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# High-intensity interval training to promote cerebral oxygenation and affective valence during exercise in individuals with obesity

## *Rehabilitative exercise training in obesity*

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## ABSTRACT

Left/right prefrontal cortex (PFC) activation are linked to positive/negative affects, respectively. Besides, larger left PFC oxygenation during exercise relates to higher cardiorespiratory fitness (CRF). High-intensity interval training (HIIT) is superior to moderate-intensity continuous training (MICT) in improving CRF. The influence of training on PFC oxygenation and affects during exercise in individuals with obesity is, however, currently unknown.

Twenty participants with obesity (14 males,  $48\pm 8$  years, body-mass index =  $35\pm 6$  kg m<sup>-2</sup>) were randomized to MICT [50% peak work rate ( $WR_{peak}$ )] or HIIT (1-min bouts 100%  $WR_{peak}$ ; 3 sessions/week, 8 weeks). Before/after training, participants completed an incremental ergocycle test. Near-infrared spectroscopy and the Feeling Scale assessed PFC oxygenation and affects during exercise, respectively.

Improvements in CRF (e.g.  $WR_{peak}$ :  $32\pm 14$  vs  $20\pm 13$ W) were greater after HIIT vs MICT ( $p<0.05$ ). Only HIIT induced larger left PFC oxygenation (hemoglobin difference from  $7\pm 6$  to  $10\pm 7$   $\mu$ mol) and enhanced affective valence (from  $0.7\pm 2.9$  to  $2.2\pm 2.0$ ;  $p<0.05$ ) at intensities  $\geq$  second ventilatory threshold. Exercise-training induced changes in left PFC oxygenation correlated with changes in CRF [e.g.  $WR_{peak}$  (% predicted),  $r=0.46$ ] and post-training affective valence ( $r=0.45$ ;  $p<0.05$ ).

HIIT specifically improved left PFC oxygenation and affects during exercise in individuals with obesity. Implementing HIIT in exercise programs may therefore have relevant implications for the management of obesity, since greater affective response to exercise is thought to be associated with future commitment to physical activity.

**Keywords.** Affect; exercise; obesity; obesity management; spectroscopy, near-infrared.

**Trial registration number.** NCT02642705 (clinicaltrials.gov)

## INTRODUCTION

Obesity [body-mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>] is defined as an abnormal or excessive fat accumulation that may impair health.(1) This condition has become a real pandemic worldwide: its prevalence has tripled over the past 40 years to reach ~650 million adults in 2016 (1). Specifically, obesity is associated with increased all-cause mortality (2) and an enhanced risk of cardiovascular diseases, type 2 diabetes, insulin resistance, hypertension and certain types of cancer (3). It is well established that regular physical activity yields positive implications for the health and well-being of individuals with obesity such as improvements in cardiorespiratory fitness (CRF) and metabolic status (4). According to the WHO recommendations, adults with obesity should perform a minimum of 150 minutes of moderate-intensity or 75 minutes of vigorous-intensity aerobic physical activity/week.(1) Unfortunately, however, less than 3% of men and 1.5% of women with obesity reach the level of recommended physical activity.(5)

In this context, there is an urgent need to offer both efficient and well-tolerated exercise training protocols to maximize health benefits and promote future adherence in a patient population who is typically reluctant to physical activity (6). In persons with obesity, high-intensity interval training [HIIT: **relatively short (seconds-to-minutes)**, high-intensity bouts of exercise interspaced by periods of recovery] has been shown more effective on improving cardiocirculatory adaptations [i.e. peak O<sub>2</sub> uptake, VO<sub>2peak</sub> (7)] and common risk factors associated with obesity [e.g. high blood glucose or insulin resistance (8)] than traditional recommended endurance training [i.e. moderate-intensity continuous training (MICT)]. Short-duration ( $\leq 1$ min) bouts of exercise interspersed with recovery phases to evaluate the tolerance to HIIT have been implemented in pathological populations (e.g. patients with diabetes) and showed good feasibility (9). It has also, however, been reported that a session of HIIT (four 3-min intense exercise bouts/2 mins of recovery) was perceived as less pleasant and enjoyable than an isocaloric MICT session in women with obesity.(10)

Addressing these matters would be key since it is well established that affective response to exercise determines future commitment to regular physical activity (11). Negative affective response typically results in avoidance of physical activity whereas positive feelings may lead to regular participation.(12) Furthermore, affective responses typically become more negative (*i.e. exercise becomes more unpleasant*) when exercise intensity increases due to the concomitant enhanced negative interoceptive input from the body and a decrement in cognitive control.(13) *However, such interoceptive input has been shown to result in more negative affective responses in individuals with obesity* compared to normal-weight counterparts regardless of exercise intensity.(14)

These appetitive and reluctant responses to exercise may be found in a context of distinct prefrontal cortex (PFC) activation patterns *referred to as PFC asymmetry*.(15) *Hence, the relative activation of left vs right PFC may be associated with positive (left > right PFC) or negative (right > left PFC) affects, respectively*.(16) Near-infrared spectroscopy (NIRS) is a powerful tool for examining functional activation of the human cerebral cortex by tracking changes in cerebral O<sub>2</sub> status in response to various stimuli, including physical exercise.(17, 18) Interestingly, left PFC oxygenation profile is influenced by training status: higher levels of PFC oxygenation and perfusion is found in aerobically-trained *vs* untrained individuals at high exercise intensities (19). However, PFC oxygenation and the affective response during exercise after exercise training have never been investigated in concert in individuals with obesity.

Given these premises, this single-blind randomized trial examined the influence of two exercise training protocols on cerebral oxygenation and affective valence during exercise in individuals with obesity. Owing to the greater reported cardiocirculatory effects of HIIT *vs* MICT, we hypothesized larger increases in left PFC oxygenation and a more positive affective response to an incremental cardiopulmonary exercise test in participants undertaking an 8-week HIIT program compared to MICT.

## MATERIALS AND METHODS

**Participants.** Twenty sedentary (<2h of self-reported, low-intensity physical activity per week) obese otherwise healthy individuals were recruited from the Pulmonary Function Tests Laboratory (CHU de Grenoble, France) or by word of mouth between March 2018 to March 2019. Participants were deemed eligible for study inclusion as per the following criteria: i) aged 18-65 years; ii) body-mass index  $\geq 30$  kg/m<sup>2</sup>; iii) no type I or type II diabetes and; iv) no chronic cardiorespiratory diseases (except treated obstructive sleep apnea). Participants underwent a medical routine assessment consisting of a standard clinical examination, a 12-lead resting electrocardiogram and spirometry. This study was approved by the local Research Ethics Board (CPP Sud-Est V, #2014-A01482-45) and was registered at clinicaltrials.gov (NCT02642705). Participants gave written informed consent prior to study participation.

**Experimental design.** Participants were randomly assigned to two distinct groups of exercise training: MICT (n=10) or HIIT (n=10). They undertook 3 weekly sessions of 45-min duration over 8 weeks. Participants were blind from the opposite group training regimen and from study hypotheses. Before and within 4 days after training, participants completed an incremental exercise test to symptom limitation with PFC oxygenation assessed by NIRS (20).

**Physical activity.** Time spent in sedentary and physical activities, steps/day and daily energy expenditure were assessed by a tri-axial accelerometer (SenseWear, BodyMedia Inc., Pittsburgh, PA, USA) worn on the upper arm over a week before exercise training. The intensity of activity for each minute of wear time was calculated and expressed using metabolic equivalents (METs) to determine average daily time (min/day) spent active. Specifically, the cut-offs used for the different intensity domains were: light (1.5–3 METs), moderate (3–6 METs) and vigorous physical (>6 METs) activity (21).

**Resting procedures.** Standard measures of height and weight and waist and hip circumference were performed. Spirometry was performed before intervention: data were expressed relative to predicted (%) using equations endorsed by the Global Lung Function Initiative (22). Whole-body magnetic resonance imaging for total fat and lean mass determination were obtained with a General Electric Sigma Advantage 1.5-T scanner (General Electric Medical Systems, Milwaukee, WI, USA) using a validated protocol previously used in our Laboratory (23).

**Incremental cardiopulmonary exercise test.** Participants exercised on a computer-controlled electronically-braked cycle ergometer (Corival, Lode BV, Groningen, The Netherlands) with breath-by-breath gas analysis (MetaMax 3B, Cortex Biophysik GmbH, Leipzig, Germany) and ECG measurement (Custo Cardio 110 BT, Custo Med GmbH, Ottobrunn, Germany). After a 2-min resting period and a 2-min warm-up (30 W in females and 50 W in males), workload was increased by 15 W and 20 W/2 min in females and males, respectively, until symptom limitation. Pedalling frequency was self-selected by participants, provided it exceeded 60 rpm. Arterial O<sub>2</sub> saturation was measured by earlobe pulse oximetry (Radical 7, Masimo Corp., Irvine, CA, USA). Blood lactate concentration (Lactate Plus®, Nova Biomedical Corp., Waltham, MA, USA) was determined after 2 min of recovery. Dyspnea and leg discomfort scores were obtained using a standard 100-mm visual analog scale. Afterwards, the single item 11-point bipolar Feeling Scale (24) assessed affective valence (i.e. pleasure-displeasure). Briefly, participants were asked to choose the number that best described how they felt at the moment: scores range from -5 (“*very bad*”) to +5 (“*very good*”) with 0 being “*neutral*”. These different scores were obtained in the last 30 s of each stage. Reference equations for peak work rate ( $WR_{\text{peak}}$ ) and peak O<sub>2</sub> uptake ( $VO_{2\text{peak}}$ ) were the ones from Neder and colleagues.(25)

**Near-infrared spectroscopy.** Left and right PFC oxy- (HbO<sub>2</sub>) and deoxyhemoglobin (HHb) concentration changes were measured throughout testing sessions using a two-wavelength (780 and 850 nm) multichannel, continuous wave NIRS system (Oxymon MkIII, Artinis Medical Systems, Elst, The Netherlands). NIRS signal was

assessed between Fp1 and F3 locations (left) and between Fp2 and F4 locations (right PFC) according to the international 10-20 EEG system (interoptode distance= 3.5 cm). HbO<sub>2</sub> and HHb were measured as difference from the initial resting period during exercise tests.(26) Total hemoglobin (HbTot) concentration was calculated as HbO<sub>2</sub> + HHb. HbO<sub>2</sub> and HbTot are mostly sensitive to blood flow and O<sub>2</sub> delivery while HHb is closely associated with changes in venous O<sub>2</sub> content and therefore tissue O<sub>2</sub> extraction.(27) The difference in hemoglobin (HbDiff) was calculated as HbO<sub>2</sub> - HHb, providing a reliable estimate of changes in tissue (de-)oxygenation status (28).

**Exercise training.** Participants trained on an electronically-braked cycle ergometer (Corival, Lode BV, Groningen, The Netherlands). In MICT, workload was set at 50% WR<sub>peak</sub>. HIIT consisted in 1-min bouts of cycling at 100% WR<sub>peak</sub> interspaced by 1 min of passive recovery. The duration of sessions was progressively increased throughout programs: MICT: from 32 min (*first week*) to 44 min (*last week*) of continuous exercise; HIIT: from 16 (*first week*) to 22 (*last week*) 1-min bouts of intermittent exercise (and equal rest periods). The relative external work performed by the leg muscles during exercise training sessions was, therefore, equivalent in participants assigned to MICT and HIIT. Sessions started with a 2-min warm-up and ended with a 2-min cool-down both performed at 30% WR<sub>peak</sub>. Pedalling frequency was self-selected by participants, provided it exceeded 60 rpm. Rating of perceived exertion [single item Rating of Perceived Exertion Scale (29), ranging from 6 (“*no exertion at all*”) to 20 (“*maximal exertion*”)], affective valence (Feeling Scale (24)) and perceived activation [single item 7-point bipolar Felt Arousal Scale (30), ranging from 1 (“*low arousal*”) to 6 (“*high arousal*”) ] were assessed throughout the 1<sup>st</sup>, 12<sup>th</sup> (at half) and 24<sup>th</sup> (last) session of exercise-training programs. Specifically, scores were obtained before and after the 2-min warm-up preceding and after the 2-min cool-down following the core of the session for MICT and HIIT. Scores were obtained during different bouts of intense exercise for HIIT, corresponding to 25%, 50%, 75% and 100% duration of the core of the session. Scores were obtained at corresponding time points during continuous exercise for MICT.



**Data analysis.** Cardiorespiratory and NIRS data were averaged over the last 30 s of the resting period and over the last 30 s of each stage during the incremental exercise test. Peak O<sub>2</sub> uptake was identified as the highest O<sub>2</sub> uptake over a 30-s period during incremental exercise. Ventilatory thresholds (VT<sub>1</sub> and VT<sub>2</sub>) were determined using gas exchange parameters.(31) VT<sub>1</sub> was determined as an increase in ventilatory equivalent for O<sub>2</sub> (VE/VO<sub>2</sub>) and end-tidal O<sub>2</sub> partial pressure with no increase in ventilatory equivalent for CO<sub>2</sub> (VE/VCO<sub>2</sub>). VT<sub>2</sub> was determined as an increase in both VE/VO<sub>2</sub> and VE/VCO<sub>2</sub> and a decrease in end-tidal CO<sub>2</sub> partial pressure. Data collected during the incremental exercise test were categorized and analyzed as low and high exercise intensities when collected  $\leq$ VT<sub>1</sub> and  $\geq$ VT<sub>2</sub>, respectively.

**Statistical analysis.** Procedures were performed on Statistica v.10 (Statsoft, Tulsa, OK, USA). Based on previous research exploring the comparative efficacy of MICT and HIIT on improving VO<sub>2peak</sub> (8, 32), we expected a 15 ± 5% increase after MICT and a 50% superiority of HIIT. With  $\alpha=0.05$  and a 2-tailed test of significance, 8 participants per group were required to provide a statistical power of 80%. Normality of distribution for continuous physiological variables was assessed with a Shapiro-Wilk test [or normal p-p plots (expected normal *vs* observed value, **depicted in Figure S1**) for NIRS parameters]. For between-group comparisons, homoscedasticity for variables whose data respected a normal distribution was assessed with a Levene test. For normally-distributed data, unpaired or paired t-test were used for between- and within-group comparison, respectively. Non-normally-distributed data (including NIRS parameters) were analyzed using Mann-Whitney U test or Wilcoxon signed-rank test for between- and within-group comparison, respectively. Discrete variables (i.e. exertional symptoms, rating of perceived exertion, affective valence and perceived activation) were analyzed using the abovementioned non-parametric approach. Independent-sample and dependant-sample Hodges-Lehman Median Difference test were applied for non-normally distributed continuous variables and for discrete variables to determine 95% confidence intervals, respectively. Effect size for normally-distributed data was calculated with a Cohen's *d* test, while effect size *r* was reported for non-normally

distributed continuous variables and for discrete variables. Effect sizes were interpreted as small, medium and large when  $d = 0.2-0.5$ ,  $0.5-0.8$  and  $>0.8$  or when  $r < 0.3$ ,  $0.3-0.5$  and  $>0.5$ , respectively.(33) Chi-squared test was used to compare between-group frequencies. Pearson product-moment correlation assessed linear relationships between variables. A two-tailed alpha level of 0.05 was used as the cut-off for significance. Where applicable (i.e. for data collected during incremental exercise test or training sessions), the cut-off for significance was adjusted by dividing 0.05 by the number of comparisons being made over time (i.e. incremental exercise test:  $\leq VT_1$  or  $\geq VT_2$ ; training sessions: from before warm-up to after cool-down).

## RESULTS

### Participants' characteristics

Resting characteristics of participants before exercise training are shown in **Table 1**. General characteristics, body composition, pulmonary function and habitual physical activity did not differ between groups at baseline ( $p > 0.05$ ). Anthropometrics and body composition were not altered by exercise training in either groups ( $p > 0.05$ , data shown in **supplementary Table S1**).

### Incremental cardiopulmonary exercise testing

Physiological and perceptual responses at the peak of incremental exercise testing before and after intervention are presented in **Table 2**. At baseline, no differences were observed between groups ( $p > 0.05$ ). Training led to an increase in  $WR_{peak}$  (absolute value and % predicted) and  $VO_{2peak}$  (absolute value, % predicted and relative to body weight) in both groups ( $p < 0.05$ ). Increases in  $WR_{peak}$  (absolute value:  $32 \pm 14$  vs  $20 \pm 13$ W) and  $VO_{2peak}$  (% predicted:  $16 \pm 7$  vs  $10 \pm 7\%$ ) were greater in HIIT vs MICT (both  $p < 0.05$ ; 95% confidence intervals = 2; 25 W and 1; 12%, respectively;  $d = 0.908$  and  $0.750$ , respectively).

## Near-infrared spectroscopy during cardiopulmonary exercise testing

Cerebral oxygenation profiles (HbDiff and HbTot) as a function of exercise intensity during incremental cycling in MICT and HIIT are presented in **Figure 1**.

*Before exercise training.* A larger increase in HbTot at **exercise intensities  $\leq VT_1$**  was observed in the left *vs* right PFC in MICT ( $p = 0.014$ ; 95% confidence intervals = 0.1; 1.8  $\mu\text{mol}$ ; effect size  $r = 0.389$ ; **Figure 1**). No significant difference was observed between prefrontal cortices in HIIT (all  $p > 0.025$ ; **Figure 1**).

*After exercise training.* HbDiff at **exercise intensities  $\geq VT_2$**  in the left PFC were lower after *vs* before exercise training in MICT ( $p = 0.003$ ; 95% confidence intervals = -4.4; -0.7  $\mu\text{mol}$ ; effect size  $r = 0.460$ ; **Figure 1**).

HbDiff at **exercise intensities  $\geq VT_2$**  in the left PFC were greater after *vs* before exercise training in HIIT ( $p = 0.014$ ; 95% confidence intervals = 0.8; 4.8  $\mu\text{mol}$ ; effect size  $r = 0.389$ ; **Figure 1**). No other training-induced difference was observed (all  $p > 0.025$ ; **Figure 1**).

Changes in HbO<sub>2</sub> and HHb as a function of exercise intensity for MICT and HIIT are shown in **supplementary Figure S2**, since no significant difference was observed (all  $p > 0.025$ ).

## Affective valence during cardiopulmonary exercise testing

Affective valence before and after exercise training as a function of exercise intensity during incremental cycling in MICT and HIIT is presented in **Figure 2**. Before exercise training, affective valence did not differ between groups at any exercise intensity ( $p > 0.025$ ). Affective valence at **exercise intensities  $\geq VT_2$**  was greater after *vs* before exercise training in HIIT, when compared at the same absolute work rate ( $p = 0.014$ ; 95% confidence intervals = -2.5; -0.5; effect size  $r = 0.389$ ; **Figure 2**).

### Correlations between variables during cardiopulmonary exercise testing

Post-pre exercise training difference in left PFC HbDiff concentration at peak exercise correlated with training-induced changes in  $WR_{\text{peak}}$  (% predicted;  $r=0.46$ ;  $p=0.044$ ) and  $VO_{2\text{peak}}$  (mL/kg/min,  $r=0.44$ ;  $p=0.049$ ; *left panels, Figure 3*) in our sample of 20 participants. No other association was found between NIRS parameters (right PFC included) and training-induced changes in exercise capacity (all  $p>0.05$ , data shown in **supplementary Table S2**).

At absolute work rates corresponding to peak exercise before exercise training, scores of affective valence after exercise training correlated with post-pre exercise training difference in left PFC HbDiff ( $r=0.45$ ;  $p=0.048$ ) and HbO<sub>2</sub> ( $r=0.46$ ;  $p=0.044$ ; *right panels, Figure 3*) concentration at peak exercise in our sample of 20 participants. Similar associations were found at absolute work rates corresponding to VT<sub>1</sub> before exercise training: scores of affective valence after exercise training correlated with post-pre exercise training difference in left PFC HbO<sub>2</sub> ( $r=0.55$ ;  $p=0.012$ ), HbTot ( $r=0.50$ ;  $p=0.026$ ) and HbDiff ( $r=0.61$ ;  $p=0.005$ ). No significant association was found between exercise-training induced changes in right PFC oxygenation and post-exercise training affective valence regardless of exercise intensity (all  $p>0.05$ , data shown in **supplementary Table S3**).

### Psychological variables during exercise training sessions

Rating of perceived exertion, affective valence and perceived activation throughout the 1<sup>st</sup>, 12<sup>th</sup> and 24<sup>th</sup> session are presented in **Table 3**. Regardless of the session, HIIT was neither perceived harder nor led to a greater perceived activation than MICT (all  $p>0.007$ ). MICT and HIIT also led to similar affective valence during exercise training sessions (all  $p>0.007$ ).

## DISCUSSION

The present proof-of-concept study investigated the hitherto unexplored influence of two exercise-training protocols on PFC oxygenation profile and its link with affective response during exercise in individuals with obesity. We found that i) both MICT and HIIT improved CRF, although the latter may yield larger adaptations; ii) only HIIT ameliorated left PFC oxygenation profile and affective response during exercise and; iii) exercise training-induced changes in left PFC oxygenation status were associated with the ones in exercise capacity and post-exercise training affective valence scores in our participants. These findings indicate that, owing to substantial improvement in CRF, HIIT might facilitate specific alterations in PFC activation and improve affective valence in response to exercise in individuals with obesity.

### **Influence of exercise training on cerebral oxygenation during exercise**

In previously inactive participants, both exercise training modalities led to a significant improvement in exercise capacity (**Table 2**). As supported by previous publications (34, 35) and as hypothesized, participants undertaking HIIT derived greater benefits than those assigned to MICT in some indicators of CRF (together with relatively large effect sizes in the 0.6-0.9 range). Interestingly, HIIT offered an average 3.5 mL/kg/min increase in peak  $\text{VO}_2$ , precisely corresponding to 1 metabolic equivalent of task (MET). As a matter of fact, a 2016 statement from the *American Heart Association* suggested that each 1-MET increase in CRF was associated with substantial (10-25%) improvement in survival.(36) Our results thus support the implementation of HIIT in individuals with obesity to maximize CRF, an issue recently considered as a “clinical vital sign”.(36)

The novelty of this study yet lies in whether HIIT would yield more favourable alterations in PFC oxygenation owing to these greater adaptations. We found that HIIT led to larger increases in left PFC HbDiff at intensities  $\geq \text{VT}_2$  after training suggesting an improved left PFC tissue oxygenation status, while no significant differences were observed in the right PFC (**Figure 1**). The relationship between enhanced CRF and (left) PFC oxygenation may be supported by the moderate correlation between differences in peak-exercise PFC HbDiff and training-

induced changes in  $WR_{\text{peak}}$  (% predicted) or  $VO_{2\text{peak}}$  (mL/kg/min; *left panels, Figure 3*). On the other hand, a lower increase in left PFC HbDiff at intensities  $\geq VT_2$  (further discussed below) was found after intervention in MICT (**Figure 1**). It might first be key to emphasize that the extant literature only applied NIRS to the left PFC.(19) In this context, PFC oxygenation is influenced by (aerobic) training status and exercise intensity: prefrontal oxygenation and perfusion are found greater in aerobically-trained *vs* untrained individuals at harder exercise intensities (i.e. close to  $VO_{2\text{peak}}$ ). (19) Interestingly, 12 weeks of HIIT (37), but not MICT (38), elevated CRF and peak-exercise PFC oxygenation during incremental cycling in patients with heart failure, corroborating the notion that HIIT may induce specific adaptations in cerebral hemodynamics. The larger increases in left PFC HbDiff at exercise intensities  $\geq VT_2$  after exercise training in HIIT in our study are therefore supported by these findings. Surprisingly, lower left PFC oxygenation status (changes in HbDiff) at intensities  $\geq VT_2$  was found after MICT, despite improvements in exercise capacity with exercise training. These lower changes in HbDiff may arise from a concurrent plateau in HbO<sub>2</sub> and an increase in HHb (although not statistically significant in the present study, shown in **supplementary Figure S2**) at near-maximal exercise intensity in trained individuals.(19) In individuals with obesity, a 4-month HIIT program resulted in greater CRF and peak-exercise HHb compared to baseline.(39) In our participants, left PFC HHb at peak exercise after intervention correlated with CRF [ $WR_{\text{peak}}$  (W) and  $VO_{2\text{peak}}$  (L/min), both  $r=0.67$ ;  $p=0.001$ ]. In this context of greater cerebral O<sub>2</sub> supply and demand, repeated exposure of the central nervous system to elevated neural input from the exercising muscles (40) might lead to its “desensitization”(19). This would enable achieving higher intensities of effort despite greater challenge to cerebral homeostasis among aerobically-trained individuals.(19, 40, 41). One might therefore hypothesize that HIIT, due to repeated bouts of exercise at maximal intensity (i.e.  $WR_{\text{peak}}$ ), may offer such favourable central adjustments in individuals with obesity.

### **Prefrontal cortex oxygenation and affective valence in response to exercise**

The second main question of this investigation lies in whether the favourable changes in PFC oxygenation after HIIT would translate into more positive affective response to exercise. We found that affective response was only improved following HIIT at intensities  $\geq VT_2$  when compared at the same absolute work rate (**Figure 2**). Moreover, **peak-exercise** intervention-induced changes in left PFC oxygenation were moderately associated with post-exercise training affective response (**Figure 3**; see **supplementary Table S3 for similar associations at lower exercise intensities**). In this context, the PFC is involved in motivational and decision-making processes and may act as a relay station in the central fatigue related network regulating central command.(42) The PFC is supplied with information about the motivational and emotional context arising from the anterior cingulate cortex and the orbitofrontal cortex and through peripheral sensory feedback.(41) Once these information are integrated, the PFC may be able to influence the subsequent response to exercise (i.e. terminate exercise or, when possible, modify pace/strategy) through the pre-motor area and the basal ganglia.(41)

Such appetitive and reluctant responses to exercise may arise from differential PFC activation.(15) The hypothesis of prefrontal hemispheric asymmetry was first raised from EEG recordings by Davidson (43): the relative activation of left to right PFC would thus be related to positive or negative affective responses (44). Bearing in mind the health benefits that exercise confers, recent findings suggest that left frontal asymmetry may be used as a marker of physical activity and sedentary behavior: greater left frontal asymmetry was negatively associated with time spent sitting but positively with the amount of habitual physical activity (45). Owing to these physio-psychological considerations, it may be key to stress the fact that HIIT induced exclusive changes in left PFC activation (**Figure 1**) together with improved affective response at the same absolute work rates (**Figure 2**).

Another key construct in exercise physio-psychology testable with NIRS is the dual-mode theory. This concept discriminates exercise completed below or above  $VT_1$ , with major implications for affective responses to exercise.(44) Affects during exercise are thus influenced by top-down cognitive processes and bottom-up interoceptive afferents, the latter being increasingly salient as intensity exceeds a

physiological steady state.(44) This leads to more negative affective valence when intensity surpasses  $VT_1$  [e.g. (46)]. It has thus been proposed that active involvement of the PFC is required to deal with such aversive stimuli.(13) A low hemodynamic response in the PFC  $\leq VT_1$  is thought to reflect a minimal metabolic demand (47) as sensory afferents from the body does not threaten homeostasis and affective responses are typically positive at such intensities (13, 44, 46). It may explain why both PFC oxygenation and affective valence were not influenced by exercise training  $\leq VT_1$  in MICT and HIIT. Conversely, the dual-mode theory supports the notion that greater (left) PFC activation after HIIT at intensities  $\geq VT_2$  may serve to better face aversive stimuli, leading to more positive affective valence at similar work rates.

### **Implications for the management of individuals with obesity**

Increased levels of physical activity is recommended not only for weight but also for the health benefits it confers as part of the first-line approach for the management of obesity.(4, 48) Yet, individuals with obesity typically perform little habitual exercise, a concern recently qualified as an “extreme avoidance of physical activity”.(6) Obesity may interact with exercise intensity resulting in lower pleasure during exercise among individuals with obesity; in turn, repeated experiences of lower pleasure would lead to future avoidance of physical activity.(6) Given that affective responses become more negative with the increase in exercise intensity (13), seeking strategies that would maximize health benefits derived from exercise training (i.e. implementing HIIT (7)) and promoting adherence to future physical activity becomes a formidable challenge in individuals with obesity.

Interestingly, it has been shown that affective responses remained positive and inhibitory control (which contribute to the ability to emotionally regulate sensations about one’s physiological status (49)) was preserved at low and moderate intensities ( $\leq VT_1$ ) during an incremental exercise in overweight individuals (50). On the other hand, further increases in exercise intensity led to negative scores of affective valence and a transient decline in inhibitory control.(50) It follows that these authors suggested that exercising at low/moderate intensities may be used to foster



adherence to exercise in sedentary overweight individuals. Our results contradict this suggestion for 3 main reasons: i) HIIT offered larger gains in CRF (a consideration not addressed in the cross-sectional study by Da Silva and colleagues (50)); ii) only HIIT ameliorated affective response to exercise, specifically at intensities  $\geq VT_2$  and; iii) scores of affective valence remained positive at intensities  $\geq VT_2$  following HIIT. Owing to the point that affective response to acute exercise (12) and, crucially, positive changes in affective response to exercise after training (11) predict future participation to physical activity, this study rather suggests using HIIT to concurrently promote future commitment to physical exercise and maximize health-related benefits in individuals with obesity.

One might yet argue that HIIT would be poorly implementable in individuals with obesity due to the aversive stimuli brought by intense exercise.(51) Research evidence inferring that such modality would lead to negative affect and, consequently potential subsequent avoidance for physical activity, revolves around the dual-mode theory (44). Specifically, this body of work (and, we admit, our above-mentioned rationale) extrapolated findings from continuous exercise above  $VT_1$  to HIIT protocols, which may be different physiologically and motivationally.(51) In this context, Jung et al. (52) compared affective responses to a session of HIIT, MICT and vigorous-intensity continuous training (VICT) in healthy, sedentary people. While general affective response was greater in response to MICT *vs* VICT and HIIT throughout exercise, HIIT yielded more positive valence during the last intense bout of exercise and the last period of recovery *vs* VICT.(52) Interestingly, HIIT was perceived as more enjoyable and led to a greater exercise preference than VICT.(52) Consequently, participants reported greater intentions to engage in MICT or HIIT over VICT at least 3 times per week over the next month.(52) In the present study, HIIT was neither perceived harder nor led to a greater perceived activation than MICT during training sessions (**Table 3**). MICT and HIIT led to a similar affective valence, with generally speaking, positive Feeling Scale scores regardless of the session or the time during a specific session being considered (**Table 3**). Diverging results have yet been described in women with obesity, in whom HIIT was perceived as less pleasant and enjoyable than MICT.(10) Potential reasons for these

discrepancies may arise from: i) different HIIT protocols (namely, intensity and duration of exercise/recovery periods); ii) different duration of intervention (a single session *vs* a full program of exercise training) or; iii) different study population under investigation (women exclusively *vs* a mixed sample of men and women) (10). Of note, greater FS scores were found after 12-24 sessions (at least, at the start of these sessions for HIIT) in the present study, supporting the fact that the amount of exercise training performed may thereafter influence affective responses later in the training program (53). In this context, HIIT might be implementable in individuals with obesity (at least in hospital-based, controlled settings) which, in turn, might contribute to their future commitment to physical exercise in line with positive affects during exercise training sessions and improvement in affective response during incremental exercise.

### **Limitations and perspectives**

Our relatively low sample size might be in line with the complexity of enrolling individuals with obesity without obvious cardiorespiratory comorbidities (54) and their typical reluctance for physical activity (6). Of note, HIIT is thought to be safe in patients with cardiac and respiratory diseases (55, 56). Although our sample size may have been small for the number of comparisons made, our cut-off for significance was adjusted accordingly. Also, there was no specific familiarization with the incremental exercise test done prior to the pre-exercise training assessment for this study to account for any learning effects. However, if a learning effect would have been found, there is no apparent reason that it would have been different between MICT and HIIT, since participants from both groups were otherwise healthy and therefore had no reason for a previous experience with an incremental exercise test. It is also noteworthy that our study mostly comprised individuals with class I-II (BMI 30-39.9 kg/m<sup>2</sup>) obesity: only 2 participants had a BMI  $\geq$  40 kg/m<sup>2</sup>. Future studies might focus on individuals with *super* obesity (BMI  $\geq$  50 kg/m<sup>2</sup>) since they present with specific restrictive ventilatory defect which might further prevent them from sustaining physical activity.(57) Lastly, our assumptions relating augmented left PFC

oxygenation and improved affective valence to exercise to future commitment to regular physical activity in individuals with obesity are of inferential nature. Future research examining potential lifestyle adjustments after exercise-training interventions is mandatory to confirm or deny this hypothesis.

## **CONCLUSION**

This proof-of-concept study innovates by investigating the influence of two exercise-training protocols on PFC oxygenation and its link with affective response to exercise in individuals with obesity. Our findings indicate that HIIT proved effective in specifically enhancing left PFC oxygenation and affective response to exercise in this population. Implementing this modality in exercise training programs may therefore have relevant implications for the management of obesity since positive affective response to exercise is associated with future commitment to regular physical activity, an issue that deserves further investigation.

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**Author contribution:** DT and PF jointly conceived the present work. SB, SD, MG, BW, RT and JLP screened participants for study inclusion. AB and SC collected the data. MM analysed the data. MM, DT, SV and PF were involved in the interpretation of the results. MM drafted the first version of the manuscript and all authors provided feedback to shape the final version of the manuscript. All authors approved the final version of the manuscript to be published and agree to be accountable for all aspects of the present work.

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**Table 1.** Resting characteristics of individuals with obesity randomly assigned to moderate-intensity continuous exercise training (MICT) or high-intensity interval training (HIIT) before 8 weeks of exercise training.

	MICT (n=10)	HIIT (n=10)	95% CI	<i>p</i>	Effect size
Sex	7 ♂/3 ♀	7 ♂/3 ♀		1.0	
Age (years)	47.8 ± 9.7	48.5 ± 7.6	-8.9; 7.5	0.86	0.080
Weight (kg)	110.2 ± 26.5	102.9 ± 18.0	-14.0; 28.6	0.48	0.322
BMI (kg m <sup>-2</sup> )	33.5 [11.4]	31.9 [5.7]	-4.1; 6.8	0.85	0.042
Waist circumference (cm)	116.9 ± 13.0	114.1 ± 12.9	-9.4; 15.0	0.63	0.216
Hip circumference (cm)	106.8 [22.0]	107.3 [14.5]	-10.0; 18.5	0.79	0.059
<b>Body composition</b>					
Total lean mass (%)	61.2 ± 9.7	62.7 ± 6.4	-9.2; 6.2	0.69	0.183
Total fat mass (%)	38.8 ± 9.7	37.3 ± 6.4	-6.2; 9.2	0.69	0.183
<b>Pulmonary function</b>					
FEV <sub>1</sub> (% predicted)	97.6 ± 13.7	104.9 ± 12.1	-19.5; 4.8	0.22	0.565
FVC (% predicted)	99.2 ± 12.8	101.5 ± 12.9	-14.3; 9.8	0.70	0.179
FEV <sub>1</sub> /FVC (%)	79.9 ± 8.6	83.7 ± 8.2	-11.7; 4.1	0.32	0.452
<b>Habitual physical activity</b>					
Sedentary time (min/day)	1042.0 ± 122.5	1077.8 ± 97.3	-143.7; 72.2	0.49	0.324
LIPA (min/day)	212.4 ± 73.5	243.6 ± 75.2	-103.2; 40.9	0.37	0.420
MIPA (min/day)	71.6 ± 35.4	81.9 ± 44.2	-48.9; 28.3	0.58	0.257
HIPA (min/day)	0.0 [1.0]	0.0 [1.0]	0.0; 0.0	0.97	0.009
Steps (n/day)	7413 ± 3211	8684 ± 2465	-4066; 1525	0.35	0.444
DEE (kcal/day)	2987 ± 673	3033 ± 645	-686; 593	0.88	0.070

Data are presented as mean ± SD for normally distributed continuous variables or as median [interquartile range] for non-normally distributed continuous variables. Consequently, effect size for normally-distributed data refers to Cohen's *d*; effect size *r* is reported for non-normally distributed variables. BMI: body mass index; DEE: daily energy expenditure; FEV<sub>1</sub>: forced expiratory volume in one second; FVC: forced vital capacity; HIPA: high-intensity physical activity; LIPA: low-intensity physical activity; MIPA: moderate-intensity physical activity. No significant difference between groups was observed at baseline (all *p*>0.05).

**Table 2.** Physiological and perceptual responses at the peak of cardiopulmonary exercise testing in individuals with obesity randomly assigned to moderate-intensity continuous exercise training (MICT) or high-intensity interval training (HIIT) before and after 8 weeks of exercise training.

	MICT (n=10)					HIIT (n=10)				
	Pre-EXT	Post-EXT	95% CI	<i>p</i>	Effect size	Pre-EXT	Post-EXT	95% CI	<i>p</i>	Effect size
<b>Power/metabolic/cardiovascular</b>										
Work rate (W)	188 ± 108	207 ± 102	11; 28	<0.001	0.181	174 ± 36	206 ± 39 *	22; 41	<0.001	0.853
Work rate (% predicted)	107.4 ± 35.1	119.8 ± 31.5	6.6; 18.3	<0.001	0.372	107.4 ± 20.8	126.9 ± 23.1	13.3; 25.6	<0.001	0.887
VO <sub>2</sub> (L/min)	2.48 ± 1.23	2.70 ± 1.16	0.12; 0.33	<0.001	0.184	2.32 ± 0.41	2.68 ± 0.45	0.24; 0.47	<0.001	0.836
VO <sub>2</sub> (% predicted)	98.8 ± 27.3	108.8 ± 25.6	5.0; 15.1	0.001	0.378	102.7 ± 24.0	118.2 ± 26.6 *	10.2; 20.8	<0.001	0.612
VO <sub>2</sub> (mL/kg/min)	22.6 ± 8.2	24.7 ± 7.9	1.1; 3.2	0.002	0.261	23.2 ± 5.4	26.7 ± 5.8	2.1; 4.8	0.002	0.625
HR (bpm)	164 ± 11	161 ± 8	-10; 3	0.29	0.312	164 ± 9	164 ± 6	-3; 4	0.90	<0.001
RER	1.01 ± 0.05	1.02 ± 0.04	-0.03; 0.04	0.62	0.221	1.03 ± 0.07	1.00 ± 0.03	-0.08; 0.02	0.21	0.557
[La <sup>-</sup> ] (mmol/L)	8.5 ± 2.3	8.1 ± 1.7	-2.0; 1.1	0.61	0.198	9.0 ± 1.8	8.8 ± 1.9	-1.4; 1.0	0.73	0.108
<b>Ventilatory/gas exchange</b>										
VE (L/min)	102.1 ± 31.3	107.7 ± 31.2	-6.5; 17.7	0.32	0.179	108.0 ± 19.9	112.3 ± 22.0	-1.9; 10.4	0.15	0.205
VE/MVV (%)	83.1 ± 16.0	88.3 ± 16.7	-5.8; 16.3	0.31	0.318	91.0 ± 13.2	94.4 ± 13.2	-2.1; 9.0	0.20	0.258
SpO <sub>2</sub> (%)	96 ± 1	96 ± 1	-1; 1	0.85	<0.001	96 ± 2	96 ± 1	-1; 1	0.78	<0.001
PETCO <sub>2</sub> (mmHg)	34 ± 4	35 ± 4	-1; 3	0.22	0.250	32 ± 2	33 ± 2	-1; 2	0.21	0.500
<b>Symptoms</b>										
Dyspnea	8.0 [2.0]	9.8 [2.0]	-0.3; 2.3	0.18	0.298	8.5 [3.0]	8.5 [3.0]	-1.3; 1.3	0.29	0.237
Dyspnea/work rate	0.051 [0.032]	0.057 [0.022]	-.008; .007	0.75	0.071	0.044 [0.016]	0.040 [0.005]	-.015; .004	0.11	0.354
Leg discomfort	8.5 [2.0]	8.0 [3.5]	-1.3; 2.0	1.0	<0.001	9.0 [4.0]	8.3 [3.5]	-1.5; 1.5	0.68	0.091
Leg discomfort/work rate	0.051 [0.032]	0.046 [0.010]	-.018; .006	0.75	0.071	0.046 [0.013]	0.040 [0.012]	-.018; .001	0.11	0.354

Data are presented as mean  $\pm$  SD for normally distributed continuous variables or as median [interquartile range] for non-normally distributed continuous variables and discrete variables. Consequently, effect size for normally-distributed data refers to Cohen's  $d$ ; effect size  $r$  is reported for non-normally distributed variables and for discrete variables. Pre-EXT: before exercise training; Post-EXT: after exercise training. HR: heart rate; MVV: maximal voluntary ventilation; PETCO<sub>2</sub>: end-tidal carbon dioxide partial pressure; RER: respiratory exchange ratio; SpO<sub>2</sub>: oxygen saturation by pulse oximetry; VE: minute ventilation; VO<sub>2</sub>: oxygen uptake; [La-]: blood lactate concentration.; \* indicates a larger increase with exercise training (delta from pre- to post-exercise training) in HIIT *vs* MICT ( $p < 0.05$ , see Results section for further statistical details).

**Table 3.** Rating of perceived exertion (RPE), feeling scale (FS) and felt arousal scale (FAS) during exercise training sessions in people with obesity randomly assigned to moderate-intensity continuous exercise training (MICT) or high-intensity interval training (HIIT).

	MICT (n=10)							HIIT (n=10)						
	<i>Pre-WU</i>	<i>Post-WU</i>	25%	50%	75%	100%	<i>Post-CD</i>	<i>Pre-WU</i>	<i>Post-WU</i>	25%	50%	75%	100%	<i>Post-CD</i>
<b>RPE</b>														
#1	6.4±1.3	7.4±1.5	10.1±1.7	11.3±2.0	12.1±2.1	12.4±2.3	10.3±3.2	7.5±2.5	7.8±1.8	10.4±2.7	11.2±2.3	11.7±2.5	11.4±2.3	9.2±2.6
#12	6.1±0.3	7.0±1.2	9.2±2.1	10.3±2.6	12.1±2.9	11.9±3.1	9.4±2.6	6.1±0.3	7.1±1.9	10.2±3.4	11.4±2.9	11.7±2.9	12.7±2.9	9.2±1.8
#24	6.4±1.0	6.6±1.0	9.3±2.4	10.7±2.6	11.6±2.7	12.0±2.7	9.2±2.4	6.2±0.4	7.0±1.2	10.6±2.6	11.3±2.5	11.6±2.8	12.8±2.2	8.5±3.2
<b>FS</b>														
#1	2.8±2.1	2.5±2.0	1.8±2.3	1.5±2.4	1.1±2.2	1.0±2.4	1.4±2.2	2.8±1.9	3.3±1.6	2.9±1.4	3.0±1.3	2.8±1.4	3.1±1.3	3.4±1.6
#12	3.8±1.9	3.4±1.9	3.3±1.9	3.0±2.4	2.7±2.5	2.9±2.3	3.2±2.3	4.2±1.7	3.9±1.7	3.1±1.5	2.3±2.2	2.2±2.3	2.1±1.9	3.2±1.2
#24	3.6±1.9	3.4±2.1	3.2±2.3	2.7±2.6	2.3±3.0	2.0±3.0	2.6±2.9	4.2±1.1	4.1±1.2	3.2±1.3	3.4±1.1	3.2±1.1	2.9±1.6	3.6±1.0
<b>FAS</b>														
#1	3.2±1.5	3.4±1.3	3.5±1.0	3.3±0.9	3.2±1.0	3.2±1.0	3.0±1.9	3.2±2.1	2.8±2.0	3.1±1.6	3.3±1.4	3.3±1.3	3.5±1.3	3.3±1.8
#12	3.7±1.7	3.7±1.8	3.5±1.7	3.7±1.6	3.7±1.6	3.6±1.7	3.6±1.7	2.8±2.1	2.7±1.9	3.1±1.5	3.1±1.4	3.2±1.4	3.5±1.2	2.9±1.8
#24	4.1±1.8	4.0±1.8	3.9±1.7	3.7±1.5	4.1±1.3	3.9±1.5	4.1±1.5	2.9±2.3	3.2±2.1	3.1±1.7	3.2±1.4	3.4±1.5	3.4±1.6	4.0±1.8

Data are presented as mean ± SD for clarity purposes. #1, 12 or 24 indicates the number of the session being considered, that is the first, at half and the last session of exercise-training programs. Pre- and Post-WU respectively refers to before and after the 2-min warm-up preceding the core of the session. 25%, 50%, 75% and 100% respectively refers to 25%, 50%, 75% and 100% of each exercise training session duration. Post-CD refers to after the 2-min cool-down following the core of the session. Statistical significance was set at  $p < 0.007$  due to the number of comparisons over time being made (see Statistical analysis for further details). No significant difference was found between MICT and HIIT (all  $p > 0.007$ ).

## FIGURE LEGENDS

**Figure 1.** Changes in left and right prefrontal cortex difference in hemoglobin (HbDiff) and total hemoglobin (HbTot) concentration as a function of exercise intensity during incremental cycling tests in individuals with obesity undertaking moderate-intensity continuous training or high-intensity interval training.

Data are presented as mean  $\pm$  SEM for clarity purposes. White and black bars depict data obtained before and after exercise training, respectively. VT<sub>1</sub>: first ventilatory threshold; VT<sub>2</sub>: second ventilatory threshold; WR: work rate. Statistical significance was set at  $p < 0.025$  due to the number of comparisons over time being made (see Statistical analysis for further details). \*  $p < 0.025$ : left *vs* right prefrontal cortex at a given exercise intensity before exercise training; †  $p < 0.025$ : after *vs* before exercise training at a given exercise intensity in a specific (left or right) prefrontal cortex. See Results section for further statistical details.

**Figure 2.** Affective valence as a function of exercise intensity during incremental cycling tests in individuals with obesity undertaking moderate-intensity continuous training or high-intensity interval training.

Data are presented as mean  $\pm$  SEM for clarity purposes. White and black bars depict data obtained before and after exercise training, respectively. Grey bars depict data obtained after exercise training at the same absolute work rate *vs* before exercise training. VT<sub>1</sub>: first ventilatory threshold; VT<sub>2</sub>: second ventilatory threshold; WR: work rate. Statistical significance was set at  $p < 0.025$  due to the number of comparisons over time being made (see Statistical analysis for further details). †  $p < 0.025$ : after *vs* before exercise training at the same absolute work rate at a given exercise intensity. See Results section for further statistical details.

**Figure 3.** Relationship between post-pre exercise training difference in left prefrontal cortex HbDiff concentration at peak exercise and exercise training-induced changes in peak work rate (% predicted) and peak oxygen uptake (mL/kg/min, *left panels*) and post-exercise training affective valence at absolute work rates corresponding to peak exercise before exercise training and post-pre exercise training difference in left prefrontal cortex HbDiff and HbO<sub>2</sub> concentration at peak exercise (*right panels*) in individuals with obesity.

Open circles and filled squares denote participants undertaking moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT), respectively. EXT: exercise training; HbO<sub>2</sub>: oxyhemoglobin; HbDiff: difference in hemoglobin; PFC: prefrontal cortex; VO<sub>2</sub>: oxygen uptake; WR: work rate(s).

Before exercise training  
 After exercise training

Moderate-intensity continuous training

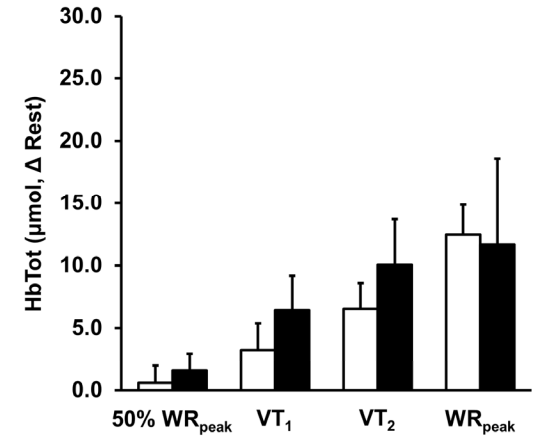
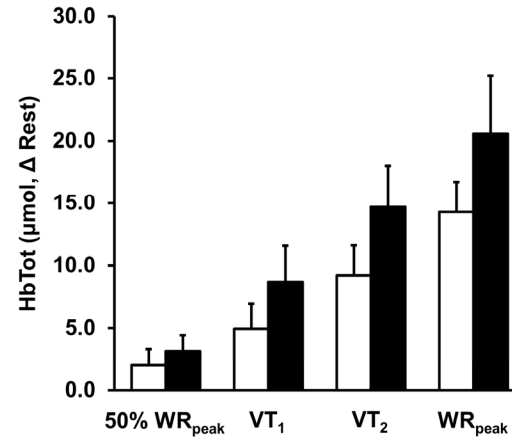
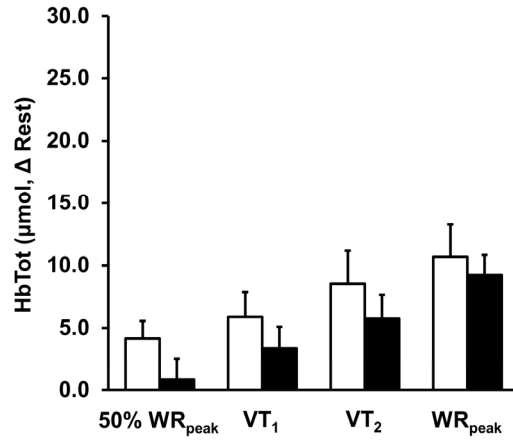
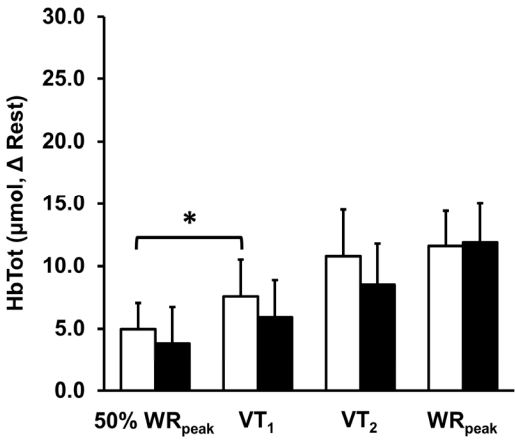
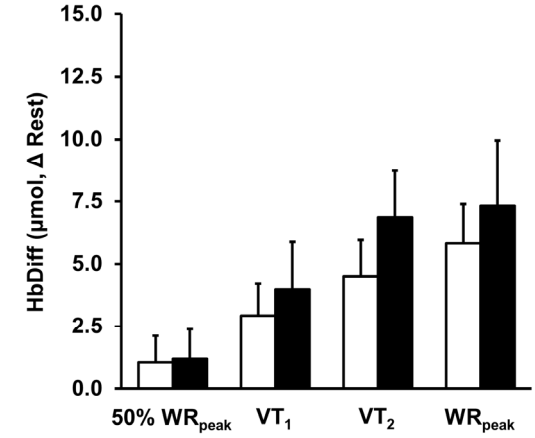
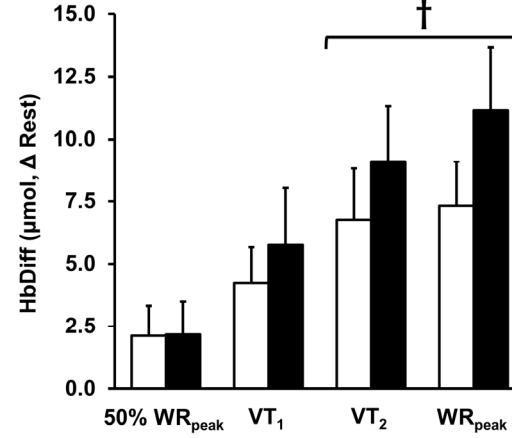
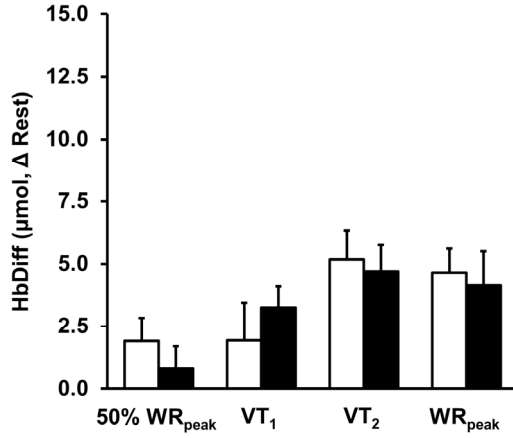
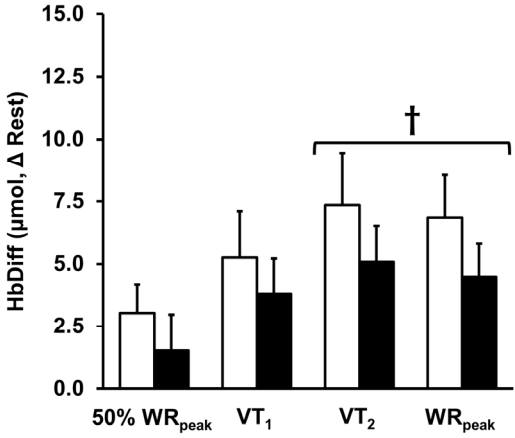
High-intensity interval training

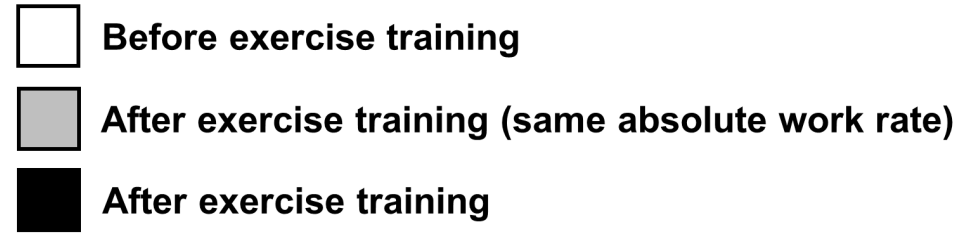
Left prefrontal cortex

Right prefrontal cortex

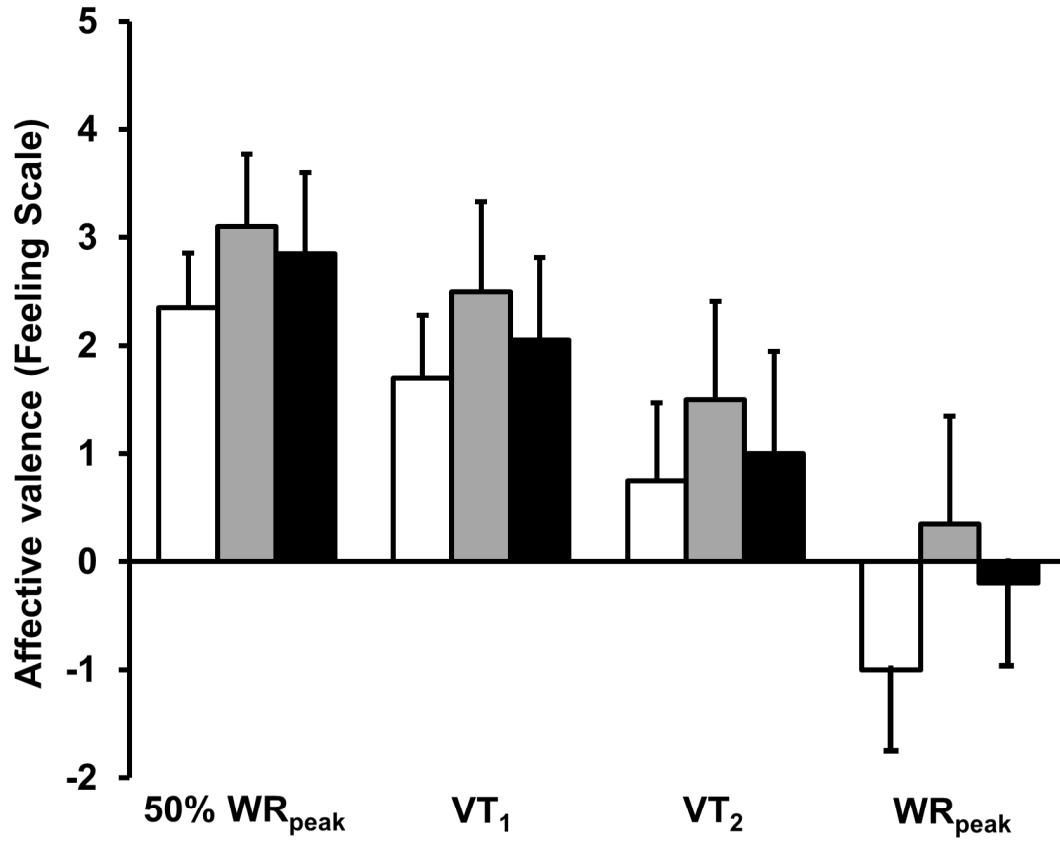
Left prefrontal cortex

Right prefrontal cortex





Moderate-intensity continuous training



High-intensity interval training

