

The effect of an acute bout of high intensity intermittent exercise on neural growth factors in young adults: Sex differences

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Received: 24 December 2021; **Accepted:** 17 May 2022; **Published:** 26 June 2022

Edited by: Pike-See Cheah (Universiti Putra Malaysia, Malaysia)

Reviewed by: Usman Bala (Gombe State University, Nigeria);

Hafizah Abdul Hamid (Universiti Putra Malaysia, Malaysia)

<https://doi.org/10.31117/neuroscirn.v5i2.146>

Abstract: The neurophysiological response to exercise on cognition is modulated through chemical pathways which involve several neurotrophic factors and the sex of the individual determines this effect. We examined sex differences in the concentration of neural growth factors (NGF); brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF) and insulin like growth factor-I (IGF- I) in response to acute high intensity intermittent exercise (HIIE). We also evaluated the relationship of NGF with gonadal hormones before and after the HIIE session. Forty healthy young adults (22 males and 18 females) performed HIIE (4 bouts of 4 minutes at 90–95% HR max with 3min active recovery at 70% HRmax). Venous blood was drawn before and immediately after the exercise session and was analyzed for the concentration of serum BDNF, VEGF, IGF-I, cortisol, estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH) and testosterone, using ELISA method. A significant sex difference ($p < 0.05$) was observed for BDNF concentration in response to HIIE and a significant increase was found in males but not in females. A significant ($p < 0.005$) positive correlation of BDNF with FSH and LH and a significant ($p < 0.05$) negative correlation of BDNF and VEGF with testosterone were found. Other NGFs (VEGF and IGF-I) did not show sex differences in response to HIIE. In conclusion, a single session of HIIE increases the serum concentration of BDNF in males and IGF-I in females and the response of NGF is different in males and females.

Keywords: High intensity intermittent exercise; neural growth factor; sex differences; gonadal hormones

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1.0 INTRODUCTION

A growing body of literature has examined the neurophysiological basis of the effect of acute exercise on cognition ([Basso & Suzuki, 2017](#); [Cirrik & Hacıoglu, 2016](#); [Hillman et al., 2008](#)). The neurophysiological

response to exercise on cognition is modulated through chemical pathways which involves brain derived neurotrophic factor (BDNF) ([Murawska-Ciałowicz et al., 2015](#)), insulin-like growth factor-I (IGF-I) ([Maass et al., 2015](#)) vascular endothelial growth

factor (VEGF) ([Skriver et al., 2014](#)), and cortisol ([Vega et al., 2006](#)). These neurophysiological substances have unique actions. BDNF, VEGF and IGF-I are called neural growth factors and are the protein substances which play an important role in maintaining cognitive functions by promoting the growth of blood vessels in neural tissue ([Maass et al., 2015](#)). BDNF is a key component in regulating neuronal growth, repair and neuro-plasticity and is involved in several functions including learning and memory and behaviour ([Jeon & Ha, 2017](#)). IGF-I helps in the process of BDNF expression, and assists in neurogenesis ([Carro et al., 2000](#)). Peripheral VEGF mediates exercise-induced angiogenesis and neurogenesis ([Voss et al., 2013](#)). The main site for the action of these neural growth factors are the hippocampus ([Maass et al., 2015](#)), the pre-frontal cortex ([Chang et al., 2018](#)) and the amygdale ([Cowansage et al., 2010](#)). These sites are responsible for learning, memory, task execution, intelligence, emotions and other cognitive functions. An optimal concentration of these neural growth factors is responsible for neural health and a reduction in their concentration is associated with psychiatric and metabolic disorders ([Dinoff et al., 2016](#)).

BDNF in the peripheral circulation crosses the blood-brain barrier by a high-capacity, saturable transport system ([Pan et al., 1998](#)). BDNF serum concentration is affected by altered BDNF release or utilization in the central nervous system ([Staats et al., 2005](#)). Baseline concentration of neural factors differs in males and females, reported in a few animal studies ([Liu et al., 2014](#); [Snigdha et al., 2011](#)). Estrogen and testosterone potentially affect BDNF expression ([Berchtold et al., 2001](#); [Sohrabji & Lewis, 2006](#)). Some human studies also reported different concentrations of BDNF in men and women and during different phases of the menstrual cycle in women ([Lommatzsch et al., 2005](#)). This variation of BDNF in women is related to the influence of estrogen on BDNF concentration ([Lommatzsch et al., 1999](#)), with estrogen inducing BDNF expression through an estrogen response element on the BDNF gene ([Scharfman & MacLusky, 2006](#)). However, the difference in the concentration of other neural growth factors such as VEGF and IGF-I is not known.

Other than hormonal influence, acute exercise has also been shown to positively influence the neural growth factors ([Griffin et al., 2011](#); [Hopkins & Bucci, 2010](#); [Schwarz et al., 1996](#)). The effect of exercise on neural growth factors depends on the exercise's intensity, with high intensity exercises increasing BDNF levels

more than low intensity exercise ([Hötting et al., 2016](#)). High intensity intermittent exercise (HIIE) is an exercise regime performed at a high intensity of 80-90% of maximal heart rate (HR max) interspersed with the intervals of rest or relative rest at lower intensities ([Hottenrott et al., 2012](#)). HIIE is an effective method for people who are short on time because it involves a lower duration dedicated to the exercise session, yet are documented to be associated with positive health benefits ([Boutcher, 2011](#); [Hottenrott et al., 2012](#); [Tsukamoto et al., 2016](#)). These health benefits include cardiovascular, respiratory, and musculoskeletal health and include effects on cognition.

The effect of exercise on the concentration of BDNF is sex specific. Dinoff et al., ([2017](#)) in the subgroup analysis of their meta-analysis showed an increased concentration of BDNF in response to acute exercise in males but no significant difference in females. The production and the breakdown of BDNF is different in males and females ([Chan & Ye, 2017](#)). Baker et al., ([2010](#)) found that 6 months of high intensity aerobic exercise showed a sex-specific effect on BDNF and IGF-I in old adults, with long term exercise training. The lower expression of BDNF could be related to the decline in the estrogen levels in elderly women after menopause ([Coelho et al., 2013](#)). But, a lack of knowledge exists about the effect of an acute high intensity exercise protocol on neural growth factors in males and females.

Sex differences are likely to be found in the effect of HIIE on cognitive neural factors, as the status of sex steroid hormones influence the expression of BDNF ([Miranda et al., 1993](#)). Sohrabji et al., ([1995](#)) reported that BDNF gene has a sequence which is closely similar to the estrogen respondent element and their binding has the capability to reduce the degradation of BDNF in females. Further, studies in animal models report that estrogen hormone interaction with exercise increases the up-regulation of BDNF in females, which increases the concentration of BDNF after acute exercise ([Berchtold et al., 2005](#)). Not only estrogen, but testosterone also has a role in the maintenance of neural function. The literature shows that testosterone is converted to estradiol in the hippocampus and carries out the functions needed for neuronal survival and synaptogenesis in males ([Hojo et al., 2004](#)). Allen et al., ([2015](#)) and a few other studies reported that testosterone through BDNF signalling in animal models is directly related to neural cell proliferation ([Verhovshek et al., 2010](#)). Alteration in LH levels also affect BDNF signalling involved in memory

improvement ([Bohm-Levine et al., 2020](#)). Nevertheless, sex differences in neural growth factor concentration. Its relation to the gonadal hormones, such as estradiol, LH, FSH and testosterone in response to acute HIIE are yet to be elucidated. There are not enough studies to draw a conclusion regarding a relationship between neural growth factors and gonadal hormones in response to exercise in humans. Also, studies lack to present sex differences in the effect of an acute high intensity exercise protocol on neural growth factors in young adults.

Finding the sex difference and the relationship of gonadal hormones with neural growth factors in response to HIIE in young adults would be useful to determine the clinical significance. It will help to evolve sex specific exercise prescription. Thus, this study was conducted with the hypothesis that high intensity intermittent exercise would affect the concentration of neural growth factors and gonadal hormones and the effect would be different in males and females.

Our study aimed to determine sex differences in the concentration of BDNF, VEGF, IGF- I in response to acute high intensity intermittent exercise and find the relationship of neural growth factors with gonadal hormones before and after the HIIE session.

2.0 MATERIALS AND METHODS

Participants were asked to volunteer from various departments of the University, of Amritsar. The sample size of 40 was calculated for the effect size of 0.552, the level of significance was kept at 5% and the power of the test was 80% using G-Power 3.1. Ink on the basis of an A priori analysis of the power ([Faul et al., 2007](#)). Forty participants between the age of 18 to 30 years arrived at the department for study purpose. They provided informed consent before the commencement of the testing procedure. The study was approved by the institutional ethical committee of Guru Nanak Dev University Amritsar, Punjab, India (Approval number 158/HG).

2.1 Inclusion criteria and exclusion criteria

The study comprised of both male and female volunteers between 18 and 30 years of age. Intelligent quotient (IQ) of participants was determined by the Multidimensional Aptitude Battery- II and all of them scored between 90 to 119, which is considered a normal intellect level. Participants were excluded on the basis of the following criteria: participants who, answered yes to any of the physical activity readiness questionnaire (PARQ) questions; had a history of

cardio-respiratory disorder; cerebro-vascular disorder; had a history of psychiatric or neurological disease; was involved in strenuous activity; had a history of use of tobacco/nicotine products such as cigarettes or tobacco; had more than two cups of coffee or tea; had a history of alcohol consumption 24 hours prior to the test or had a poor sleep which the Pittsburgh Sleep Quality Index measured.

Detailed menstrual history of female participants was taken, including the questions about current or past menstrual abnormalities, length of the menstrual cycle, last menstrual period (LMP), and history of hormone replacement therapy or use of oral contraceptives. Based on menstrual history female participants were asked to report to the department for testing between 4th to 7th day of LMP to match with the hormone levels of the early follicular to pre-ovulatory phase. During the early follicular phase, The estradiol level is relatively constant and low. By day seven, the dominant follicle is established, and the estradiol level rises significantly. During this phase, the elevated estradiol level suppresses the FSH level by negative feedback on the hypothalamus and pituitary gland and triggers a rapid rise of LH ([Reed & Carr, 2000](#)).

Participant's height, weight, resting heart rate and physical activity level (using International Physical activity questionnaire/ IPAQ- Short form) was documented prior to the commencement of the testing.

2.2 Exercise protocol

HIIE protocol was of 4 bouts of 4 minutes (4*4) at 90–95% HRmax with 3 min active recovery at 70% HRmax in accordance with Helgerud et al., 2007. HR max (beats/min) was calculated by the formula: $HR_{max} = 206.9 - 0.67 * \text{age (years)}$ as described previously ([Fox et al., 2013](#))

Warm up for 3 minutes before training and cool down for 2 minutes at the pedalling frequency and intensity according to participant preference was performed, between 8 and 12 on the 20-point Borg's Rating of Perceived Exertion (RPE) scale. During each high-intensity cycling session, participants cycled against a work load of 100-150 W and between 15-18 Borg's RPE, and during the recovery interval, they averaged 89 RPM and 8-12 Borg's RPE. A polar heart rate monitor (Polar Vantage V Pro Multisports Watch) was used to keep track of the participant's heart rate. After one minute of high intensity bout start and after each high intensity bout session, Borg's RPE grading was

recorded. All of the training sessions took place in the neurophysiology lab of MYAS-GNDU Department of Sports Sciences and Medicine, Guru Nanak Dev University, Amritsar.

2.3 Blood testing

A total of ten millilitres of venous blood was withdrawn 5 ml each before and immediately after the exercise session from the antecubital vein into anticoagulant-free tubes between 10 a.m. and 12.30 p.m. to minimize the effect of a circadian rhythm of BDNF concentrations. After 1 hour of incubation serum was separated by centrifugation, aliquoted and stored at -20 degree Celsius until analysis. ELISA analyses were performed using a 5 ml blood sample, which was collected into a serum separating tube to analyse serum components and centrifuged for 5-10 min at 3,000 revolution per minute (RPM), at 4 degree Celsius. The ELISA kits used for the analysis of serum components were as follows: QAYEE- BIO Human Brain Derived Neurotrophic Factor ELISA kit, QAYEE- BIO Human Vascular endothelial growth factor ELISA kit, DRG® IGF-I 600 ELISA, DBC Cortisol ELISA kit, Calbiotech Total Estrogens ELISA kit, Calbiotech Follicle Stimulating Hormone (FSH) SA ELISA kit, Calbiotech Luteinizing Hormone (LH) ELISA kit, Calbiotech Testosterone ELISA kit. All analyses were conducted according to the manufacturer's instructions.

2.4 Statistical analysis:

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS version 21.0). Normality of the data was assessed with Shapiro-Wilk test, and the data of blood variables assessed was presented as the mean and standard deviation. A two-way (session: pre/post)X 2 (sex: male and female) repeated measures analyses of variance (ANOVA) was used to examine the effect of acute HIIE on the levels of serum BDNF, VEGF, IGF-I, cortisol, testosterone, LH, FSH and estradiol.

To analyze the influence of gonadal hormones (testosterone, LH, FSH, Estradiol) on the response of neurotrophic factors (BDNF, VEGF, IGF-I) in response to HIIE intervention, MANCOVA was performed, keeping male and female gonadal hormones as covariates separately. Pearson's product-moment correlations were used to examine the relationship of serum neurotrophic factors (BDNF, VEGF, IGF-I) with gonadal hormones (testosterone, LH, FSH, estradiol) before and after the HIIE session. Statistical significance was set at $P < 0.05$.

3.0 RESULTS

The demographic characteristics of the participants are described in **Table 1**. Male and female participants had similar physical characteristics and there was no significant difference (independent t-test, $p > 0.05$) in all the variables between males and females.

Table 1: Demographic characteristics of the participants.

Variable	Males (Mean $\pm$ S.D.)	Females (Mean $\pm$ S.D.)
N	22	18
Age (Years)	23.00 $\pm$ 2.81	23.33 $\pm$ 3.30
BMI (Kg/ m ²)	22.81 $\pm$ 2.66	23.19 $\pm$ 2.95
Resting Heart rate (Beats / min)	74.28 $\pm$ 8.7	77.66 $\pm$ 6.25
IQ score	92.28 $\pm$ 6.75	98.64 $\pm$ 12.27
IPAQ score (MET* min / week)	4897.32 $\pm$ 2942.76	6217.06 $\pm$ 3097.38
PSQI score	3.24 $\pm$ 1.66	1.86 $\pm$ 0.99

S.D. = standard deviation

3.1 Variations in heart rate and rating of perceived exertion during the exercise intervention

During different stages of the HIIE session, we observed changes in heart rate and rating of perceived exertion which are shown in **Figure 1**. There was an increase in the heart rate and perceived exertion levels after the period of warm up as the intensity of exercise was enhanced. Still, it returned to the baseline levels after the completion of cool down period.

3.2 Effect of HIIE session and interaction of sex and exercise session

Figure 2 shows the concentration of neurotrophic factors and other hormones of the blood before and after HIIE session in male and female participants. The concentration of estradiol ($t_{\text{males}} = -3.380$, $p = 0.002$; $t_{\text{females}} = -6.114$, $p = 0.0001$), cortisol ($t_{\text{males}} = -2.219$, $p = 0.036$; $t_{\text{females}} = -3.96$, $p = 0.001$) and increased significantly in both males and females after the session of HIIE. Concentration of FSH decreased significantly ($t_{\text{males}} = 2.395$, $p = 0.025$; $t_{\text{females}} = 3.571$, $p = 0.003$) both in males and females post HIIE. A significant increase in serum BDNF ($t = -4.25$, $p = 0.0001$) was observed only in males after HIIE. A significant increases in IGF- I ($t = -4.52$, $p = 0.0001$) was seen only in females after HIIE. All other analysed components of blood showed no significant changes after HIIE. The repeated measure ANOVA revealed significant interaction of sex with HIIE session [$F(1,14) = 4.668$,

$p=0.049$] for BDNF concentration. There was a significant effect of HIIE session [$F(1,14)= 9.67$, $p= 0.008$] on BDNF concentration. In contrast the other neurotrophic factors VEGF [$F(1,14)= 0.062$, $p=0.807$] and IGF-I [$F(1,14)=0.201$, $p=0.661$] did not show a statistically significant interaction effect of sex and HIIE session. A significant main effect of HIIE session was observed on IGF-I [$F(1, 14) = 10.41$, $p=0.006$]. A significant effect of HIIE session [$F(1,14)= 18.31$, $p=$

0.001] and sex [$F(1,14)=6.34$, $p=0.025$] was found on cortisol in spite that the interaction between sex and HIIE session was not significant [$F(1,14)=4.508$, $p= 0.052$]. The effect sizes (Cohen's d) were assessed for the changes in concentration of blood neurotrophic factors and other assessed components in males (BDNF, $d=0.17$, VEGF, $d= 0.02$, IGF-I, $d= 0.24$ and cortisol $d= 0.35$) and females (BDNF, $d=0.003$, VEGF, $d=0.0007$, IGF-I, $d=0.48$ and cortisol $d=1.03$).

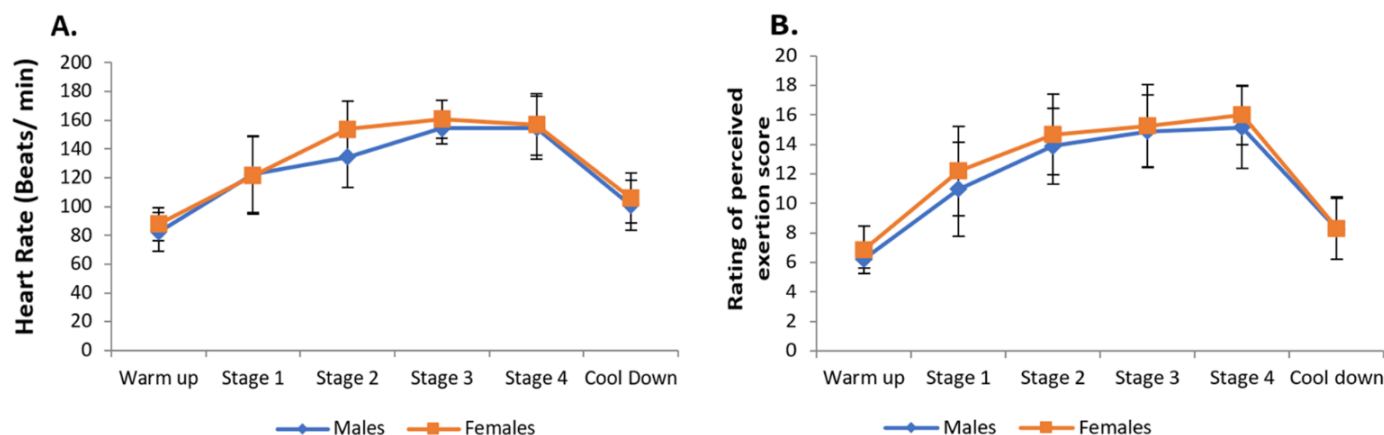


Figure 1. Variations in heart rate (A) and rating of perceived exertion (B) during warm up, cool down and at various stages of HIIE session in males and females.

3.3 Results from MANCOVA

The MANCOVA analysis showed a marginally significant difference between males and females for the adjusted means of BDNF [$F(3,73) = 0.092$, $p= 0.056$, Wilk's lambda = 0.876, $\eta^2 = 0.0098$) when testosterone was taken as a covariate, however a significant main effect of sex was observed between the subjects (Table 2). Effect of session (pre/post) was not significant ($F(3,73) = 0.447$, $p= 0.447$, Wilk's lambda= 0.964, $\eta^2 =0.034$). The interaction of sex and session was not significant ($F(3,73) = 0.025$, $p=0.994$, Wilk's lambda= 0.999, $\eta^2 =0.001$) for BDNF. We found no significant effect of sex and interaction of sex and session for VEGF and IGF-I.

The MANCOVA analysis showed a significant difference between males and females for the adjusted means of BDNF when female gonadal hormones were kept as co-variables (Table 3). No significant interaction of session and sex indicated that the effect of HIIE intervention is significantly different in males and females when the effect of estradiol, LH and FSH was controlled. No main effect of sex, session or sex*session interaction was found significant for VEGF and IGF-I.

We included our female participants for intervention and testing in the early follicular to pre-ovulatory phase on the basis of their menstrual history, to match the hormone levels of all participants during the menstrual cycle. We found that estradiol concentration showed a significant rise after HIIE in both the sexes but the rise was more (33.11%) in females during the early follicular phase of the menstrual cycle compared to males (8.28%).

3.4 Correlation of neurotrophic factors and gonadal hormones

The correlation was assessed separately for males and females before and after the HIIE session (Table 4). A significant positive correlation between FSH and estradiol with BDNF was observed both before and after the HIIE session in females. A significant positive correlation was obtained between BDNF and LH, only before the HIIE session in females. A significant negative correlation was found between BDNF and testosterone both before and after HIIE in males. A significant negative correlation was observed between testosterone and VEGF in males. A significant correlation was observed between LH, FSH and IGF-I after the HIIE session in females.

Table 2. Effect of exercise session and sex on concentration of neural growth hormones when effect of testosterone was controlled.

	Session			Sex			Session*sex		
	F	p	η^2	F	p	η^2	F	p	η^2
BDNF (ng/ml)	0.614	0.436	0.008	7.331	0.008*	0.089	0.041	0.839	0.001
VEGF (pg/ml)	0.125	0.724	0.002	3.560	0.063	0.045	0.007	0.934	0.0001
IGF- I (ng/ml)	1.588	0.212	0.021	0.008	0.929	0.0001	0.003	0.960	0.0001

'F'- F value, 'p'-significance value and ' η^2 '- Partial eta squared value demonstrating effect size.

Table 3: Effect of exercise session and sex on concentration of neural growth hormones when effect of female gonadal hormones (estradiol, LH, FSH) was controlled.

	Session			Sex			Session*sex		
	F	P	η^2	F	p	η^2	F	p	η^2
BDNF (ng/ml)	0.323	0.572	0.004	9.133	0.003*	0.111	1.622	0.207	0.022
VEGF (pg/ml)	0.215	0.644	0.003	1.890	0.173	0.025	0.286	0.594	0.004
IGF- I (ng/ml)	0.522	0.472	0.007	0.103	0.749	0.001	0.094	0.760	0.001

'F'- F value, 'p'-significance value and ' η^2 '- Partial eta squared value demonstrating effect size.

4.0 DISCUSSION

We aimed to determine sex-specific effect of high intensity intermittent exercise on the concentration of neurotrophic factors in young adults. For this purpose, 4 sessions of high intensity intermittent exercise for 4 minutes each at intensities between 90-95% of HR max, with 3 minutes of active rest in between the sessions were used (Helgerud et al., 2007) as an intervention of the study. Blood for the assessment of neurotrophic factors and other hormones was extracted before and after the intervention. Males and females showed a different response for neurotrophic factors in response to HIIE intervention.

4.1 BDNF

Previous literature on the effect of a single HIIE session on BDNF concentration has shown that, HIIE briefly increased BDNF concentration (Cabral-Santos et al., 2016). Similarly, we showed that BDNF increased after the HIIE session, but this increase was small (0.23%) in females and did not reach a statistically significant level, however the increase in males was statistically significant (10.2% increase). These findings suggest sex variability in the concentration of serum BDNF after a single HIIE session. A significant sex and session interaction for BDNF concentration in our study, showed that the effect of HIIE on BDNF concentration was influenced by the sex of the participant. This finding was in line with our hypothesis.

Meta analytical evidence showed that a bout of acute exercise increased BDNF concentration only in males and not in females, consistent with our results (Dinoff et al., 2016). BDNF is produced centrally in the brain (Rasmussen et al., 2009) and peripherally in muscles (Mousavi & Jasmin, 2006). The expression of BDNF mRNA is increased in the muscle cells after acute exercise (Matthews et al., 2009). Sex difference in the concentration of BDNF after HIIE could be described by a larger volume of skeletal muscles in males compared to females (Schorr et al., 2018), resulting in a greater expression of mRNA related to BDNF in males compared to females in response to acute HIIE. Muscular BDNF increases phosphorylation of AMP-activated protein kinase (AMPK) and acetyl coenzyme A-carboxylase-beta (ACCBeta) and acts as a contraction-induced protein that contributes to the health benefits associated with exercise, by increasing fat oxidation in skeletal muscles (Pedersen et al., 2009). The concentration of peripheral BDNF is directly related to the concentration of BDNF centrally (Klein et al., 2011), and peripheral BDNF crosses blood-brain barrier via a complex mechanism involving a chain of transport system (Pan et al., 1998). Thus, it is postulated that peripheral BDNF possibly reaches the central nervous system, brings about the processes of neurogenesis and neuroplasticity, and maintains cognitive functions in response to acute exercise (Lee & Son, 2009).

Table 4. Correlation of pre- and post-concentration of BDNF, VEGF and IGF-I with pre- and post-concentration of testosterone, LH, FSH, and estradiol.

Variables				Males		Females	
				Pearson's correlation coefficient	Significance (p)	Pearson's correlation coefficient	Significance (p)
BDNF	Pre	Testosterone	Pre	-.360*	0.038	-.302	.137
	Post		Post	-0.448*	0.012	0.115	0.341
	Pre	LH	Pre	-0.009	0.484	0.621*	0.007
	Post		Post	-0.145	0.245	0.428	0.056
	Pre	FSH	Pre	-0.069	0.372	0.603*	0.009
	Post		Post	-0.070	0.369	0.610*	0.008
	Pre	Estradiol	Pre	0.172	0.206	0.450*	0.046
	Post		Post	0.193	0.177	0.606*	0.008
VEGF	Pre	Testosterone	Pre	-0.600**	0.001	-0.352	0.099
	Post		Post	-0.198	0.171	0.339	0.108
	Pre	LH	Pre	0.216	0.150	0.293	0.145
	Post		Post	-0.050	0.405	0.144	0.304
	Pre	FSH	Pre	-0.056	0.395	0.429	0.055
	Post		Post	-0.087	0.340	0.373	0.085
	Pre	Estradiol	Pre	0.176	0.199	0.234	0.201
	Post		Post	0.191	0.180	0.451*	0.046
IGF-I	Pre	Testosterone	Pre	-0.229	0.136	0.418	0.061
	Post		Post	-0.011	0.480	0.010	0.486
	Pre	LH	Pre	0.109	0.302	0.130	0.322
	Post		Post	0.115	0.292	0.483*	0.034
	Pre	FSH	Pre	0.003	0.459	-0.332	0.114
	Post		Post	-0.177	0.199	-0.468*	0.039
	Pre	Estradiol	Pre	-0.050	0.407	0.341	0.107
	Post		Post	0.132	0.264	-0.070	0.402

Bold values shows $p < 0.05$.

Schmidt-Kassow and colleagues analysed the levels of BDNF after the cessation of acute high intensity continuous exercise for 5 to 30 minutes and, reported a higher rate of BDNF clearance from peripheral circulation in women as compared to men after high intensity continuous exercise ([Schmidt-Kassow et al., 2012](#)). Consistent with their findings, a lower concentration of BDNF in response to HIIE in women indicates a higher rate of degradation of peripheral BDNF concentration in women as compared to men (who showed an increase in BDNF concentration in response to HIIE even after cool down periods of two minutes in our study). It suggests that the concentration of BDNF remains elevated for a longer duration in males after HIIE and decreases at a greater rate in females during the recovery period.

4.2 VEGF

VEGF acts as an effective mediator involved in the formation and proliferation of blood vessels and

triggers the production and differentiation of endothelial cells ([Ferrara, 2004](#)). The amount of VEGF is found to be increased in response to exercise. It promotes neural cell proliferation ([Morland et al., 2017](#)) and helps to modulate the concentration of BDNF in the hippocampus ([Cotman et al., 2007](#)) in animal models. Previous literature measuring the effect of acute continuous and intermittent exercises on VEGF in humans indicates conflicting findings following acute exercise ([Gavin et al., 2004](#); [Kraus et al., 2004](#); [Wahl et al., 2014](#)). Serum VEGF increase in response to HIIE, was observed in our study (2.73% rise in males and 0.06% rise in females), which was not statistically significant (**Figure 2G**). Sex hormones influence serum levels of VEGF ([Berciano Guerrero et al., 2010](#)) and acute exercise affects the levels of these sex hormones ([Monje et al., 2020](#); [Otağ et al., 2016](#)). Our results demonstrated that the effect of HIIE on VEGF concentration was similar in both the sexes, similar to a previous literature showing similar

variations in the VEGF concentration in platelet rich plasma in males and females (Evanson et al., 2014). Thus, our hypothesis was not proven, which could be

attributed to a higher inter-individual variation in the concentration of serum VEGF as compared to the other neurotrophic factors like BDNF and IGF-1 in our study.

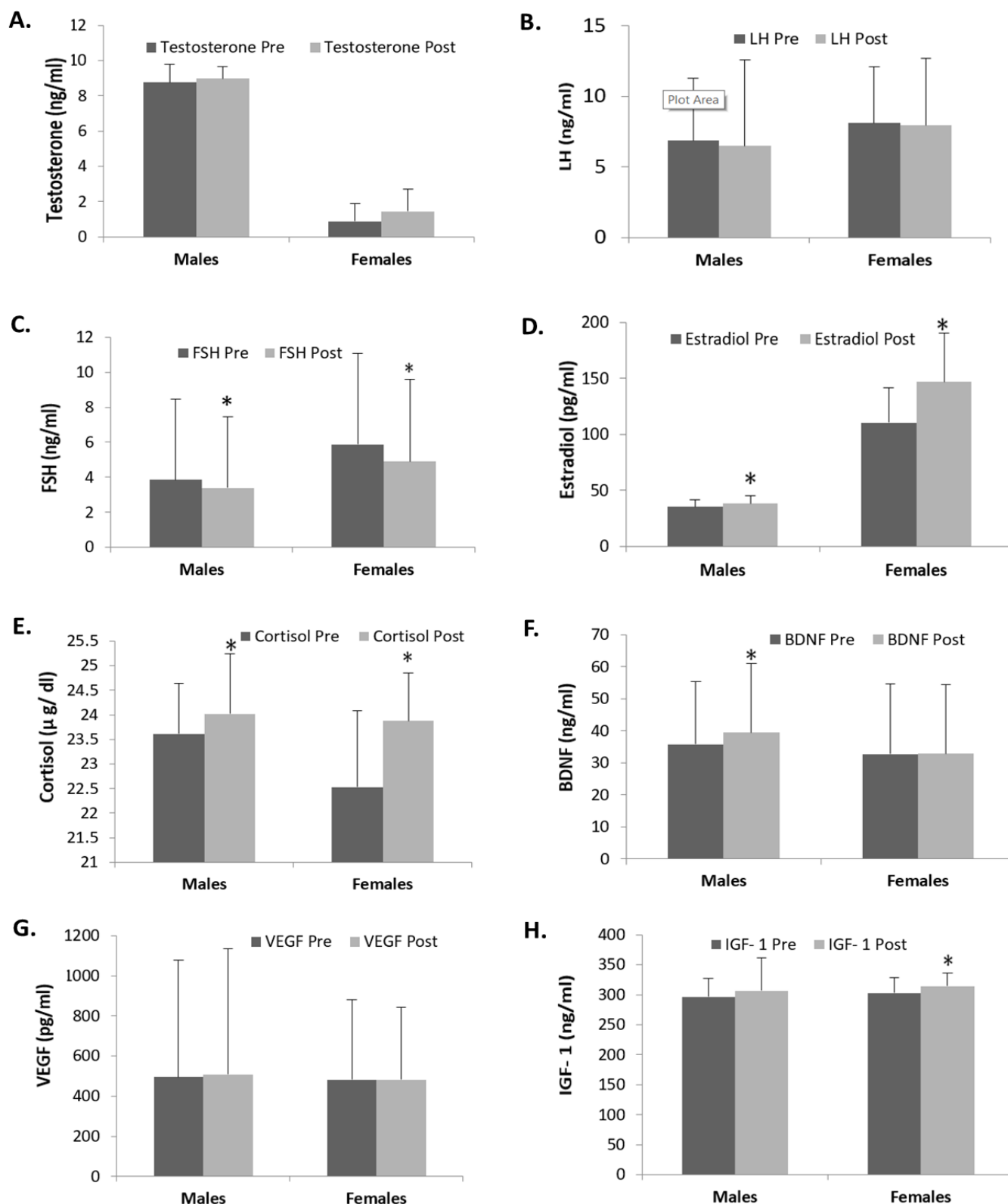


Figure 2. The average values of concentration of testosterone (A), LH (B), FSH (C), estradiol (D), cortisol (E), BDNF (F), VEGF (G) and IGF-I (H) before and after the HIIE session in males and females. (*) Significant difference between pre and post HIIE values at $p < 0.05$. Error bars represented standard deviation values.

4.3 IGF-I

Previous studies have documented that IGF- I was involved in neuroprotective function in the adult human brain (Torres-Aleman, 2000). IGF- I mediates the role of exercise -induced neuronal growth and assists in the functioning of BDNF and VEGF for delaying neuronal degeneration ([Cotman et al., 2007](#)).

Effect of HIIE on IGF-I has been previously studied ([Copeland & Heggie, 2008](#); [Herbert et al., 2017](#)), and it was found that HIIE increased IGF-I concentration significantly which was consistent with our results. One possibility for this significant rise in IGF-I concentration would be the mechanism of increased discharge of IGF from liver cells in response to the HIIE- induced release of growth hormone ([Schwarz et al., 1996](#)). The other possible mechanism could be the high intensity of the exercise session, as the acute response of IGF is dependent on the intensity of the exercise session, and high intensity exercise increases IGF levels significantly compared to lower intensities ([Peeri et al., 2014](#)). The rise in the IGF-I level, which is related to an increase in the spontaneous excitatory post-synaptic currents and neuro-plasticity in the above mentioned study, were similar in males and females in response to HIIE in our study. These findings support previous findings of El-Sayes et al., (2019) involving the effect of moderate intensity continuous exercise on IGF-I levels.

4.4 Cortisol

Cortisol concentration increases in response to the physiological stress to manage the challenges needed for physical activity and to maintain homeostasis by regulating other stress systems ([Aubets& Segura, 1995](#)). Changes in cortisol concentration in response to exercise is dependent on the intensity, duration and the type of exercise ([Brownlee et al., 2005](#); [Hill et al., 2008](#)), and HIIE is a type of exercise that provides a stimulus enough to increase the levels of cortisol in serum ([Wahl et al., 2010](#)). We intended to observe the sex differences in serum cortisol levels in response to an acute HIIE session. HIIE involves successive sessions of high intensities with lower intensity bouts in between, which points towards a great demand placed upon metabolism during the exercise session, perceived as a physiological stress situation ([Cabral-Santos et al., 2015](#)). Therefore, this physiological stress was reflected as a significant rise in the stress hormone 'cortisol' in our study. Other studies that used an exercise protocol of moderate intensity continuous exercise in trained runners, found no sex differences in cortisol concentration ([Vislocky et al., 2008](#)), and this is similar to our findings. Overall, these evidences suggest

that no sex difference exists in the level of cortisol concentration in response to HIIE.

4.5 Female gonadal hormones (Estradiol, LH, FSH)

The effect of the HIIE session was different on female gonadal hormones in males and females in our study. A more significant increase was seen in females during the early follicular to pre-ovulatory phase in response to HIIE as compared to males. Otağ et al., (2016), found an increase in the level of estradiol and a decreased level of FSH during the luteal phase in female soccer players in response to an acute maximal aerobic exercise, which was in accordance with our findings. It shows that, independent of the phase of the menstrual cycle, the HIIE response of estradiol and FSH is similar to that of acute maximal aerobic exercise in healthy young females. Acute exercise increases the metabolic functions of peripheral adipose tissue ([Stanford & Goodyear, 2016](#)), which contains aromatase cytochrome P450 enzyme, needed to produce estradiol both centrally as well as locally ([Cohen, 2001](#)). Thus, it is postulated that acute HIIE increases the production of estradiol in a similar manner, which was seen as a significant increase in its concentration in response to the HIIE intervention in our study.

The concentration of the other gonadotrophic hormone, LH was also evaluated before and after the HIIE session in our study. Our findings were consistent with the previous literature ([Williams et al., 1994](#)), showing no significant effect of acute exercise on LH concentration in young adults. LH is released from the anterior pituitary gland in response to signals from Gonadotrophic releasing hormone (GnRH), released in a pulsatile fashion from the hypothalamus ([Barbieri, 2014](#)). Increased concentration of gonadal steroid hormones, estrogen, progesterone, and testosterone exert a negative feedback mechanism, which decreases the concentration of LH ([Clarke et al., 2015](#)). The concentration of estradiol and testosterone was increased in response to HIIE in our study and thus a decreased concentration of LH in response to HIIE in our study could be attributed to the negative feedback associated with their rise.

The changes in these gonadal hormones are related to cognitive performance ([McEwen& Alves, 1999](#)). A relationship between estradiol, LH, and BDNF signalling has been found in animal models ([Bohm-Levine et al., 2020](#)), which indicates the presence of estradiol with intact BDNF signalling is necessary to improve cognitive performance in rats. A significant positive co-relationship between neurotrophic factors and gonadal

hormones (Estradiol, LH, FSH) in response to HIIE, and a significant difference between the two sexes for BDNF concentration, shows that gonadal hormones affect BDNF concentration in a sex specific manner in young adult humans and the concentration of BDNF increases in females with the increase in the female gonadal hormones.

4.6 Male gonadal hormone (testosterone)

The concentration of mean serum testosterone was found to be slightly increased both in males and females after the HIIE session; however, the change did not reach a statistical significance in males and females. These findings are supported by a previous study by Monje et al., (2020), who showed a similar, non-significant effect of 10*4 min of HIIE session on salivary testosterone in both males and females.

Earlier reports of animal study (Skucas et al., 2013) demonstrated that a decrease in the levels of testosterone in adult male rats was associated with an increase in BDNF reactivity and its effect on improvement in synaptic transmission through hippocampal mossy fibres. Their study provided evidence of a negative association of testosterone with BDNF expression, which was consistent with our covariate analysis of variance findings. A significant negative relationship was observed between testosterone and BDNF post HIIE session in our study, which could also be explained by the mechanism of conversion of testosterone into estrogen to enhance BDNF expression, as shown in previous literature (Fusani et al., 2003). A significant negative association of testosterone were observed with VEGF before HIIE intervention in males which was inconsistent with the findings of (Zhang et al., 2016) who demonstrated that injecting testosterone increased VEGF mRNA expression in mice.

4.7 Limitations

The present study involved the investigation of blood parameters of females at one time point of the menstrual cycle only (that is between the early follicular to pre-ovulatory phase). It is not clear if HIIE induces a different response of neurotrophic factors and other hormones at other points of the menstrual cycle. It is essential to note that the data of this study

was acquired from a healthy, active, and young adult population. Further work is required to ascertain if these findings extend to aging or clinical populations.

5.0 CONCLUSIONS

We concluded that the effect of HIIE on BDNF is dependent on the sex of an individual and a session of HIIE increases serum BDNF concentration significantly in males but not in females. We demonstrated that the sex of the participant affect the response of BDNF to HIIE intervention significantly when adjusted for the effect of gonadal hormones, and a significant positive relationship is found for BDNF with female gonadal hormones (FSH and LH) in response to HIIE session. A significant negative relationship was found between BDNF and VEGF with testosterone concentration in our study. Other neurotrophic factors (VEGF and IGF-I) did not show the effect of sex, however a significant increase in IGF-I was seen only in females. There was also a significant change in female gonadal hormones (FSH and Estradiol) in response to HIIE session. More specifically, FSH concentration decreased both in males and females after the intervention; whereas estradiol was increased both in males and females after the HIIE session.

Overall, our results suggest that a single session of HIIE increases the serum concentration of neural growth factors, specifically BDNF, which is different in males and females. This change in the neural growth factors is affected by changes in the concentration of gonadal hormones in response to HIIE.

Acknowledgements: The study was supported by a grant received from Ministry of Youth Affairs and Sports, Government of India (Numbered: 953/17-18/FU, Dated: 12th October, 2017). Equipment, tests, and Research Fellows were all funded by this grant. We thank all the participants for their voluntary involvement in this study.

Author contributions: P.K. and S.S. conceived and designed the experiments; P.K. performed the experiments; P.K. and A.S.analyzed the data; S.S. contributed reagents/materials/analysis tools; P.K. wrote the paper.

Conflicts of interest: The authors declare no conflict of interest.

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