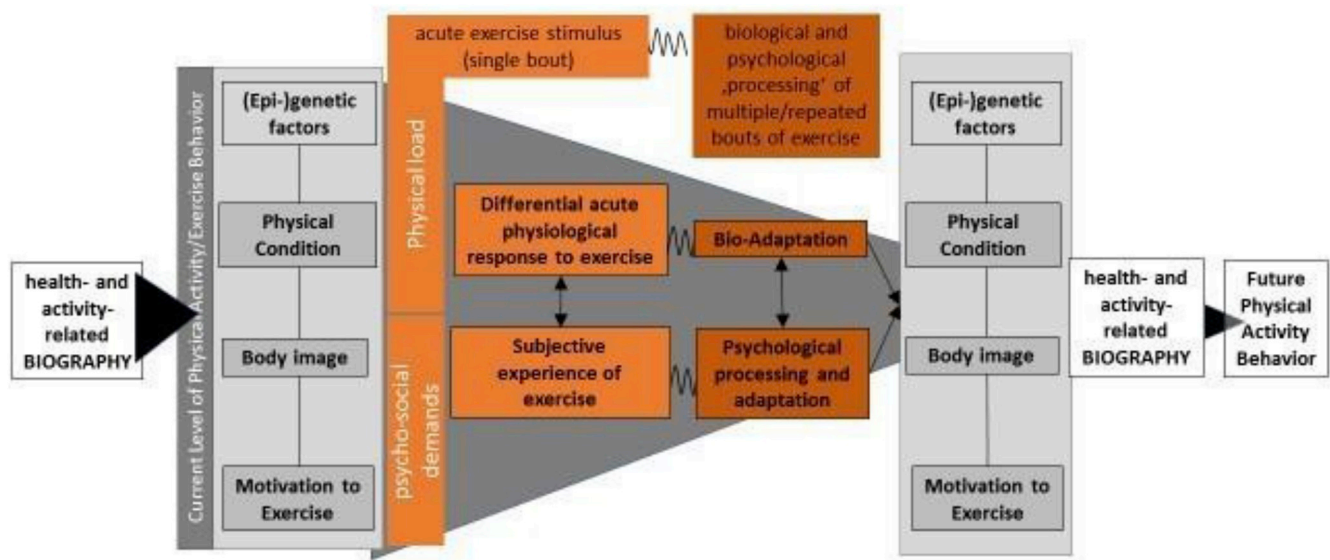


Fig. 1. Transdisciplinary model of responsiveness to physical activity.

dissatisfaction, as well as the development of eating disorders or the severity of body image disturbances in clinical populations [21]. On the other side, internalization of weight-related criticism, for example, goes along with a significantly reduced willingness to be physically active [22]. Obese people tend to avoid diets and regular physical activity if they integrate discrimination experiences into their self-concept [23–25]. It is assumed that the relationship between body representation and physical activity is bi-directional: One's own body image (e.g. body dissatisfaction) might present a motive for engaging in physical activity [26] and physical activity in turn, might influence body representation. By now, however, there is almost no systematic research on the individual response to different forms of physical activity with respect to the individual body representation.

2.4. The affective responsiveness to physical activity

Over the last years, exercise psychology has put an increasing emphasis on inter-individual differences in the affective response to physical activity [27,28]. Recent studies document a substantial inter-individual variability in affective responses to exercise dependent on the intensity of physical activity [29,30]. At vigorous intensity levels there seems to be a particularly high inter-individual variability. In very high exercise intensities, interoceptive cues (e. g. heavy breathing or muscular pain) are supposed to overrule cognitive processes and strengthen the link between interoceptive factors and the affective response to activity [31]. However, it is still unclear to which extent the physiological response correlates with the affective response to physical activity.

Furthermore, research on the affective response to physical activity depending on different training regimens, such as HIIT versus MICT, has revealed somewhat contradictory results. While Martinez et al. [32], Kilpatrick et al. [33] and Little et al. [34] conclude that heavy interval training is more enjoyable for the participants than heavy continuous training, other studies report HIIT regimes as inappropriate for a largely sedentary population, particularly because of the lack of enjoyment [35]. The controversial discussion is very well documented in an article by Biddle & Batterham [36]. While Biddle argues that high-intensity exercise has a psychologically aversive nature which, in turn „will predict drop out or a marked reduction in exercise intensity over time during self-regulated exercise bouts“, Batterham refers to a compelling number of articles that are „reporting comparable exercise enjoyment and confidence to engage in a HIIT protocol“ [36 p2]. However, due to

limited and inconclusive research, reliable conclusions for the individual affective and motivational processing of the different exercise regimes are not possible.

2.5. The variety of physiological responses to physical activity

It is well documented that the physiological effects of physical activity are dependent on the intensity and the type of exercise [37]. However, most physiological and health-related outcomes of physical activity vary highly from person to person [38,39]. A genetic explanation for this variation is the association between single nucleotide polymorphisms (SNPs) and the extent of phenotypic adaptation. For example, SNPs of the Brain-Derived Neurotrophic Factor (BDNF) or of the nuclear hormone receptor peroxisome proliferator-activated receptor δ (PPAR δ) and its transcriptional coactivator PPAR γ coactivator 1 α (PGC-1 α) have been shown to be related to physiological and affective responses to exercise [40,41]. Other researchers state that the beneficial effects of physical activity on cardiometabolic risk factors, the risk of cardiovascular disease and cancer, are modulated by a number of co-variables, such as pre-existent fitness, gender, anthropometry, life time exposure to physical activity, and others [42–47]. Moreover, it has been shown recently that the failure of adapting insulin sensitivity to exercise training is associated with impaired upregulation of mitochondrial fuel oxidation genes and an augmented pro-inflammatory state in skeletal muscle [47]. Finally, recent data indicates that the adaptive response to exercise, particularly skeletal muscle adaptation, is controlled by epigenetic mechanisms, such as differential DNA methylation, histone modification, and microRNA (miRNA) expression [for review see Refs. [48,49]].

Apart from this, there is an ongoing discussion about the percentage of non-responders to physical activity with respect to risk factor reduction. In some studies, this percentage is estimated at up to 20% of all exercisers [46,50]. In contrast, however, a recent study [51] concludes that non-responding to physical activity in terms of a blunted increase of maximum oxygen consumption (VO_{2max}) is a myth – i.e. that everybody can physiologically benefit from regular physical activity – and that the only relevant factors are the type and the dose of activity, which have to be individually tailored. Moreover, an immediate change in the type of training, e.g. from MICT to HIIT may allow supposed non-responders to MICT to adapt successfully to HIIT.

In this context, more recent research suggests that more vigorous exercise such as HIIT may be superior to continuous exercise performed

with low or moderate exercise intensities. Thus, most studies could prove an advantage of the HIIT with the improvement of VO_{2max} [52]. With regard to more clinical endpoints, such as insulin sensitivity, blood pressure or BMI, the advantage of HIIT over low or moderate was less uniform [53–56].

2.6. Research desiderates

Existing research suggests that people should get individually tailored advice on how to be physically active. What has not been thoroughly analysed by now is how the subjectively experienced individuality of a person (represented in his/her biography, the body image, and the motivation to exercise) and the individual physiological stress response to a standardised bout of exercise (training session) influence the adaptive response to exercise regimes. How physiological and affective responses to physical activity correlate has also been hardly investigated.

3. Study concept and methods

3.1. Central research questions

It can be summarized that the individual responsiveness to physical activity has only been partly studied by now. Furthermore, the existing findings are to a certain extent ambiguous. Against the background of this research desideratum, our project focuses on the following questions:

How do individuals physiologically, epigenetically, cognitively and affectively respond to two sequential intervention training programs with significantly different intensities but the same energy consumption? To which extent do the type and the sequence of the interventions influence the final outcome?

Specific sub-questions will be addressed in five study modules, which have their own central research questions (see below). Beyond these individual questions, the joint project aims to analyse overarching research questions regarding the biopsychosocial response to physical activity, such as for example:

- To which extent do physiological, epigenetic, and affective responses correlate?
- What role does the individual stress response to a standardised bout of exercise play with regard to the individual physiological, epigenetic, and affective responsiveness to physical activity?
- What role does the health- and activity related biography play with regard to the individual physiological and affective responsiveness to physical activity?
- Are there typical activity- and health-related biographies and do they correlate with physiological and affective responses to physical activity and the individual body image?
- How does the reconstruction of training experiences during the intervention relate to the in-situ affective and physiological outcomes?
- What role does the individual body representation (the satisfaction with the own attractiveness, interoceptive abilities, the perception of the own physical capacity or the degree of body acceptance in general) play with regard to the individual physiological and affective responsiveness to physical activity? Does the individual body image change dependent on different forms of physical activity?
- Do the data allow to categorise the subjects regarding responsiveness-related characteristics? Can high- and low-response groups be identified?
- Are specific epigenetic markers predictive for a “high” or “low” affective and/or physiological response to a particular type of training?
- How are biological adaptations, changes in motivation and body image related? To which extent are these relations modulated by type and

sequence of exercise regimes or factors such as gender, and social networks?

Due to these joint research questions, our study is characterised by an integral approach. This means on the one hand that all participants will have to participate in all experiments/tests/interviews. On the other hand, the collected data will be stored in a joint database.

Not least, the project aims at identifying translational strategies that can be transferred to specific target groups. In this regard, the following questions will be relevant:

- What are the main specifics that have to be considered for the individualised development of training programmes, when a trans-disciplinary approach is applied?
- How can personalised training recommendations be integrated into the subjects’ life-worlds?

3.2. Sample and subject recruitment

Thirty men and thirty women, aged 20–40 yrs, will be recruited for the study. Further inclusion criteria are:

- Non-smokers
- BMI between 18,5 and 30,0 kg/m²
- Currently not meeting WHO-recommendations for moderate physical activity (less than 150 min/week)
- Less than 60 min/week of exercise during leisure time (including sports participation, endurance-oriented activities, muscle strengthening) and no regular exercise for several weeks during the last six months
- Maximum oxygen uptake (VO_{2max}) between 25 and 50 ml/min/kg
- No current or former eating disorder or obesity
- No severe internistic or neurological previous illness
- No pregnancy or breastfeeding period
- German as a native language

Reasons for exclusion are:

- Chronic diseases or findings that results in a decreased ability to participate in a physical activity intervention
- Medication or supplement intake within the last 4 weeks, which according to the physicians might interfere with the study results (exception: contraceptives)
- Counter indication(s) for local anesthetics
- Clinically relevant deviations in the lab results
- Pathological indications in the resting-ECG
- Vein conditions that do not allow for multiple blood sampling
- Participation in a medication study within the last three months
- Drug use, alcohol abuse
- Current psychotherapy

Participants are primarily recruited via the university mailing list and the university clinics mailing list. Additionally, postings on the MPI Experimental Database, advertisements, newspaper articles, and online presence on the homepage of the institute of sports science are employed to raise awareness for the study. Interested parties are provided with detailed information on the study protocol and are asked to fill in a physical activity questionnaire (European Health Interview Survey – Physical Activity Questionnaire (EHIS-PAQ)) in order to assess current physical activity levels. Furthermore, an additional telephone screening to check eligibility criteria is done. Finally, a medical examination takes place prior to final enrolment in the study. As a part of this examination, interested parties are once again informed about the study protocol and requirements, and a written informed consent is obtained.

Data collection takes place at the institute of sports science, the department of sports medicine and the Max Planck Institute Tübingen.

The participants are enrolled at the Department of Sports Medicine of the University Clinic Tübingen by physicians and trained personnel. The data is entered by the members of the research team. All collected data is anonymized and stored on a safe database at the University of Tübingen, which can only be accessed by members of the research team.

3.3. Two-period sequential-training-intervention (STI)

Women and men will be randomly assigned to two training groups. As exercise intensity is a potential factor, which influences the individual response to training, we will compare two different concepts of endurance training using a sequential training intervention design. This means that the participants start with MICT respectively HIIT and then switch to HIIT respectively MICT without a wash-out period between the two interventions. Each training period will last 6 weeks and consists of three weekly training sessions. This procedure allows us to compare the outcomes of HIIT vs. MICT after the first follow-up analysis and the influence of the sequence of both interventions on the final outcome after the second follow-up.

Training of group MICT will consist of Moderate Intensity Continuous Training, while HIIT will be realised via a High-Intensity-Interval-Training. Energy consumption will be adjusted to be nearly identical in both trainings sessions and is planned to be approximately 8 MET-hrs. per session.

Group MICT will perform continuous cycling exercise at a power output (PO) corresponding to 90% of the first lactate threshold (LT) for 60 min three times a week [57–59]. The HIIT group will perform a 10-min warm-up at a PO corresponding to 70% of maximal heart rate (HR_{max}), followed by 4 x 4-min intervals at a PO corresponding to 90% HR_{max} with a 4-min active resting period at 30 W between each interval (such exercise intensity was chosen to allow participants to reach 70% HR_{max} during the recovery period) [60]. After the last interval, a cool-down period will be performed for 5 min at 30 W, totalizing 43 min of exercise. MICT and HIIT will be performed on a calibrated cycling ergometer and will be supervised by trained personnel. Exercise intensity will be controlled throughout the whole period of the training intervention. During every training session, PO, cadence, and 3-channel ECG assessing heart rate will be recorded to control for the default training intensity.

To increase adherence, the participants receive each € 500 for completing the whole study protocol. In order to secure adherence to the intervention program, they get an individually tailored training plan. Additionally, the participants receive written notifications of the diagnostic schedule before the baseline analysis. Beyond the € 500 incentive for completing the whole study protocol, adherence to training will be increased by offering two training sites and by setting fixed, yet adjustable training dates. If subjects cannot keep an appointment, an alternative date is scheduled if possible. In cases of non-appearance a telephone or direct query will be made. If a subject achieves less than 15 training sessions in the 6-week training period, the subject will be excluded from the study.

After the first 6-week training period and the repeated data collection at follow-up I, the second 6-week training period will be started without a wash-out period, therefore generating an intended carry-over effect. In the second training period, the participants have to attend to the training regime that was not selected in the previous period in order to assess whether a blunted response to the first training mode reflects a real non-response to exercise or can be counteracted by choosing an alternative exercise intensity.

3.4. Testing procedures and study protocol

Biopsychosocial data including indices of physical fitness will be collected at baseline (week 1), at follow-up I after the first training period (week 8), and at follow-up II after the second training period (week 15) (see Fig. 2). The detailed variables, which will be assessed are

summarized in Table 1.

To delineate the physiological and affective response during acute exercise, a bout of cycling exercise will be performed at week 0, 8 and 15. After a 10-min warm-up at a PO corresponding to 90% of the first lactate threshold, participants will cycle at a constant PO corresponding to the midpoint between the first and the second lactate threshold for 50 min. Such exercise intensity is within the heavy-intensity domain (i. e., vigorous exercise intensity) [61] and a MET-range between 6 and 9, dependent of the individual VO_{2max} .

Venous blood samples will be drawn at baseline, week 8, and week 15 3 h prior to as well as directly and 3 h after the reference training session. A total of four muscle biopsies will be obtained from the M. vastus lateralis at baseline, week 8, and week 15 (three one day prior to and one 2 h after the reference training session – the latter only at baseline).

Biological specimens for genetic or molecular analysis are collected and stored at the Department of Sports Medicine, University Clinic Tübingen. Skeletal muscle specimens will immediately be shock-frozen in liquid nitrogen and stored at $-80^{\circ}C$ until further use. They will be analysed for differential gene expression as well as epigenetic markers, such as DNA methylation, histone modifications, and microRNA (miRNA) patterns using standard molecular biology technologies. Serum and plasma will be aliquoted and also stored at $-80^{\circ}C$. These samples will be employed to determine metabolic characteristics and also to assess concentrations of circulating miRNAs.

The study is constantly monitored by physicians and trained personnel in order to prevent and manage possible adverse events and unintended effects of the interventions. All diagnostics, including potential unintended events and effects, are documented in case report forms for each participant.

In addition, we plan to document everyday activity three times, each time over a period of 7 consecutive days (at baseline, follow-up I, and follow-up II) using accelerometers.

3.5. Data analyses and statistical methods

Formally, the study uses a two-period sequential-training-intervention (STI) design with 1:1 allocation to both sequences. A computer was employed by the Institute for Clinical Epidemiology and Applied Biometry at the University of Tübingen to generate random numbers which were used to sort the cases. The allocation to the different study groups remained concealed to the researchers. The randomization list was created using the software nquery 7.0 with mixed block sizes and two binary stratification factors age ($\leq 32 / > 32$ ys) and sex.

The primary endpoint has been chosen to be VO_{2max} which is a physiological surrogate parameter relevant for all subsequent interdisciplinary analyses. Based on the results of this parameter, a subsequent trial with „clinically“ important outcomes and a much larger sample size will be applied for funding after this study. In the terminology of clinical trials, we are in a Phase II situation, with surrogate primary endpoint, and we are generating evidence for a „Phase III-trial“ on the subject. The second important parameter of general interest will be the drop-out rate compared between both sequences of interventions. This rate, however, might be biased towards overoptimistic results (too small drop-out rates in both groups) due to the honorary for successful termination of the trials for probands. For VO_{2max} , we found in a meta-analysis of Weston et al. a delta (Baseline vs. after exercise) of 2.6 ml/kg KG/min for MICT (25.2. minus 22.5) and of 5.2 ml/kg KG/min for HIIT (27.9 minus 22.5) [62]. Thus, there was a difference of 2.6 ml/kg KG/min between both. An analysis of the standard deviations of all included study arms (calculated from sample size and standard error in Table 1 of Weston et al. [63]) showed a consistent picture of about 10% for the value of the SD (the mean of SDs was 9.46, the median 9.33, 47 of 55 study arms showed a standard deviation between 9% and 11%). Thus, we may assume a standard deviation of 10%. An effect size of 75% (for which our study was powered, see below) corresponds to 7.5%. 7.5% of 28 is 2.1

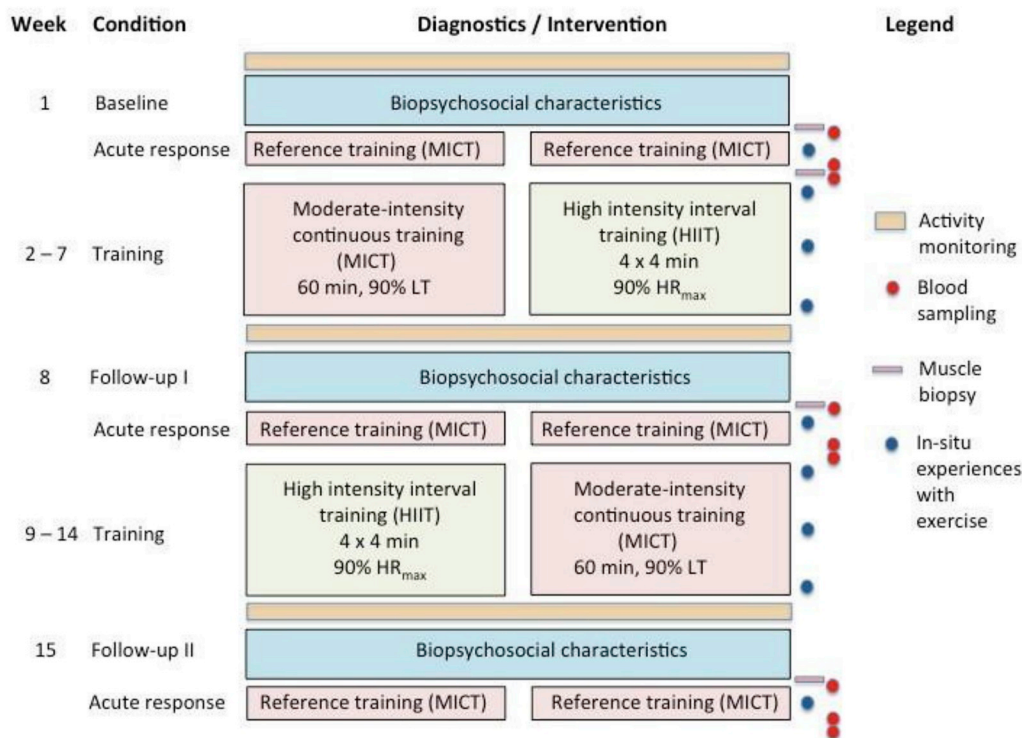


Fig. 2. Time line and protocol of the study. HR_{max} , maximal heart rate; LT, first lactate threshold.

which is close to the difference HIIT minus MICT in Weston et al. [62].

Due to the application of a sequential intervention design, a comparison of the single interventions will only be done after the first follow-up. The primary focus of our comparative longitudinal analyses is therefore on the sequences of the two interventions, not on the single interventions. Thus, the aim of the study is to identify the optimal sequence, not the optimal intervention. This leads to interindividual comparisons. With 60 subjects and two degrees of freedom spent on the strata age and sex, effect sizes (difference of means divided by standard deviation) of about 75% (exactly: 74.9%) can be shown. (type 1 error 0.05, two-sided, type 2 error 0.20, nquery 7.0.). Note that the same power holds for the comparison of interventions in the first phase (secondary analysis). Adjustment for multiple testing will be difficult and will not be done across subprojects.

The analysis will be done using an Ancova with baseline as continuous covariate and sequence as factor of interest. Additionally, the stratification factors age (binary) and sex will be included in the primary analysis. As secondary analysis, a mixed model with treatment, time and the interaction as fixed and participant as random factors will be included. Note that the time vs. treatment interaction which corresponds to the (unfavourable) carry over effect in a cross over design is here part of the secondary analysis. The primary analysis population is a modified ITT population: Subjects, who do not contribute measurements from both periods will be excluded, for subjects who contribute measurements from only one period (mostly period 1) multiple imputation using the information from the documented period will be applied. As sensitivity analysis, only complete cases will be analysed. No interim analysis will be done.

3.6. Ethic approval and consent to participate

IRB approval: The 'Ethics Committee of the Medical Faculty, University of Tübingen' reviewed and approved this study (reference number: 882/2017BO1). All participants are informed about the study procedure, the audio recordings of interviews, subsequent data storage, and confidentiality and anonymity regarding the data. We collect

written informed consent from all participants that we are allowed to use the data for research purposes and publish research articles by using a standard study consent form.

4. Study modules

4.1. Study module 1: Individual response to physical activity as a biographical effect

4.1.1. Central problem

The motivation and willingness to be physically active is shaped by the experiences people have made in their individual life world. Research about health-related *social contagion* [64] for example shows that "people imitate the diet or exercise habits of their least fit friends, or use those friends' fitness as a benchmark for their own" [[65]; p.662]. Biographical analyses can shed a light into the complexity of such activity- and health-related experiences. In this regard, they can explain why people dislike or enjoy physical activity and how behavioural patterns develop. Furthermore, the biography may have an impact on how individuals adapt on a psychosocial level to physical activity. Additionally, this module collects longitudinal data on psychosocial changes (well-being, subjective health, quality of life, and social adaptation) using questionnaires (Table 1).

4.1.2. Central research question

Which role do biographies play regarding the individual response to physical activity?

In this regard, the project focuses on the following questions:

- How do health- and physical activity-related behavioural patterns develop across the life?
- How is physical activity perceived in the individual socio-cultural and historical life world?
- How do critical life events and transitions contribute to the uptake of or drop-out from physical activity?

Table 1
iReAct assessments.

	TIMEPOINT					
	t-1	t0	Training	t1	Training	t2
Week	-1	1	2-7	8	9-14	15
Assessments by Study Modules						
Screening and Study Inclusion	X					
Study Module 1						
Biographical Mapping [76,77]		X				
Psychosocial Process Monitoring [76,77]				X		X
Demographic Questionnaire [78]		X				
ALPHA Questionnaire [79]		X				
Social Support for PA Scale (adapted version) [80]		X				
Satisfaction with Life Scale [81, 82]		X		X		X
WHO-Five Well-Being Index [83]		X		X		X
WHO-QOL-BREF [84]		X		X		X
Subjective Vitality Scale [85]		X		X		X
FEW-16 Questionnaire [86]						
PHQ-9 Depression Inventory [87]		X		X		X
GBB-24 Questionnaire [88]		X		X		X
Social Adaption Self-Evaluation Scale [89,90]		X		X		X
Study Module 2						
Body Scan		X				X
Biometric Body Avatars		X		X		X
Interoception Task		X		X		X
EDI-2 Questionnaire [91]		X		X		X
Drive for Thinness Scale [91]		X		X		X
Body Dissatisfaction Scale [91]		X		X		X
PACS Questionnaire [17]		X		X		X
Study Module 3						
7-Day Accelerometry (handed out before diagnostics)		X		X		X
EHIS-PAQ [92]	X			X		X
Attitudes towards Exercise Questionnaire [93]		X		X		X
Self-Determined Motivation to Exercise Questionnaire [94]		X		X		X
Exercise-Specific Self-Efficacy Questionnaire [95]		X		X		X
Motives and Goals for Exercise [96]		X		X		X
PRETIE-Questionnaire [97]		X		X		X
Activity-related Affect Regulation Questionnaire [98]		X		X		X
Affective response to reference training session (MICT) Feeling Scale [99]		X		X		X
Felt Arousal Scale [100]			week 2, 4, 7		week 9, 11, 14	
Enjoyment of Exercise and Perceived Competence Scale [27]			week 2, 4, 7		week 9, 11, 14	
Further determinants of subjective experience of activity (e.g., social context)			week 2, 4, 7		week 9, 11, 14	
Study Module 4						
Medical History, medical examination	X					
Anthropometry: BMI, abdominal girth; percent body fat and muscle mass (BIA)		X		X		X
Resting and exercise electrocardiogram (ECG)		X		X		X
		X		X		X

Table 1 (continued)

	TIMEPOINT					
	t-1	t0	Training	t1	Training	t2
Week	-1	1	2-7	8	9-14	15
Resting and exercise blood pressure						
Cardiac dimensions and function (echocardiography)		X		X		X
Spiroergometry and lactate diagnostics		X		X		X
Arterial stiffness (pulse wave velocity)		X		X		X
Microvascular Endothelial Function (NIRS)		X		X		X
Blood analyses (Lipids, glucose, insulin)		X		X		X
Metabolic stress response to reference training session (plasma metabolome)		X		X		X
Training monitoring (power output, heart rate)			During training		During training	
Study Module 5						
Molecular response to reference training (muscle biopsy 2 h post-exercise)		X				
Epigenetic analyses (Resting muscle biopsies)		X		X		X

- How does the social environment (e.g. social support or networks) influence the development of health- and activity-related practices?
- Which positive and negative experiences have individuals made in different physical activity settings?
- How do individuals adapt to physical activity from a psychosocial and reconstructive health perspective? Which role does the sequence of training regimes play in this regard?

4.2. Study module 2: Body talk: Investigating changes in body image as an individual response to physical activity using biometric avatars

4.2.1. Central problem

Although cross-sectional evidence suggests an improvement of body image and interoception as an effect of physical activity, the individual response to physical activity (and specific training conditions) concerning body representation has hardly been studied. Furthermore, previous studies have predominantly relied on questionnaire data which might be less valid and sensitive to change than new approaches integrating modifiable body stimuli.

4.2.2. Central research question

The major goal is to investigate the body representation of sedentary individuals and its dynamic changes as an individual response to physical activity on a longitudinal basis.

We would like to answer the following questions:

- How is body representation of sedentary individuals characterized in terms of estimated/ideal discrepancies, body related attitudes and interoceptive performance? How are these variables associated with individual characteristics such as gender and individual biography or physiological fitness?
- How does body representation change as a response to (different types of and different sequences of different types of) physical activity?
- How are changes in body representation associated with other individual dynamic characteristics?

4.3. Study module 3: Individual affective and motivational response to different exercise regimes in sedentary adults

4.3.1. Central problem

Some researchers strongly question the potential of high intensity training for the promotion of public health. They argue that those interventions do not sufficiently reach inactive people due to the negative side-effects on affective responses to high intensity training [e.g. Refs. [66,67]]. Contrary, some interventional studies report higher enjoyment in, higher preference for and greater adherence to HIIT in contrast to MICT in insufficiently active people [67–70]. Comparably, the two recent reviews including both active and inactive people, show that HIIT can elicit similar responses on pleasure and enjoyment as MICT [71,72]. However, the authors also point out that findings are still inconsistent regarding the affective response to different exercise regimes, especially in sedentary people.

Additionally, Stork and colleagues [71] illustrate that one has to consider the time point of assessment, when drawing conclusions about affective responses to exercise. They outline: even if participants are reporting equal or greater enjoyment of, and preference for HIIT *after* the exercise is finished, affective measurements *during* the ongoing training bout appear to be more negative in HIIT than in MICT. For these in-task affective responses, evidence shows that they can be predictive of adherence and future exercise participation in continuous training [e.g. Refs. [73,74]]. Yet it is not clear if this relationship also holds for high intensity exercise regimes and if the sequence of training regimes influences the outcome.

4.3.2. Central research questions

- Comparing MICT and HIIT in a group of sedentary adults, which inter-individual and intra-individual differences occur in acute affective response during and after exercise? Does the sequence of the two interventions influence the affective response during and after exercise?
- How do these acute affective responses change over a multi-week training period? Could we observe different dynamics depending on the kind (MICT, HIIT) and the sequence of training regimes?
- Which personal (e.g. gender, individual goals) and activity-related (e.g. intensity, volume) characteristics contribute to the variability of acute affective response to exercise?
- How are exercise motivation and training adherence affected by different types and sequence of exercise regimes and corresponding affective responses to exercise?

4.4. Study module 4: Individual response to physical activity: Physical fitness, stress response and disease-related endpoints

4.4.1. Central problem

The individual response of cardiorespiratory fitness (CRF) and disease related cardiometabolic risk factors varies highly. At present, it is unclear whether the extent of trainability is based primarily on individual factors or is the result of an individual variability of the required dose of exercise. In both cases, it is desirable to obtain valid instruments which allow a prediction of the individual's training responsiveness to improve individual training counselling in the preventive setting.

4.4.2. Central research questions

The topic of study module 4 addresses the question of how the response or non-response rate in terms of physiological and disease-related risk factors to exercise training depends on the type of exercise (MICT versus HIIT) and the sequence of the two training regimes. Moreover, module 4 will elaborate, how the adaptive response is modulated by the physiological response to acute exercise and further co-variables. In particular, we will ask:

- Does non-response of physiological (e.g. physical fitness) and disease-related risk factors to MICT decline as the intensity of training increases? Does the sequence of the two interventions determine the physiological response?
- Is a different pattern of the acute stress response to a given bout of exercise related to the individual adaptive response to physical activity?
- Does gender affect the rate of low responders to two standardised training protocols (MICT, HIIT)? Does the sequence of the two interventions determine the physiological response differently dependent on gender?
- Are there gender-specific patterns of the acute stress response to a given bout of exercise which are associated with a different adaptive response to physical activity?

4.5. Study module 5: Epigenetic characteristics and changes as molecular basis for the individual response to exercise?

4.5.1. Central problem

Skeletal muscle is highly malleable and can respond to physical activity in a complex and multimodal manner. Examples of adaptation reactions are changes in muscle cell metabolism and myofibre type. The molecular basis for these adaptation reactions are altered gene expression patterns, as an individual's temporal and spatial transcriptional response to a particular type of exercise eventually determines his or her physiological response [for review, see Ref. [75]]. Most interestingly, recent work suggests that these transcriptional responses are controlled by epigenetic mechanisms, i.e. molecular mechanisms that robustly control gene expression without altering the DNA base sequence [for review, see Refs. [48,49]]. Thus, based on a refined knowledge of a possible inter-relationship between a specific type of exercise and the epigenetic reaction evoked by this regimen, it might be possible to develop individualised concepts for training programmes.

4.5.2. Central research questions

- Which types of epigenetic changes do different types of physical activity induce in the skeletal muscle? Does the sequence of the two interventions influence epigenetic changes?
- How can they or even an individual's basal epigenetic characteristics at rest be correlated with skeletal muscle transcriptional and the individual's physiological response to exercise?
- Which DNA and histone methylation patterns and which miRNA expression profiles can we observe in skeletal muscle tissue at rest and after a single bout of exercise?
- Can these patterns be correlated with expression patterns of adaptation-relevant genes, myofibre distribution, the individual's physiological response to a single bout of exercise, and/or his/her trainability, i.e. the response to a specific exercise regimen (MICT vs. HIIT) and to a specific sequence of exercise regimes?

Table 1 summarizes all assessments by study module that take place during the training intervention.

5. Discussion

To analyse the individual response to different forms of physical activity from a biopsychosocial perspective is highly relevant. Interventions, which claim to effectively and sustainably promote the individual's health, have to take into account that not every form of physical activity leads to the same responses across individuals. Likewise, not every activity is equally rewarding for a person, not at least due to his/her activity- and health-related biographical experiences and motivational prerequisites. In this regard, the expected results of the study contribute to the advancement of personalised health promotion and prevention strategies using one of the most effective instruments –

physical activity.

Ethics approval and consent to participate

Ethics approval was obtained by the 'Ethics Committee of the Medical Faculty, University of Tübingen' on the 22 January, 2018 (reference number: 882/2017BO1). All participants are informed about the study procedure, the audio recordings of interviews, subsequent data storage, and confidentiality and anonymity regarding the data. Written informed consent is collected from all participants that we are allowed to use the data for research purposes and publish research articles by using a standard study consent form.

Consent for publication

Written informed consent is collected from all participants that we are allowed to use the data for research purposes and publish research articles by using a standard study consent form.

Availability of data and material

The datasets generated and/or analysed during the current study are not publicly available. For further information, please contact the corresponding author.

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Authors' contributions

Conceptualization and design of the study: AT, GS, BM, KG, SZ, SM, AMN. Manuscript drafting: AT, GS, AMN, HG. Statistical advisory support and generating of allocation sequence: PM. Critical revision of manuscript before submission: AT, GS, HG, FMM, TS, DS, MW, SM, PM, BM, KG, SZ, AMN. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

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