

The effects of different aerobic exercise intensities on serum serotonin concentrations and their association with Stroop task performance: a randomized controlled trial

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Abstract

Purpose Acute exercise improves selective aspects of cognition such as executive functioning. Animal studies suggest that some effects are based on exercise-induced alterations in serotonin (5-HT) secretion. This study evaluates the impact of different aerobic exercise intensities on 5-HT serum levels as well as on executive functioning considering 5-HT as a potential mediator.

Methods 121 young adults (23.8 ± 3.6 years) were examined in a randomized controlled trial including three exercise intervention (35 min) groups (low intensity, 45 % of the maximal heart rate (HR_{max}); moderate intensity, 65 % HR_{max} ; high intensity, 85 % HR_{max}) and one control group. 5-HT levels and response inhibition (measured by a computerized Stroop test) were assessed pre- and post-intervention.

Results There was a significant ($p = 0.022$) difference between groups regarding serum Δ 5-HT levels. Post hoc tests indicated significant ($p = 0.013$) higher 5-HT serum levels for the high-intensity group compared to the control group while other groups did not differ significantly from each other. Serum Δ 5-HT levels and exercise intensity were shown to be linearly associated through polynomial contrast analysis ($p = 0.003$). Furthermore, ANOVA revealed a significant difference for Stroop parameter reading ($p = 0.030$) and a tendency for reverse Stroop effect ($p = 0.061$). Correlation analysis showed that augmented 5-HT levels were associated with improved results in response inhibition.

Conclusions This study indicates that intensive acute exercise increases serum 5-HT levels compared to a control group. These findings might be relevant for many other related research fields in exercise science, since 5-HT receptors are expressed on many different cell types including endothelia and immune cells.

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Keywords Exercise · Physical activity · Serotonin · 5HT · Cognition · Executive function

Abbreviations

Δ 5-HT levels	5-Hydroxytryptamine levels at $t_1 - t_0$
5-HT	5-Hydroxytryptamine
a.m.	Ante meridiem
ANOVA	Analysis of variance
BBB	Blood–brain barrier
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
Bpm	Beats per minute
CG	Control group
CNS	Central nervous system
GXT	Graded exercise test
HI	High intensity
HLPC	High-performance liquid chromatography
HR	Heart rate
HR _{max}	Maximal heart rate
IGF-1	Insulin-like growth factor 1
LI	Low intensity
MI	Moderate intensity
Min	Minutes
MWT-B	Multiple choice vocabulary test
RCT	Randomized controlled trial
RPM	Revolutions per minute
Rpm	Rotation per minute
RT	Reaction time
SERT	Serotonin transporter
SPSS	IBM SPSS Statistics
TRP	Tryptophan depletion
VEGF	Vascular endothelial growth factor
WTS	Wiener test system

Introduction

5-HT plays an important role in a wide variety of cognitive processes (Cools et al. 2008; Harmer 2008; Haider et al. 2006). Central 5-HT levels have been reported to be increased after acute physical exercise in rodents (Chaouloff 1989; Chennaoui et al. 2000; Mizutani et al. 2013; Wilson and Marsden 1996). Animal studies indicate that changes in brain serotonin metabolism following both acute and chronic exercise are time course dependent and differ between brain regions (Dey et al. 1992).

Although many studies looked for 5-HT precursors (tryptophan) or metabolites, few studies described the influence of acute exercise on 5-HT in human trials. Studies only focus on peripheral 5-HT concentrations, since invasive procedures looking for cerebral 5-HT levels are hardly feasible in humans. Increased 5-HT concentrations after acute exercise were reported in urine (Ohmatsu et al.

2014) as well as in whole blood samples (including platelet stored 5-HT) (Fumoto et al. 2010).

Since a significant positive correlation between serotonin levels in cerebral spinal fluid and both, blood plasma and serum could be shown in animals as well as in humans (Audhya et al. 2012; Nakatani et al. 2008; Ohmatsu et al. 2014), peripheral 5-HT levels might be used as rough indicator to predict central 5-HT concentrations. Furthermore, 5-HT transporters (SERT) have been detected in mouse brain capillary endothelial cells at the BBB (Young et al. 2015; Nakatani et al. 2008).

Keeping this physiological relation in mind, exercise-induced elevation of peripheral 5-HT levels could be one possible mechanism underlying reported positive effects of acute exercise on cognitive performances.

However, urine as well as whole blood 5-HT levels might not be appropriate parameters to infer on cerebral concentrations. Against the backdrop of above-stated recent findings showing 5-HT BBB transport, free and unbound serum 5-HT are more likely to represent cerebral serotonin levels. In whole blood samples, 5-HT is mainly stored in platelets. This 5-HT can neither pass through BBB nor induce any 5-HT triggered mechanisms, such as modifying endothelial- or immune functions which also impact cerebral function (Watts et al. 2012; Holst et al. 2015).

The knowledge about acute exercise-induced alterations in serum 5-HT levels is still sparse. Acute elevated serum 5-HT levels were only reported after extreme stimuli, such as an ultramarathon (Agawa et al. 2008) as well as exhaustive exercise in the heat (Zhao et al. 2015) and in paraplegic patients (Steinberg et al. 1998).

Therefore, the primary aim of this study was to investigate the effect of different aerobic exercise intensities on serum 5-HT levels in young and healthy individuals.

While acute exercise-induced alterations in serum 5-HT have hardly been investigated yet, effects of acute exercise on subsequent cognitive performances are well documented (e.g. Verburgh et al. 2014; Winter et al. 2007). Among other cognitive domains, a large number of studies show acute exercise-induced facilitation of inhibitory control depending on task performance (e.g. Chang et al. 2012; Chu et al. 2015a). Inhibitory control as one of the core executive functions displays one's ability to selectively focus on what we choose and suppress attention to other stimuli (Diamond 2013). While it was shown to be affected by preceding exercise, there is evidence for a role of 5-HT in inhibitory control processes. Several studies showed that increased central 5-HT turnover leads to enhanced inhibitory control whereas reduced central 5-HT levels are associated with increased impulsivity (Cools et al. 2008; Homberg et al. 2007). Against this backdrop, alterations in 5-HT due to preceding physical exertion might be the underlying mechanism of reported acute exercise-induced inhibitory control facilitation.

The secondary aim of this study was, therefore, to investigate a potential association between acute exercise-induced changes in serum 5-HT and Stroop task performance.

Materials and methods

Participants

Participants were recruited via announcements of the study in courses at the German Sport Science University and in training sessions of local sports associations. All subjects of the present study participated voluntarily. Students did not receive course credit or comparable advantage for participation.

Ethics

The experimental protocol was approved by the ethics committee of the German Sports University Cologne and is in accordance with the declaration of Helsinki. All participants provided written informed consent prior to participation.

Sample size

Current knowledge of serum 5-HT-induced mechanisms and interactions seems not sufficient for an a priori definition of a physiologically relevant increase. Therefore, sample size calculation was based on secondary research question whether the applied exercise treatment affects Stroop task performance.

According to this study's design, sample size calculation was conducted for detecting potential interaction effects between the within-subjects factor time point (t_0 vs. t_1) and the between-subjects factor treatment on cognitive testing performance as a 2×4 mixed analysis of variance (mixed ANOVA). One-way ANOVA testing of baseline post-assessment difference values (Δ -values) (as conducted in our analyses below) was shown equivalent to interaction effect of a mixed ANOVA (e.g. Hager 2004). Recent meta-analysis shows quite small effects of acute exercise on executive functioning dependent test scores (Chang et al. 2012). Therefore, sample size calculation was conducted based on an expected effect of $f = 0.2$ with a statistical test power ($1 - \beta$) set at 0.95 and probability of false-positive decision and committing a type I error (α), respectively, set at 0.05. Correlation of participants' Stroop testing scores at t_0 and at t_1 was estimated at $r = 0.45$. The power analysis revealed that 112 participants would be required to be distributed evenly on the four groups to achieve the desired $1 - \beta$.

Exclusion criteria

Subjects were excluded from study participation if they were younger than 18 or older than 35 years of age, had a Body Mass Index (BMI) below 18 or above 30, participated in any kind of professional sports or reported any history of cardiopulmonary, neurological, metabolic or psychiatric diseases. Additionally, participants with any of the following were excluded: intake of any prescription medication (other than oral contraceptives), consumption of illegal drugs, acute infections, pregnancy, extensive physical training during the previous 2 weeks, experience with the applied cognitive tasks or any limitation in the ability to exercise or complete the cognitive testing procedures. Moreover, participants' were not allowed to consume any caffeinated or alcoholic products during the days of their study participation.

Procedure

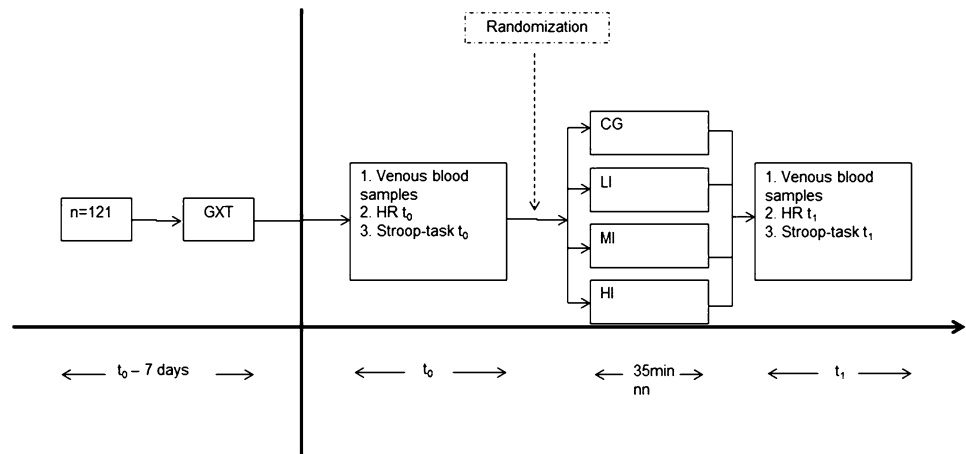
To determine participants' baseline characteristics and to explore their physical fitness to estimate potential training heart rate, participants were invited 7 days before the intervention to perform a graded exercise test (GXT). On the actual testing day, all analyses/interventions were conducted between 9 and 11 a.m. Participants were instructed to restrain from any kind of food or drink intake after waking up on the morning of the testing. After venous blood samples were drawn and resting state heart rate (HR) was assessed, participants performed the Stroop task (Pre = t_0). Immediately after completing the cognitive testing, participants were randomized into one of three exercise groups or into one control group. Participants were allocated (1:1:1:1) into treatment groups using an adaptive biased-coin randomization method (software-based urn randomization) to achieve an equal distribution regarding potential confounding factors (sex, age, fitness, BMI as well as HR, lactate, 5-HT and cognitive testing baseline values). Immediately after 35 min of intervention blood samples and HR data were collected and a parallel version of the Stroop task was conducted again (Post = t_1). Due to exercise-induced dehydration, which impacts plasma/serum volume and thereby influences 5-HT levels (Popova et al. 2001), exercise groups' participants were instructed to drink 250 ml of pure water after the acute bout of exercise. The study design is illustrated in Fig. 1.

Assessments

Graded exercise test

The GXT was undertaken 7 days prior to the actual testing to evaluate participants' fitness level and to set exercise

Fig. 1 Study design. *CG* control group, *LI* low-intensity group, *MI* moderate-intensity group, *HI* high-intensity group, *min* minutes, *GXT* graded exercise test, *HR* heart rate, t_0 pre-exercise, t_1 post-exercise



intensity for the following intervention. Participants were instructed to constantly pedal at 70 revolutions per minute (RPM) beginning at 50 W and increasing the workload every 3 min by 30 W until volitional exhaustion on a stationary cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands). In the end of each step and after cessation of the test, heart rate (HR) was captured (FT1-Polar heart rate monitor and Wear Link soft-strap transmitter, Polar Electro, Finland). To ensure that participants worked out until physical exhaustion, lactate samples of capillary blood (20 μ l) were withdrawn parallel to each HR measurement. True maximal effort was assumed if participants met both of the following criteria: capillary lactic acid concentrations of more than 8 mmol/l (Biosen S-Line, EKF Diagnostics, Barleben, Germany) as well as a failure of heart rate to increase. As a measure of physical fitness watts per kilogram of bodyweight (W/kg) was calculated for each participant for the last completed step at GXT.

Intervention and control group treatment

Three exercise groups (low intensity, LI; moderate intensity, MI and high intensity, HI) were established on the basis of individual maximum HR (HR_{max}) participants had achieved during proceeded GXT. Subjects, who were randomized to LI exercised at 45–50 %, participants assigned to MI performed at 65–70 % and participants assigned to HI performed at 85–90 % of their HR_{max} . All exercise sessions started with a 5-min warm-up during which laboratory staff adjusted the wattage to get the participants into the requested heart rate range for 30 min. To assure compliance with particular exercise group's intensity, participants' HR was monitored throughout the whole training session. If participants' heart rate fell outside the given HR window, work load was immediately, manually adjusted.

In contrast to most other studies dealing with acute effects of exercise on cognition, this study did not comprise

a non-supervised control group (CG) treatment, such as reading or watching video for the same amount of time. To minimize expectation effects, also known as Hawthorne effect, we implemented a CG treatment which implies both, a comparable social stimulus through supervision as well as a comparable psycho-physiological paradigm (low physiological activation with motoric components). Therefore, the control group treatment consisted of a constantly instructed 35 min low-intensity myofascial release training with a foam roll also known as black-roll. HR was assessed before and after CG treatment.

Stroop task

The Stroop task is one of the most common procedures to assess response inhibition (Chu et al. 2015b). In the present study, the German version of the computerized Stroop task from the Wiener Test System (WTS) (Schuhfried GmbH, Mödling, Austria) was applied. This task uses four different colours (red, blue, green, and yellow) and includes the following assignments: reading colour word displayed in black font colour (reading baseline), naming ink colour of differently coloured rectangles (naming baseline), naming ink colour of colour words in incongruent format (Stroop effect) and denominating semantically expressed word displayed in incongruent colour (Reverse Stroop effect). Conditions are tested in separate consecutive testing blocks. Each testing block includes 128 items, which are presented successively. Participants' react using a special keyboard which comprises four correspondingly coloured buttons. WTS Stroop testing software calculates the medians of their reaction time (RT) at reading baseline (RTreading) and at naming baseline (RTnaming). The testing software computes a Stroop effect variable (Stroop effect) as measure of interference control by subtracting RTnaming from median RT at Stroop condition. The Reverse Stroop effect variable is the balance between median RT at Reverse

Stroop condition and RT reading. All those four variables were evaluated in the analyses.

5-HT

Blood samples were drawn at t_0 and t_1 . After the clotting was completed, the tubes (8.5 ml) were centrifuged for 10 min at a rotation of 1200 rpm. The samples were stored at -80° and finally analysed at the end of the study. The measurements of serum 5-HT were performed by high-performance liquid chromatography (HPLC) with colorimetric detection (Agilent HP 1200, Santa Clara, USA). According to the manufacture manual, reference levels for serum 5-HT concentrations range from 80–400 $\mu\text{g/l}$, while linearity (measuring range) ranges from 5–1000 $\mu\text{g/l}$.

Statistics

Potential baseline differences between treatment groups in age, BMI, W/kg, 5-HT and cognitive testing scores were investigated using separate one-way analyses of variance (ANOVAs). Chi-square test was used to determine potential association between gender (female vs. male) and treatment (CG vs. LI vs. MI vs. HI). This procedure allows interpretation of potential differences regarding gender distribution among groups. Due to central limit theorem, we assumed approximate normality of sampling distribution. Potential baseline differences between treatment groups regarding education level and intelligence categories were analysed using separate Kruskal–Wallis tests.

For HR, 5-HT and cognitive testing outcomes baseline post-assessment difference values (Δ -values) were calculated. Accordingly, Δ -values represent changes in participants' values from t_0 to t_1 . To determine differences between treatment groups regarding HR, 5-HT and cognitive testing scores, separated one-way ANOVAs on Δ -values were conducted. As effect sizes indicating the amount of variance explained by between-subject factors (treatment group) partial η^2 were calculated. If one-way ANOVA revealed a significant difference between treatment groups regarding any variable, this difference was further investigated carrying out Bonferroni-corrected post hoc pairwise comparisons. For interpretation of 5-HT mean group differences Cohen's d values were calculated. Interpretation of Cohen's d values follows as suggested by Cohen (1988) having a $d < 0.5$ representing a small effect, a $0.5 < d < 0.8$ representing a moderate effect and a $d > 0.8$ representing a large effect. Furthermore, in case of ANOVA indicating a significant effect, the trend of Δ -value means from CG to HI was investigated using trend analysis (polynomial contrasts).

To explore potential associations between 5-HT and cognitive performances Pearson's bivariate correlation

coefficients were calculated separately for each treatment group and tested for significance using general linear model. Assumption of normality had not been tested for above-mentioned reasons.

For all inferential statistical analyses, significance was defined as p value less than 0.05. All descriptive and inferential statistical analyses were conducted using SPSS 22® (IBM®, Armonk, NY, USA). Two-tailed probability tests were used throughout all inferential statistical testing. Test power calculations were conducted using free of charge available statistical test power computation software GPower 3 (Faul et al. 2007).

Results

No group differences were detected for participant characteristics [age, BMI, fitness level (W/kg)] and baseline outcomes of HR, lactate, serum 5-HT concentrations as well as Stroop test variables. Chi-square analysis revealed no significant association between gender and treatment ($\chi^2(3) = 1.205$, $p = 0.752$) meaning that treatment groups did not differ more than by chance regarding frequency of males and females. Participants' characteristics, baseline values as well as ANOVA results are listed in Table 1.

To determine if groups were distinguishable in terms of exercise intensity parameter HR (manipulation check) an ANOVA on Δ -heart rate values was conducted. ANOVA revealed significant group differences ($p < 0.001$). Post hoc tests showed significant differences between all groups with exception of CG vs. LI. Post hoc results are depicted in Fig. 2.

Regarding alterations in serum 5-HT levels, ANOVA showed a significant difference between the groups ($p = 0.022$, partial $\eta^2 = 0.078$) (Table 2). Subsequent post hoc tests revealed a significant group difference between the CG and the HI group ($p = 0.013$, $d = 0.67$), indicating higher 5-HT serum concentration in the HI group after exercise (Fig. 3a). Post hoc analysis did not show further significant group differences (CG vs. LI: $p = 1$, $d = -0.27$, CG vs. MI: $p = 0.747$, $d = -0.35$, LI vs. MI: $p = 1$, $d = -0.14$, LI vs. HI: $p = 0.334$, $d = -0.57$, MI vs. HI: $p = 0.750$, $d = -0.44$). However, polynomial contrast analysis revealed that serum 5-HT and exercise intensities are significantly linearly associated ($F(1.119) = 9.523$; $p = 0.003$). This linear intensity-dependent increase in 5-HT can also be retraced from Fig. 3a.

In view of the Stroop test, ANOVA indicates a significant difference for the outcome Δ -reading ($p = 0.030$) and a tendency for Δ -reverse Stroop effect ($p = 0.061$, partial $\eta^2 = 0.073$). ANOVA results for all Stroop test outcomes are listed in Table 2. Post hoc tests showed a significant

Table 1 Description and group comparison of participants anthropometric data, fitness level and baseline values

	CG (<i>n</i> = 31) f, 11; m, 20		LI (<i>n</i> = 30) f, 10; m, 20		MI (<i>n</i> = 30) f, 7; m, 23		HI (<i>n</i> = 30) f, 9; m, 21		<i>p</i> value 0.752
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Age (years)	23.97	3.371	24	3.714	23.37	3.891	23.9	3.726	0.898
BMI (kg/m ²)	22.223	2.428	23.329	1.961	22.507	1.859	21.984	1.75	0.061
Fitness (W/kg)	3.61	0.606	3.488	0.734	3.635	0.54	3.714	0.447	0.524
LAC (mmol/l)	1.352	0.777	1.109	0.264	1.315	0.441	1.133	0.414	0.158
HR (<i>t</i> ₀) (bpm)	75.129	13.058	73.933	11.145	75.533	14.333	71.433	10.315	0.569
5-HT (μg/l)	170.61	185.78	105.66	62.47	122.72	48.71	132.03	63.36	0.104
Stroop _{reading} (ms)	0.664	0.094	0.659	0.069	0.658	0.068	0.657	0.075	0.984
Stroop _{naming} (ms)	0.625	0.081	0.623	0.069	0.615	0.073	0.617	0.069	0.936
Stroop effect (ms)	0.067	0.067	0.072	0.056	0.089	0.060	0.084	0.057	0.446
Rev Stroop effect (ms)	0.124	0.079	0.167	0.096	0.136	0.074	0.164	0.096	0.160

f female, *m* male, *M* mean, *SD* standard deviation, *CG* control group, *LI* low intensity, *MI* moderate intensity, *HI* high intensity, *BMI* Body Mass Index, *HR* (*t*₀) heart rate baseline, *bpm* beats per minute, *5-HT* 5-hydroxytryptamine, *ms* milliseconds

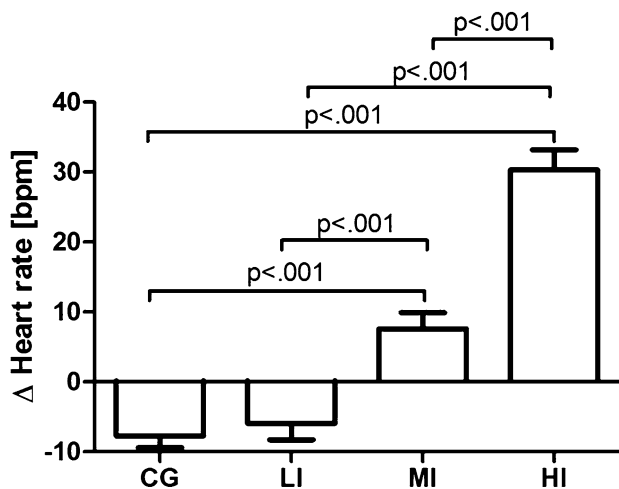


Fig. 2 Manipulation check, including post hoc comparison of Δ -heart rate values in beats per minute (bpm). Data are presented as means $\pm$ standard error of the mean (SEM). *CG* control group, *LI* low-intensity group, *MI* moderate-intensity group, *HI* high-intensity group

difference for Δ -reading between the *LI* and the *HI* group ($p = 0.034$, $d = 0.78$) and a tendency for the Δ -reverse Stroop effect between the *LI* and the *MI* group ($p = 0.064$) (Fig. 3).

Correlation analyses of those parameters which significantly differ between intervention groups were conducted to determine potential association. A correlational analysis of 5-HT serum levels and reverse Stroop effect data at baseline was conducted across all groups, since no treatment had yet been applied at *t*₀. A significant negative correlation was found ($p = 0.003$, $r = -0.268$), indicating that higher 5-HT serum levels might be associated with decreased reaction time. Furthermore, delta values of 5-HT and Δ -Stroop variables shown to be significantly influenced by exercise intensity (Δ -reading and Δ -reverse Stroop effect) were correlated within each treatment group. However, only Δ 5-HT and Δ -reverse Stroop effect within the *HI* group showed a significant correlation. A significant negative correlation was found ($r = -0.392$, $p = 0.035$).

Table 2 ANOVA results for 5-HT serum level and Stroop test outcomes

	CG (<i>n</i> = 31)		LI (<i>n</i> = 30)		MI (<i>n</i> = 30)		HI (<i>n</i> = 30)		<i>p</i> value
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
Δ 5-HT (μg/l)	8.975	122.08	35.187	59.689	43.841	67.582	78.388	87.665	0.022*
Δ Stroop _{reading} (ms)	−0.0686	0.0595	−0.0508	0.0429	−0.08	0.0413	−0.0858	0.0464	0.030*
Δ Stroop _{naming} (ms)	−0.0525	0.0434	−0.0385	0.0466	−0.0396	0.0267	−0.0574	0.0389	0.172
Δ Stroop effect (ms)	0.0183	0.0586	0.0117	0.0560	0.0186	0.0694	0.0111	0.0432	0.928
Δ Rev Stroop effect (ms)	0.0108	0.0594	−0.0269	0.0753	0.0224	0.0791	−0.005	0.0798	0.061

Significant ANOVA results are marked with asterisk; post hoc tests are illustrated in Fig. 3

M mean, *SD* standard deviation, *CG* control group, *LI* low intensity, *MI* moderate intensity, *HI* high intensity, Δ 5-HT 5-hydroxytryptamine *t*₁ – 5-hydroxytryptamine *t*₀, *ms* milliseconds

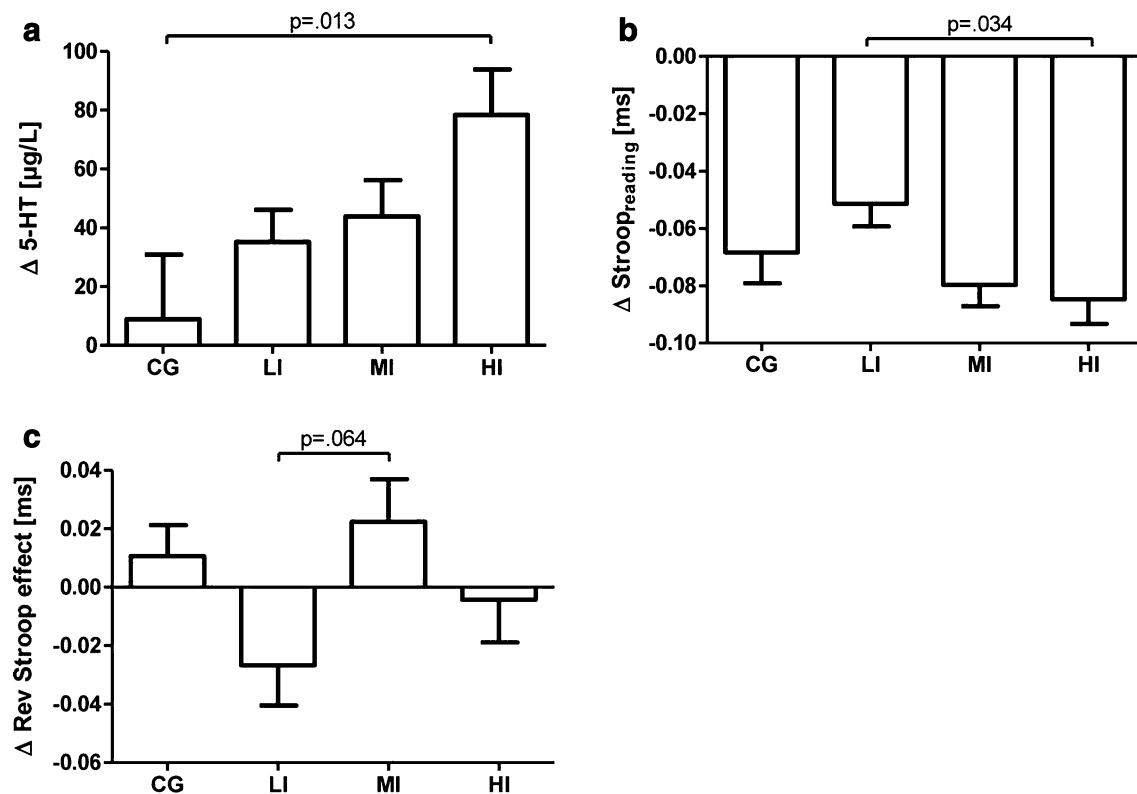


Fig. 3 Post hoc results for changes (Δ) in 5-HT serum levels in $\mu\text{g/L}$ (a) and significant/tendentious alterations in Stroop test outcomes in ms (b, c). Data are presented as means $\pm$ standard error of the mean

(SEM). *CG* control group, *LI* low-intensity group, *MI* moderate-intensity group, *HI* high-intensity group

Discussion

To our knowledge, this is the first study demonstrating that acute intensive aerobic exercise influences serum 5-HT levels in healthy young humans. However, partial η^2 of 0.078 and a corresponding variance explanation below 10 %, respectively, illustrates that serum 5-HT levels must be influenced by several factors. It was shown that intense aerobic exercise increases serum 5-HT levels quite noticeably. Calculated effect size Cohen's d of 0.67 illustrates that a 35-min intense aerobic ergometer session is moderately more effective in terms of serum 5-HT increase than a very low intensity myofascial release training of the same duration. Furthermore, we could show that enhanced serum 5-HT levels are associated with improved response inhibition in terms of the Stroop parameter reading and the reverse Stroop effect. In contrast to most other trials in the context of exercise and 5-HT, this study investigated serum 5-HT and not its metabolites, precursors or storages. This is highly relevant since it is unbound serum 5-HT which represents the effective and active form of that hormone/neurotransmitter (Lincoln 1995; Watts et al. 2012).

To explain the exercise-dependent increase in serum 5-HT, different mechanisms should be considered: first,

studies demonstrated that a shear stress-induced activation of platelets, the store of blood 5-HT, results in elevated 5-HT serum levels (Lu et al. 2013). The mentioned shear stress is mainly mediated by enhanced blood flow, which can be driven by physical exercise.

Second, the literature reported an increased uptake of unbound tryptophan (precursor of 5-HT) at the BBB during exercise. It was discussed that enhanced lipolysis during exercise results in an increased compulsion of tryptophan from its plasma binding proteins (albumin) through free fatty acids (Weicker and Strüder 2001). More tryptophan may promote central biosynthesis and release of 5-HT (Patrick and Ames 2015; Wilson and Marsden 1996). Since 5-HT transporters (SERT) were described in mouse brain capillary endothelial cells at the BBB, increased 5-HT levels in the CNS might lead to augmented peripheral serum 5-HT levels as well. Wakayama et al. indicate that central 5-HT can cross the BBB through the SERT to obtain homeostasis with peripheral monoamine concentrations (Wakayama et al. 2002). According to this, several studies could show a significant positive correlation with serotonin levels in cerebral spinal fluid and blood plasma in both animals and humans (Audhya et al. 2012; Nakatani et al. 2008; Ohmatsu et al. 2014).

Third, exercise activates the biosynthesis of pteridine derivatives, such as tetrahydrobiopterin, which is an important co-factor of the tryptophanhydroxylase. This is the key enzyme for 5-HT production and, therefore, exercise might elevate 5-HT synthesis by increasing tetrahydrobiopterin (Hashimoto et al. 2004).

When discussing the role of altered hormone/neurotransmitter levels, it is indispensable to have a look on the receptor site as well, thereby regarding the whole transmission system. It is well described that physiological and pathophysiological alterations in transmitter concentrations may be equalized by adaptations of receptor expression (Chennaoui et al. 2000, 2001). In view of 5-HT receptors and exercise, Weicker and Strüder (2001) identified increased concentrations of 5-HT (2A) receptor density on isolated platelet membranes during a 3-week moderate endurance training of untrained participants. In contrast, a 4-week excessive training program of well-trained endurance athletes showed a decline of 5-HT(2A) receptor density (Weicker and Strüder 2001). Moreover, several animal studies revealed that exercise interventions have a distinct influence on central 5-HT receptor expression (Chennaoui et al. 2000, 2001). Together with the results of Soares et al. (1994) who showed that serum 5-HT levels differ between physically fit and sedentary young adults, these findings imply that the impact of exercise on 5-HT and its various receptors depends on training state as well as the exercise paradigm. Further research has to show, if a repeated exercise-induced acute increase in serum 5-HT results in chronic alterations/adaptions of 5-HT receptors on different cell types.

We demonstrated that serum 5-HT levels increase in dependence of exercise intensity. Literature indicates a positive correlation between peripheral and cerebral serotonin concentrations (Audhya et al. 2012; Nakatani et al. 2008; Ohmatsu et al. 2014). As mentioned in the introduction, it was shown that increased central 5-HT levels lead to enhanced inhibitory control (Cools et al. 2008; Homberg et al. 2007) whereas reduced central 5-HT levels are associated with increased impulsivity. In line with these findings, the results of the correlation analysis suggest an association between serum 5-HT levels and the cognitive performance. Since this association is relatively weak, it should be kept in mind that several other factors are involved in these processes (Lin and Kuo 2013). Therefore, it remains speculative if and how the mentioned increase in peripheral 5-HT contribute to alterations in cognitive functioning. As described above, augmented serotonin levels within the central nervous system are time course dependent and differ between various brain regions after acute physical exercise (Dey et al. 1992). Executive functions such as response inhibition are described to be located in the prefrontal cortex (Ball et al. 2011). Obviously, our study design does not

allow to state about these regional differences. However, Hüther and Rütger showed via immunohistochemical methods that the serotonergic density of innervation is particularly distinctive in the prefrontal cortex, implying that serotonergic neurotransmission plays an important role within executive functioning (Hüther 2000). Correspondingly, we could show significant correlations between serum 5-HT levels and some conditions of the Stroop task. No matter, if this connection can be replicated in future studies, serum 5-HT can only serve as rough indicator to explain cognitive functioning, regarding the complexity of regional differences of central 5-HT and 5-HT receptor expression. Regarding the significant group differences in Stroop task performance (Stroop_{reading}) our results support those of a meta-analysis by Chang et al. (2012) who reported most beneficial effects of acute exercise, after a short delay and when exercise is done at high intensity.

In addition to acute effects of exercise on cognition, regular physical activity has been mentioned to alter the structure of several brain regions, such as the hippocampus, for example, by stimulating neurogenesis. Many studies have shown that acute exercise increases peripheral as well as central levels of growth factors such as BDNF, VEGF and IGF-1 (Ferris et al. 2007; Hopkins and Bucci 2010; Neeper et al. 1995; Rojas Vega et al. 2006). The results of the present study suggest that 5-HT levels, which are also known to be involved in neurogenesis (Beckman and Santos 2013; Klempin et al. 2013), are similarly affected by exercise, thereby contributing to structural adaptations of the CNS. In fact, the described relationship of exercise, 5-HT and neurogenesis is not new. However, our results support the role of 5-HT in this context.

Alterations in serum 5-HT concentrations during and after acute physical exercise might also be relevant for many other related research fields of exercise science and sports medicine, since 5-HT receptors occur in many tissues and cells that have direct contact with unbound serum 5-HT [e.g. endothelia (Watts et al. 2012) as well as immune cells (Holst et al. 2015)]. Interestingly both cell lines have previously been described to be strongly influenced by exercise. Therefore, it would make sense to investigate the role of 5-HT and its downstream effectors in the named cell lines.

Although we served highest standards of a randomized controlled trial (RCT) including a large sample size, we only covered the effects of acute exercise on serum 5-HT levels and response inhibition for young and fit healthy adults. Further studies with different populations such as patients with depressive disorders as well as more comprehensive methodological approaches (e.g. downstream signalling, receptor expression, etc.) are needed to improve the clinical relevance. Furthermore, following studies should comprise more detailed information about participants' fat

mass, hydration status and body composition (e.g. bioimpedance analysis, hematocrit), since these factors influence 5-HT production, concentration and responsiveness (Hodge et al. 2012; Popova et al. 2001). The control treatment consisted of very low intensity tasks exclusively. Therefore, HR was documented only before and after the intervention. To gain a more precise idea of CG intervention intensity, HR should be monitored throughout the whole session in future studies. Regarding the establishment of different intensity groups, one might argue that participants' peak power which was reached during GXT is more appropriate to monitor/control exercise intensity. However, controlling exercise intensity via HR is commonly used and, therefore, has more practical implications.

Conclusions

This study provides evidence that acute intense aerobic exercise increases serum 5-HT concentrations. Furthermore, these alterations were associated with improved performance in selective aspects of the Stroop task. Besides its potential relevance for several aspects of the central nervous system, including cognitive functions, exercise-induced alterations in serum 5-HT may also be of great interest in related research fields, such as exercise–immunology and exercise–endothelia interactions.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest to declare.

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