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Effects of low- and high-intensity exercise on emotional face processing: an fMRI face-matching study

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Abstract

Physical exercise has positive effects on mood and it reduces clinical depression and states of anxiety. While previous work mostly used subjective measures to study the effect of exercise upon emotions, this study for the first time employed blood oxygen level dependent functional magnetic resonance imaging (fMRI) to unravel associated neuronal changes of the emotional face-processing network in response to acute exercise. A total of 25 male athletes underwent fitness assessments to define two standardized 30 min exercise interventions (low and high intensity). The Positive and Negative Affect Schedule (PANAS) was completed pre- and post-exercise and neuronal responses to neutral, happy and fearful facial expressions were determined using an fMRI-based face-matching paradigm. Complete data sets were acquired in 21 participants (mean age, 27.2 ± 4.2 years). Both exercise interventions induced significant increases of the PANAS positive affect scale. Modulations of brain activation patterns following acute exercise were found only for fearful facial stimuli *vs* forms: reduced brain activation in posterior cingulate cortex/precuneus for the low condition and reduced activity in caudate nucleus and ventral anterior putamen for the high condition. In conclusion, this study provides first *in vivo* evidence that acute strenuous exercise interferes with emotional face-processing brain regions in an emotion type-specific manner.

Key words: emotion; physical activity; affect; aerobic exercise; fear

Introduction

Mental disorders are highly prevalent causes of long-term disability. Among these, depression and anxiety disorders are the largest contributors to 'lost working years' (Knudsen *et al.*, 2012). Both show high rates of comorbidity (Nabavi *et al.*, 2015) and treatment resistance, constituting a major health care problem (Samuels *et al.*, 2011; Ammar *et al.*, 2015). Previous research has provided ample evidence that physical exercise can decrease symptoms of depression and anxiety (Stanton and Reaburn, 2014; Wegner *et al.*, 2014; Ensari *et al.*, 2015; Rebar *et al.*, 2015), suggesting exercise interventions as an alternative treatment strategy and/or prophylactic approach in affective disorders (Pedersen and Saltin, 2015). As a foundation for broader 'clinical' applications of exercise, experimental data on the impact of exercise type, exercise intensity and exercise duration on affective states and underlying neuronal networks are urgently required.

In humans, mood changes become already evident after a single bout of exercise, as shown for cycling (Hansen *et al.*, 2001;

Hallgren *et al.*, 2010; Hogan *et al.*, 2013), running (Hoffman and Hoffman, 2008) and resistance training (Focht *et al.*, 2015). Effects range from strong affective sensations referred to as 'Runner's High' (Boecker *et al.*, 2008a; Raichlen *et al.*, 2012; Fuss *et al.*, 2015), or more general states of positive mood (Hoffman and Hoffman, 2008; Hallgren *et al.*, 2010; Focht *et al.*, 2015) and increased stress resistance (Hopkins *et al.*, 2012), along with specific anxiolytic (Smith, 2013) or anti-depressive effects (Heggelund *et al.*, 2014).

Few functional magnetic resonance imaging (fMRI) studies have investigated the effects of acute exercise bouts, and only very few have studied affective processing in the broadest sense: Bothe *et al.* (2013) tested the impact of a moderate exercise training session on the dopaminergic reward system in highly trained and untrained subjects using a monetary incentive delay task. They found the exercise intervention to diminish neural responses to anticipation and feedback of monetary rewards. Evero *et al.* (2012) showed that exercise alters neuronal responses to food cues in brain regions important in food reward and, similarly, work investigating cigarette craving following exercise reported hypo-activations in brain areas associated with reward (like the caudate nucleus), concomitant with shifts of activation toward default mode network (DMN) areas (Janse Van Rensburg *et al.*, 2009). A recent study by Tozzi *et al.* (2016) recorded resting-state fMRI to identify functional networks linked with mood-related benefits of exercise. They investigated 38 healthy sedentary volunteers randomized to an aerobic exercise (16 weeks) or control group and recorded mood changes over time. This longitudinal study reported increased functional connectivity between the parahippocampal gyrus and areas involved in sensorimotor integration and mood regulation in the exercise group, but not in the control group, indicating that 'these functional changes might be related to the benefits of regular physical activity on mood'. So far, fMRI has not been used to explicitly study effects of acute exercise bouts on central processing of affective stimuli, and no study has yet addressed the question how brain networks mediating affective modulation are affected by the intensity of the exercise bout.

Therefore, the rationale of the current study was to fill a lack of knowledge in the current understanding of body–brain interactions by investigating the effects of acute exercise bouts on emotional face processing at the behavioral and brain network level using whole brain fMRI at three Tesla. In particular, we tried to unravel whether neuronal activity within emotional face-processing brain regions (Fusar-Poli *et al.*, 2009) is modulated by acute exercise bouts. Moreover, we examined whether the intensity of an exercise bout plays a relevant role in determining behavioral mood changes and associated neuronal responses in brain areas specialized in emotional (neutral, happy, fearful stimuli) face processing. We hypothesized (i) that brain activations in athletes exposed to pictures of emotional faces are modulated by endurance exercise and (ii) that dose-dependent effects of exercise can be identified, both on the behavioral and the imaging level.

Methods

Participants

Male participants aged between 20 and 40 years were recruited via social media, announcements and flyers, searching for experienced runners, exercising at least three times/week for 45 min for the past 2 years. Subjects were neurologically and psychiatrically healthy and had no orthopedic or general health problems that may have prohibited physical activity. All participants were

Table 1. Participants' characteristics

Variable	M ± SD
Age (years)	27.1 ± 4.1
BMI (kg m^{-2})	23.6 ± 1.4
HR$_{rest}$ (bpm)	75 ± 14
HR$_{max}$ (bpm)	194 ± 7
Speed$_{max}$ (km h^{-1})	16.1 ± 1.3
Education (years)	17.8 ± 2.8

BMI, body mass index; HRrest, heart rate at rest; HRmax, maximum heart rate during incremental exercise test; speedmax, highest speed achieved during incremental exercise test; M, mean; SD, standard deviation

screened by a physician at the German Sport University Cologne, including medical history taking, physical examination and a 12-channel resting electrocardiogram (MAC 1200 ST, GE Medical Systems Information Technologies GmbH, Freiburg, Germany). Participants were excluded in case of any cardiac risk factors or MRI contraindications (i.e. metal and/or electronic implants, claustrophobia, etc.).

In total, 25 healthy male athletes were included in the study. One subject had to be excluded from the final analyses due to injuries (caused by private activities), two volunteers did not finish the study and one subject was excluded due to imaging artifacts. The resulting final sample size was *N* = 21 subjects. The sample characteristics are summarized in Table 1.

At study entrance a set of questionnaires was administered with the aim to provide descriptive characteristics (e.g. age, educational background, handedness, etc.). Additionally, psychiatric questionnaires were carried out, including the Mini International Neuropsychiatric Interview (MINI; German Version 5.0; Sheehan *et al.*, 1998), the State and Trait Anxiety Inventory (STAI; Spielberger *et al.*, 1983) and the Beck Depression Inventory (Hautzinger *et al.*, 1994). According to the Edinburgh Handedness Inventory (Oldfield, 1971), 20 subjects were right dominant (mean laterality quotient, 82.5 ± 15.0) and one was ambidextrous (laterality quotient, 21.7). None of the participants showed results indicating psychiatric diseases (MINI). All participants scored below the threshold value for clinical relevant depression (mean, 1.2 ± 2.0; score ≤9, no depression). STAI trait scores were on average 31.2 ± 6.0 (range, 20 = not being afraid to 80 = maximum intensity of anxiety), indicating a low general anxiety score. Mean verbal intelligence quotient estimated by a German vocabulary test was 106 ± 10, indicating normal verbal intelligence (Schmidt and Metzler, 1992).

A written informed consent was received from participants after providing a detailed explanation regarding the procedure, potential discomforts and risks. The study conformed to current local guidelines and the Declaration of Helsinki and was approved by the local Ethics Committee of the University Hospital Bonn (340/13).

Physical fitness assessment

All participants underwent a treadmill-based incremental exercise test (Woodway PPS Med, Woodway GmbH, Germany), starting at a speed of 5 km h^{-1}, with a 1% gradient set throughout. Each stage lasted 3 min and running speed was increased by 1 km h^{-1} per stage. At the end of each stage a blood sample (20 μL) was taken from the earlobe and used to measure blood lactate concentration. Additionally, heart rate (HR; POLAR, Kempele, Finland) and a rating of perceived exertion (RPE; Borg, 1982) were recorded at the end of each stage. RPE scale ranged from '6–no exertion at all/extremely light' to '20–maximal exertion'. All participants performed the incremental test to volitional
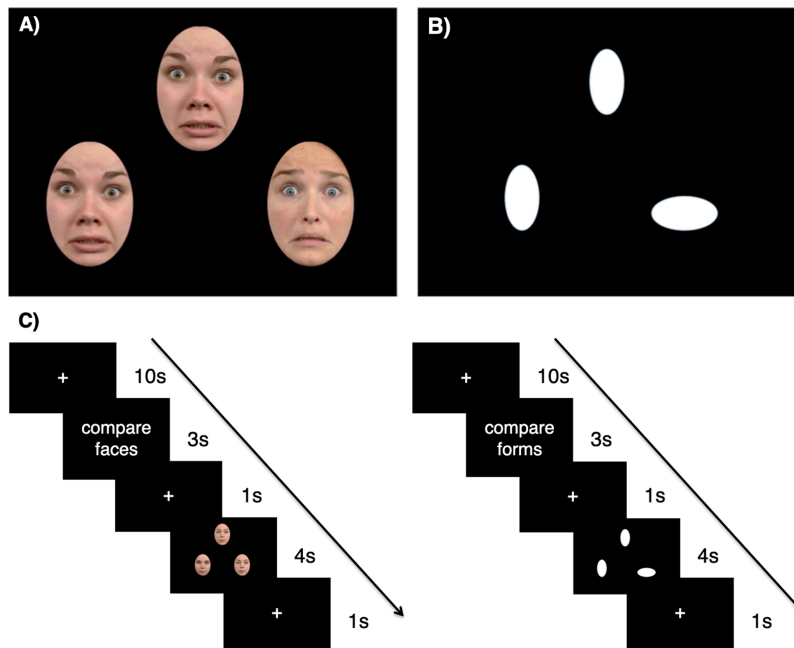
Fig. 1. fMRI paradigm. (A) Examples of fearful face stimuli used in the paradigm; (B) examples of form stimuli used in the paradigm; (C) schematic presentation of the sequence and timings of the paradigm.

exhaustion and attained at least two of the following criteria: high levels of blood lactate (>8 mmol·L^{-1}), RPE of ≥ 18 and/or HR of ± 10 bpm of age-predicted maximum (220-age; Hollmann *et al.*, 2012). Blood lactate samples were analyzed using the BIOSEN C-Line lactate analyzer (EKF-diagnostic GmbH, Barleben, Germany). To ensure comparable relative exercise intensity across all participants, the lactate threshold (LT) was individually determined from a plot of blood lactate concentration against running speed. LT was defined as the first sustained increase in blood lactate above baseline values (Wasserman and McIlroy, 1964) and determined via visual inspection.

Experimental procedure

Neural responses to different emotional facial expressions were measured using an fMRI-based Hariri face-matching block paradigm performed pre- and post-exercise. To minimize the acute influences of exercise prior to the assessments, all participants were instructed to avoid exercise training and alcohol intake 24 h prior each testing session and to refrain from drinking caffeine and eating 2 h before the experiment. Prior to the exercise intervention, HR, blood lactate and the Positive and Negative Affect Schedule (PANAS; Krohne *et al.*, 1996) were taken. Each intervention was performed on a treadmill and started with a 5 min warm-up at 5 km h^{-1}, followed by the 30 min exercise intervention. During the exercise interventions HR was recorded every minute, and blood lactate and physical exertion were recorded every 5 min. After the exercise intervention, a 5 min cool-down period at 5 km h^{-1} occurred. Directly post-cool down, participants again completed the PANAS. Post-exercise fMRI was performed ~45 min after the end of the exercise intervention. Participants performed three exercise bouts at different intensities (low, high and self-selected). The low exercise intensity was performed at 35% under LT to ensure a very easy exercise condition that challenges primarily the aerobic energy supply; high exercise intensity was performed at 20% above LT. Each intensity was scheduled for

a different day, and the order was randomized. Testing days were accomplished within in a minimum of 2 weeks and a maximum of 12 weeks. As this manuscript focuses exclusively on the comparison of standardized and metabolically defined exercise intensities, data from the self-selected intervention will be reported elsewhere.

fMRI paradigm

To identify neuronal responses to emotional facial expressions we used a well-established face-processing fMRI paradigm (Hariri *et al.*, 2002b; Pezawas *et al.*, 2005). In the experimental intervention, three facial stimuli (derived from the Radboud Faces Database of Facial Affect series; Langner *et al.*, 2010) with the same gender and emotional valence (fearful, happy or neutral) were presented simultaneously. The face presented at the top of a black screen was defined as target image and participants were asked to match one of two facial images presented at the bottom of the screen with the target image (i.e. identity matching; Figure 1A). As a sensorimotor and visual control task, participants were asked to match simple geometric forms (circles, vertical and horizontal ellipses; Figure 1B). To confirm that subjects pay attention to the presented stimuli during the whole task, subjects were asked to indicate their choice via button presses with their right hand. In order to ensure continued processing of the visual stimuli during the entire block subjects were instructed to visually fixate the target image even after giving their responses. Each trial was presented for 4 s with a 1 s inter-stimulus interval (Figure 1C). During baseline and rest periods, participants were asked to maintain visual fixation on a small white cross located at the center of the screen. Trials were balanced to present both genders equally. The fMRI paradigm consisted of 24 experimental blocks, 6 for each condition (happy, fearful, neutral, forms). Each block consisted of four stimuli, lasted for 20 s and began with a brief 3 s instruction: 'Compare Faces' or 'Compare Forms'. The order of the blocks was pseudo-randomized.

To make sure that participants matched identity not based on static facial cues, faces were shown as ovals without hair and ears, thereby laying the focus on the facial expression. Stimuli were presented on an LCD monitor (NordicNeuroLab Inc., Milwaukee) positioned at the rear of the MRI scanner (orientated centrally to the bore) using the software Presentation (Presentation Software®, Version 16.5, 2004, Neurobehavioral Systems Inc., Albany, CA, USA) and viewed via a mirror mounted to the head coil. To ensure that all participants understood the task, a practice session was performed with detailed instruction on a computer outside the scanner before testing.

MRI acquisition

All MRI examinations were performed at the Department of Radiology, University Hospital Bonn, with a 3T clinical MRI System (Ingenia 5.1.7, Philips Healthcare, Best, The Netherlands), equipped with an 8-channel head coil. Per session 356 T2*-weighted volumes were acquired with a single shot echo-planar imaging sequence. The parameters were as follows: 44 slices acquired in ascending order, TR: 2400 ms, TE: 30 ms, flip angle: 80°, orientation: tilted angulation, SENSE = 2, matrix: 64×64, acquired voxel size: $3 \times 3 \times 3$ mm³. The total scan duration for each functional scan was 14:31 min.

For anatomical reference a 3D-T1 weighted data set was acquired within each run with the following parameters: slice orientation: sagittal, acquisition matrix: 256×256, acquired voxel size: $1 \times 1 \times 1$ mm³, sequence type: 3D FFE, TR: 7.6 ms, TE: 3.9 ms, flip angle: 15°, total scan duration: 4:39 min.

Data analysis

To verify that the data are normally distributed, the Shapiro–Wilk test was used. It turned out that the data for PANAS negative affect scale and lactate values did not correspond to a normal distribution. Since simulation studies have shown that the paired *t*-test and the repeated measures ANOVAs are relatively robust to normal distribution assumption violations (Vasey and Thayer, 1987)—especially if, in addition to the normal distribution assumption, no further assumption has been violated (Berkovits *et al.*, 2000), data were processed using parametric tests. *P*-values of less than 0.05 were regarded as statistically significant. In addition to *t*-values, *F*-values and *P*-values, the correlation coefficient 'r' as an effect size will be reported, with $r = 0.10$ representing a small effect, $r = 0.30$ a medium effect and $r = 0.5$ a large effect. All statistical analyses of behavioral data were performed using SPSS 24 (SPSS Inc., Chicago, Illinois).

Exercise intervention

For each exercise-based parameter (speed, HR, blood lactate and RPE) average values for the 30 min of each exercise intervention (low and high) were calculated. To compare low- *vs* high exercise intensity, parameters were analyzed using a paired *t*-test (e.g. HR low intensity *vs* HR high intensity).

PANAS

The PANAS scores were entered into a 2 (intervention: low/high) $\times$ 2 (time: pre-/post-exercise) $\times$ 2 (scale: positive affect scale/negative affect scale) repeated measures analysis of variance (ANOVA). Afterwards, scores for positive affect and negative affect were entered in two separate 2 (intervention:

low/high) × 2 (time: pre-/post-exercise) ANOVAs. *Post hoc* paired *t*-tests with Bonferroni correction were performed.

fMRI: pre-processing

Pre-processing and analysis were performed using Statistical Parametric Mapping version 12 (SPM12; Wellcome Department of Imaging Neuroscience, London, UK) implemented in Matlab (The Mathworks Inc., Sherborn, MA, USA). First, a mean T1 of all acquired structural images (of each MRI session) per participant was created using longitudinal registration (Ashburner and Ridgway, 2012). The mean T1 image was normalized to the MNI template provided by SPM12. Pre-processing of the functional image series included realignment using the first image as the reference, applying a 5th degree B-Spline interpolation (quality of 1). Further pre-processing steps were slice time correction and co-registration of the fMRI time series to the derived individual mean T1 data sets. The functional time series were normalized applying the transformation derived during the normalization step of the meanT1 data set (Ashburner and Friston, 2005). The interpolation method for the normalization steps was set to 5th degree B-Spline. Finally, the data were spatially smoothed using an 8 mm full width at half maximum Gaussian kernel.

fMRI: analysis

A general linear model (Friston *et al.*, 1995) was set up as a block design. The design matrix contained five separate regressors: instructions, fearful faces, happy faces, neutral faces and forms. Additionally, the six motion parameters (derived during the realignment step) were entered as nuisance factors. All sessions of a subject (pre-high exercise, post-high exercise, pre-low exercise, etc.) were entered into one first-level model defined as separate sessions. First-level contrasts were created to assess effects of each emotion (fearful, happy and neutral) over the baseline condition (forms). The forms condition was used as the baseline intervention instead of neutral faces due to mounting evidence that neutral faces may not be processed as emotionless (Thomas *et al.*, 2001; Herba and Phillips, 2004; Cooney *et al.*, 2006).

First, to identify possible baseline differences between the two pre-exercise fMRI sessions on the different examination days (pre-low exercise and pre-high exercise), we entered the data in a paired test for each emotional valence (fearful faces > forms, happy faces > forms, neutral faces > forms) separately. In the case of significant baseline differences pre-exercise, we extracted those clusters as a mask thresholded at $P < 0.001$ cluster corrected for family wise errors (FWEs). This mask was then used for explicit masking in our repeated measures ANOVA. Thereby we could exclude possible effects driven by baseline differences.

Second-level analysis allowed us to determine differences in activation between interventions and time points at the group level. Contrast images e.g. 'fearful faces>forms' were entered into a 2 (time: pre/post) × 2 (intervention: low/high) repeated measures ANOVA. Each facial expression was analyzed in a separate ANOVA. *Post hoc* comparisons were calculated as t-contrasts in our ANOVA design. Significance was considered for the main effects at a statistical threshold of $P < 0.001$, corrected for FWE at cluster level. Anatomical localizations of the activation peaks were determined using the SPM Anatomy Toolbox version 2.2 (Eickhoff *et al.*, 2007) and the AAL WFU PickAtlas (Tzourio-Mazoyer *et al.*, 2002; Maldjian *et al.*, 2003) since not all brain regions are equally detailed in the atlases.
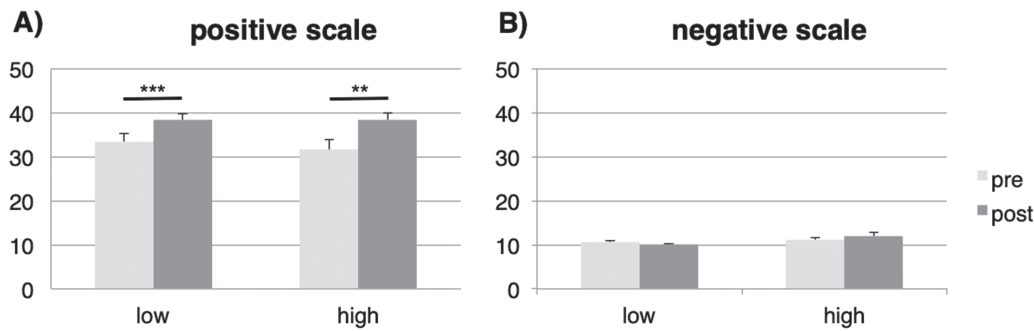
Fig. 2. PANAS values measured for the low and high condition. (A) positive scale; (B) negative scale. Time points acquired were pre- and directly post-exercise; M ± SEM, N = 21; ***P < 0.001, **P < 0.01.

Results

Exercise intervention

Paired *t*-test analysis revealed significant differences between the high and low exercise intensity for blood $lactate_{low}$: 2.8 ± 2.0, blood $lactate_{high}$: 10.2 ± 3.3, t(20) = −10.1, P < 0.001, r = 0.91; HR_{low} low: 128 ± 18, HR_{high}: 187 ± 7, t(20) = −15.8, P < 0.001, r = 0.96; running $speed_{low}$: 7.0 ± 0.8, running $speed_{high}$: 12.8 ± 1.3, t(20) = −21.0, P < 0.001, r = 0.98 and RPE_{low}: 9.3 ± 2.0, RPE_{high}: 18.5 ± 1.3, t(20) = −21.2, P < 0.001, r = 0.98.

PANAS

The 2 × 2 × 2 ANOVA revealed a significant main effect of time (F(1,20) = 32.39, P < 0.001, r = 0.79), a significant main effect of scale (F(1,20) = 219.77, P < 0.001, r = 0.96) and a significant time × scale interaction (F(1,20) = 17.16, P = 0.001, r = 0.68). There were no significant main effects of intervention and no significant interactions for time × intervention, scale × intervention or time × scale × intervention.

The 2 × 2 ANOVA for only the positive affect scale revealed a significant main effect of time (F(1,20) = 27.74, P < 0.001, r = 0.76). There was no main effect of intervention or an interaction time × intervention. *Post hoc* comparisons revealed a significant increase from pre- (33.5 ± 8.3) to post- (38.4 ± 6.6) low intensity (t(20) = −5.66, P < 0.001, r = 0.78) and from pre- (31.7 ± 10.5) to post- (38.4 ± 6.9) high intensity (t(20) = −3.91, P = 0.001, r = 0.66) (Figure 2).

The separate 2 × 2 ANOVA for the negative affect scale only revealed a significant main effect of condition (F(1,20) = 6.37, P = 0.020, r = 0.49). There was no main effect of time or an inter-action time × intervention. *Post hoc* comparisons revealed no significant differences pre-exercise interventions and also no significant differences between conditions.

fMRI data

Main effects. Looking at the main effects of the task (both pre-low and pre-high intervention together) in each emotional valence (fearful faces > forms, happy faces > forms and neutral faces > forms) revealed that the task elicited typical activation clusters that have been shown previously for the Hariri task (Hariri *et al.*, 2000, 2002a; see Supplementary Figure S1) and belong to the face-processing system (Fox *et al.*, 2009; Fusar-Poli *et al.*, 2009): visual areas (fusiform gyrus, inferior occipital gyri, lingual gyrus), limbic areas (amygdala and parahippocampal gyrus), prefrontal areas (medial frontal gyrus) and the cerebellum (lobule IX).

Fearful faces vs forms. ANOVA revealed a significant main effect of time with an activation cluster in the posterior cingulate gyrus (PCC)/precuneus in the right and partially left caudate nucleus and right ventral anterior putamen (Figure 3). There was no significant main effect of intervention and no intervention × time interaction.

T-contrasts in our ANOVA for the low intensity pre- *vs* post-exercise showed a significant decrease in PCC/precuneus (Figure 4A and C; Table 2). In the t-contrast in which pre- *vs* post-high exercise was contrasted, a decrease in the right and partially left caudate nucleus and right ventral anterior putamen (Figure 4B and D; Table 2) was observed. These changes in activation are driven by a stronger deactivation to fearful faces and more activation to forms (see Supplementary Figure S2). All reported fMRI data are significant at cluster level (P < 0.001, FWE-corrected).

Happy faces vs forms. The ANOVA with the first-level contrast happy faces > forms showed no significant main effect of time or intervention and no interaction.

Neutral faces vs forms. The ANOVA with the first-level contrast neutral faces > forms showed no significant main effect of time or intervention and no interaction.

Discussion

This is the first study to investigate the effects of acute aerobic exercise bouts at two different prescribed exercise intensities (low/high) on affect scales and affective network activations in humans. Behavioral results demonstrated increases in positive affect scale after both exercise interventions, i.e. independent of exercise intensity, but no effects on negative affect scale. Imaging results showed that acute exercise rather exclusively modulates brain activation patterns induced by fearful faces *vs* forms, with significant main effects of time in the PCC/precuneus, right and partially left caudate nucleus and right ventral anterior putamen. *Post hoc* testing revealed that both exercise intensities led to decreased activation in emotional face-processing brain regions: the low exercise intensity was associated with reduced brain activations in PCC/precuneus; the high exercise intensity was associated with reduced fear-related activity in ventral basal ganglia structures. Hence, results suggest acute emotion type-specific and exercise intensity-dependent modulatory effects of exercise on affective states and associated brain networks.

Behavioral mood changes independent of the Hariri task were assessed using the PANAS questionnaire and revealed a
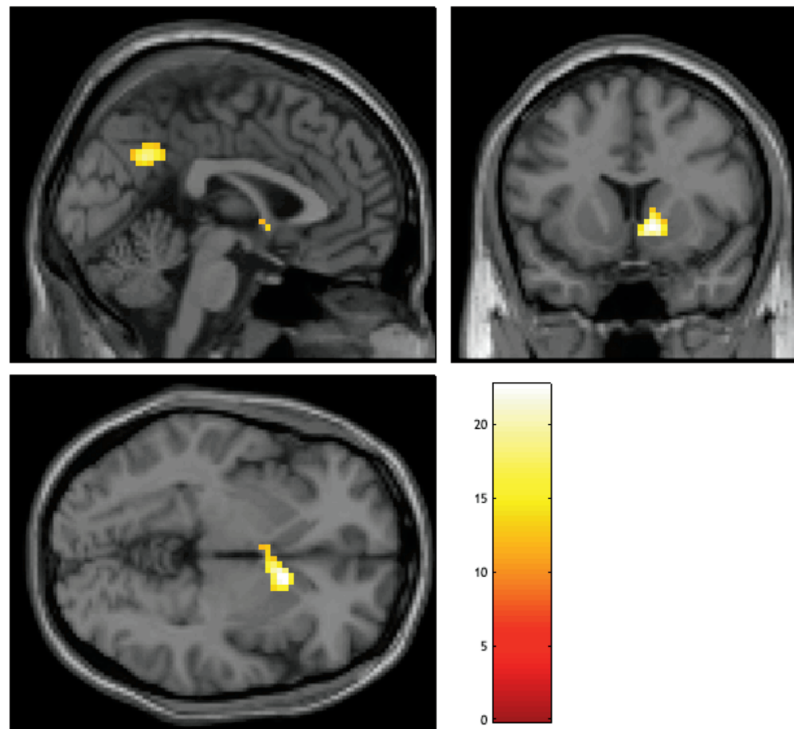
Fig. 3. Second-level results from 2 × 2 ANOVA with first-level contrast fearful faces > forms. Main effect of time (F-contrast) with activation clusters in PCC and caudate nucleus; data is thresholded at $P < 0.001$ with an FWE cluster threshold $k = 72$; $N = 21$; clusters are overlaid onto a single-subject anatomical image for visualization.

Table 2. Peak coordinates of activation clusters during matching fearful faces > forms

| | | Cluster | | Coordinates | | |
	side	P-value (FWE-corr)	k	x	y	z
LOW pre > post						
Precuneus/PCC	R	0.026	102	0	−55	35
Precuneus/PCC	R			12	−52	32
HIGH pre > post						
Ventral anterior putamen	R	0.050	83	15	14	−4
Ventral caudate nucleus	L			−6	2	−7

significant increase in positive affect scale directly after both exercise interventions. In line with previous studies (Bixby *et al.*, 2001), but contrary to our initial hypothesis, no significant differences were found in the positive affect scale between the low and high intensities. Another study investigating the acute effects of exercise on stress parameters also revealed a general increase in positive affect using the PANAS (Zschucke *et al.*, 2015). Conversely, no significant differences were identified between pre- and post-exercise values in the negative affect scale. At first sight, this negative finding is counter-intuitive, given that longitudinal and acute exercise interventions have previously shown decreases in negative mood symptoms like anxiety (Ensari *et al.*, 2015; Stonerock *et al.*, 2015) and depression (Khanzada *et al.*, 2015; Rebar *et al.*, 2015). As there were no differences in negative affect scale pre- to post-exercise in this study it is likely that the subjective ratings for the negative affect variables were near the bottom of the range pre-exercise, thus representing a

floor effect and leaving little/no room for decreases in negative affect.

The presented fMRI data indicate that acute exercise bouts (i) modulate brain activity during emotional face processing and (ii) carry intensity-related effects, hence supporting both a priori hypotheses: during processing of fearful faces *vs* forms, the low-intensity exercise intervention decreased activity in PCC/precuneus, whereas the high-intensity exercise intervention decreased activity in ventral parts of the basal ganglia.

The PCC and the precuneus are both part of the DMN, in which neuronal activity is increased during rest conditions (Gusnard *et al.*, 2001; Raichle *et al.*, 2001; Grimm *et al.*, 2009) and decreased during active task conditions (McKiernan *et al.*, 2003). Studies using fMRI showed involvement of the precuneus in various tasks including visuo-spatial imagery, episodic memory retrieval and self-processing operations, namely first-person perspective taking and an experience of agency (Cavanna and
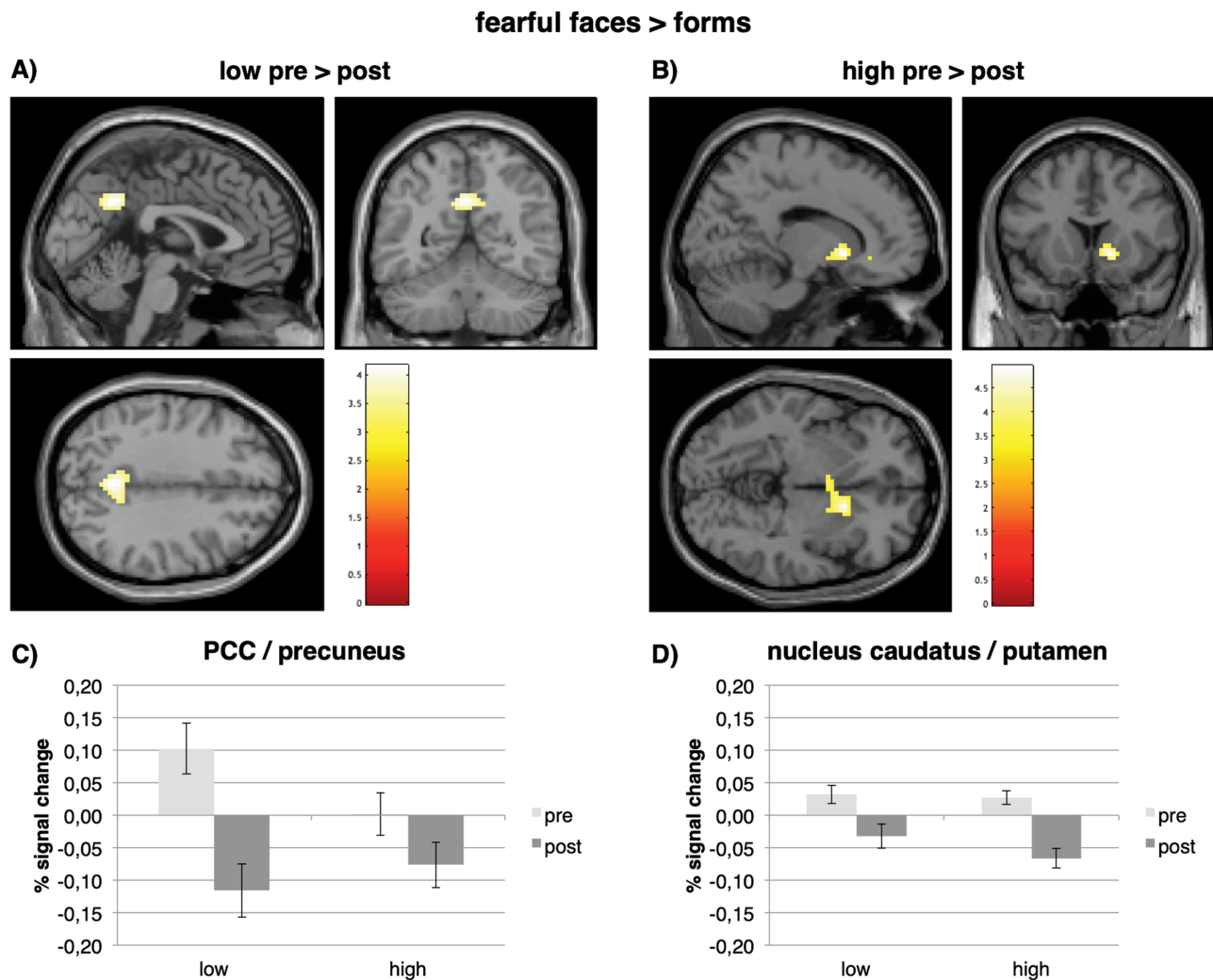
fearful faces > forms

Fig. 4. Second-level results from t-contrasts (first-level contrast fearful faces > forms). (A) *Post hoc* t-contrasts pre *vs* post for low intervention with activation clusters in PCC; data are thresholded at $P < 0.001$ with an FWE cluster threshold $k = 102$. (B) *Post hoc* t-contrast pre *vs* post for high intervention with activation clusters in right and partially left caudate nucleus and right ventral anterior putamen; data are thresholded at $P < 0.001$ with an FWE cluster threshold $k = 83$. (C) Percent signal change in the PCC/precuneus from pre- and post-low- and high exercise intervention. (D) Percent signal change in the right and partially left caudate nucleus/right putamen from pre- and post-low- and high exercise intervention; clusters are overlaid onto a single-subject anatomical image for visualization.

Trimble, 2006). The precuneus has also been identified to react to fearful faces (Zhao *et al.*, 2017) and is part of the extended face-processing network (Fox *et al.*, 2009). Sreenivas *et al.* (2012) reported that brain responses to emotional faces from different categories generally deactivate both areas, the PCC and pre-cuneus across different emotions. Therefore, the effects shown in the PCC/precuneus might simply reflect a modulation in face processing *per se*. On the other hand, an fMRI study con-firmed the emotional implication of the precuneus and the PCC in which these regions were found commonly activated by attribution of emotions to the self and other people (Ochsner *et al.*, 2004). Moreover, the precuneus has been suggested to be involved in assessing emotional responses and was found to be important for the perception of the emotional content of music as well as for the emotional response evoked in the listener (Tabei, 2015). The PCC receives strong afferent input from regions involved in emotional and social behavior, including the subgenual anterior cingulate cortex, orbital frontal cortex, dor-solateral prefrontal cortex and superior temporal sulcus (Gold-man-Rakic *et al.*, 1984; Musil and Olson, 1993; Van Hoesen *et al.*,

1993; Carmichael and Price, 1995; Morris *et al.*, 1999; Allison *et al.*, 2000). Evaluating valences of unpleasant and pleasant words was shown to be associated with significant bilateral activation of the PCC, as compared to evaluating emotionally neutral words (Maddock *et al.*, 2003).

The PCC and precuneus have also been implicated as impor-tant regions mediating abnormal emotion processing in psycho-logical disorders like social phobia and depression. Increased activity in the PCC has been observed in affective disorders and reported to correlate with severity of anxiety symptoms in major depression, obsessive–compulsive disorder and social phobia (Bench *et al.*, 1992; McGuire *et al.*, 1994; Perani *et al.*, 1995; Reiman, 1997). To determine differences in DMN activity between social phobia patients and healthy control subjects, Gentili *et al.* (2009) studied face perception with emotional and neutral stimuli. These authors identified reduced deactivation in the precuneus and the PCC in the social phobia patients, as compared to controls. Another study in patients with depression also found reductions of emotion-related PCC deactivations as compared to controls (Ho *et al.*, 2015). A decrease in DMN activity, as found

in our study, may counteract this effect, thus pointing toward exercise-related modulation of PCC and precuneal activity during emotional face processing. Shared reductions of posterior DMN activity was found in the ANOVA indicating a significant time effect, but *post hoc* testing found the low-intensity exercise intervention to be the primary driver of this effect. Hence, the dependence of PCC/precuneus activity on exercise intensity needs further investigation.

We also observed a significant main effect of time in ventral structures of the basal ganglia, notably the caudate nucleus, and this effect was primarily mediated by the high exercise intensity intervention where the comparison pre *vs* post revealed significantly decreased activation in right and partially left caudate nucleus and right ventral anterior putamen. The basal ganglia were originally linked predominantly with sensorimotor behavior (Nelson and Kreitzer, 2014). However, there is clear meta-analytic evidence from functional neuroimaging studies to support their role also for processing of emotions and reward (Arsalidou *et al.*, 2013). Studies investigating hateful faces (Zeki and Romaya, 2008) and faces with expressions of disgust or contempt (Sambataro *et al.*, 2006) also elicited putaminal activations in areas in line with our findings; hence, corroborating the notion that this structure is involved in the processing of negative emotional faces.

The fact that neuronal down-regulation was found especially for fearful (but not happy or neutral) faces indicates a weaker reaction to threatening stimuli that might be reasoned by an endorphin release after physical activity. In a placebo-controlled study, Ipser *et al.* (2013) investigated the effects of the mu-selective opioid agonist buprenorphine on fear sensitivity using an emotion recognition paradigm: buprenorphine, but not placebo, resulted in a highly specific reduction of the ability to recognize fearful facial expressions. Exercise-induced opioidergic effects have been reported recently in humans: Boecker *et al.* (2008b) used a PET ligand activation approach and reported reductions in fronto-limbic opioid receptor availability after 2 h of endurance running, indicating an increase in central acting endogenous opioids. These findings were recently confirmed and extended with mu-selective PET ligands (Hiura *et al.*, 2017; Saanijoki *et al.*, 2018). Of course, other neurohumoral mechanisms may play a role as well, but unfortunately, we are not able to dissociate these on the basis of the current data.

While one might speculate on exercise intensity-dependent effects, we have to point out that the effect of exercise intensity was not discernable by directly comparing the two exercise intensities, nor did we find areas showing gradual decreases of activity from low to high intensity. However, both interventions did show qualitative differences, indicating that distinct neuronal networks are modulated by different exercise intensities. This is a novel finding that should be further substantiated experimentally by using a larger variety of exercise conditions to allow extrapolating dose–response curves of exercise intensity and associated emotional responses.

Limitations and prospects

There are some limitations that must be considered: firstly, the study population consisted only of males in order to exclude potential hormone cycle-linked humoral factors. To generalize findings, future studies need to investigate gender-balanced cohorts. Second, no randomized control intervention was implemented, so it cannot be excluded with certainty that effects shown in the pre-post comparisons are driven by factors other than exercise, e.g. task repetition effects. Although we would like

to make the point that the demonstration of activation changes (pre *vs* post) in typical regions of the emotion-processing network after high- and low-intensity exercise are concordant to the assumption that the effects are primarily driven by the exercise intervention. A third critical issue is the impact of the time span between the exercise intervention and post-exercise fMRI scans, which was ~45 min, and should be optimized in future studies to capture the possibility that even larger effects may occur closer to the end of exercise. Fourth, the cluster interference method, which considers cluster size, is still a criticized method for fMRI data (Eklund *et al.*, 2016, 2018), as it is prone to a higher rate of false positives. However, in our fMRI analysis we use a high cluster defining threshold of $P = 0.001$, which was shown to perform well in parametric methods (Eklund *et al.*, 2016). We also would like to make the point that we found activation changes in brain regions that are actually linked to emotional processing. Fifth, due to the exploratory design of this study we are not able to define which exercise component causes the observed neuronal modulations. This will be subject to further investigation. Finally, one should consider employing further dedicated emotion-related questionnaires pre-/post-exercise such as the STAI state and other more effective emotion paradigms that can induce stronger affective brain states and respective activations in emotion-related brain regions. This will be particularly important when attempting to further unravel links between imaging and behavioral effects induced by exercise.

Conclusions

At the behavioral level, the significant general increases in positive affect scale are in accord with previous studies showing that acute exercise bouts have a generally positive impact on mood. We provide the first *in vivo* evidence that acute strenuous exercise interferes with emotion-processing brain regions during fearful face processing. While these findings clearly indicate emotion type-specific effects, as well as differential modulatory mechanisms after low- and high-intensity exercise, further studies are needed to explore the underlying mechanisms in more detail, in particular those mediating dose-dependent effects of exercise. While additional research is needed to understand the dose-dependent effects of exercise, this study highlights the benefit of combining exercise with a neuroimaging-based behavioral paradigm to understand how exercise regimens can benefit clinical populations with affective disorders.

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Supplementary data

Supplementary data are available at *SCAN* online.

Conflict of interest.

None declared.

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