Physiology and Pharmacology

Physiol Pharmacol 22 (2018) 1-10 **www.phypha.ir/ppj**

Original Article

Executive functions are related to serum testosterone and basal metabolism rate fluctuation but not lymphocyte dopamine receptor expression in the young healthy participants

Mitra-Sadat Sadat-Shirazi[1,2], Ghorbangol Ashabi[3], Nima Babhadiashar[2], Mohammadreza Bahrami Hessari[4], Nasim Vousooghi[1,2], Mohammad-Reza Zarrindast[2,5]*

1. Department of Neuroscience, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran
2. Iranian National Center for Addiction Studies (INCAS), Tehran University of Medical Sciences, Tehran, Iran
3. Department of Physiology, Faculty of Medicine, Tehran University of Medical Sciences, Tehran, Iran
4. Faculty of Psychology & Education, Allameh Tabataba'i University, Tehran, Iran
5. Department of Pharmacology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Herein, we evaluated linkages between executive functions (EFs) performances and dopamine receptor (DR) mRNA and testosterone level in the young Iranian male people.

Methods: All 140 participants were normalized using depression, anxiety and stress scale questionnaire. Remained 108 volunteers were tested against drug abuse and then volunteers were distinguished by Wisconsin Card Sorting Test (WSCT). According to WCST, participants were divided into two low and high EFs performance. Afterward, anthropometric factors, body mass index (BMI) and serum testosterone level were measured in low and high EFs groups. Blood samples were collected, and biochemical and anthropometric data were evaluated; serum testosterone and DR mRNA expression were assessed in participants.

Results: Data showed there are no differences between two groups in Na^+, K^+, glucose, urea, creatinine, glutamic pyruvic transaminase, glutamic-oxaloacetic transaminase and other biochemical serum agents (P>0.05) but BMI was increased in low EFs compared with high EFs (P=0.000). Interestingly, there is no difference in DR expression between two groups (P>0.05).

Conclusion: Our data presented that fluctuation of EFs performances in healthy adult male cases might depend on BMI and serum testosterone; while dopamine receptors in the blood lymphocytes had no substantial role in the EFs. High serum testosterone reduced EFs in the young adults.

Keywords:
Executive function;
Dopamine receptor;
Testosterone;
Young people;
Blood lymphocytes;
Body mass index

Received: 29 Jul 2017
Accepted: 3 Jan 2018

***Correspondence to:**
M.R. Zarrindast

Tel: +98-2166402569
Fax: +98-2166402569

Email:
zarinmr@ams.ac.ir

Introduction

Executive functions (EFs) also called executive control or cognitive control is series of top-down cognitive processes and essential for cognitive control of behavior (Espy, 2004). EFs have three cores, including (1) inhibitory control, (2) working

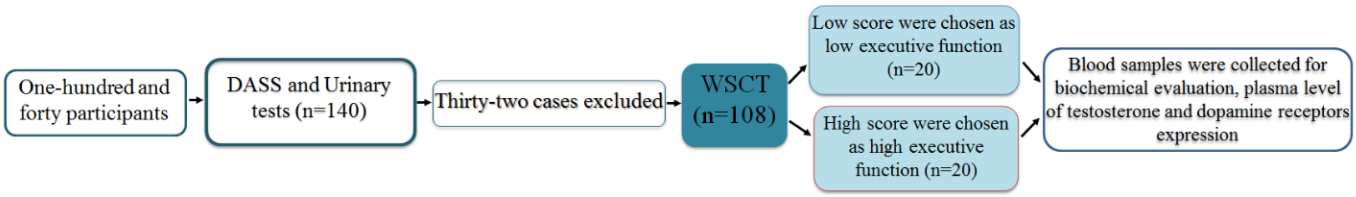

Fig.1. Timeline procedure of experimental procedure. Depression Anxiety Stress Scales (DASS), Wisconsin test (WSCT).

memory and (3) cognitive flexibility; with these cores, higher-order functions such as reasoning, problem-solving and planning were built in mind (Diamond, 2013). Also, EFs are involved in many aspects of life such as mental health (Baler and Volkow, 2006), schizophrenia (Barch, 2005), conduct disorder (Fairchild et al., 2009), physical health like obesity, overeating and poor treatment adherence (Miller and Cohen, 2001; Riggs et al., 2010; Will Crescioni et al., 2011). In addition, emerging evidence showed EFs impairment could increase the risk of antisocial behavior (De Brito et al., 2013).

The prefrontal cortex (PFC) primarily is one of the most prominent regions of EFs processing (Miller and D'Esposito, 2005). Also, some studies described that dopaminergic system has essential roles in EFs performances (Cools et al., 2001; Cools et al., 2003; Cools, 2008; Kaplan and Oudeyer, 2007; Lewis et al., 2003; Sawaguchi and Goldman-Rakic, 1994). Dopamine receptors (DR) divided into two groups: D1DR-like (including D1DR and D5DR) and D2DR-like (D2DR, D3DR and D4DR) (Butini et al., 2016). Stimulation of dopamine D1 in PFC might facilitate working memory as a key element of EFs performances (Slifstein et al., 2015; Vijayraghavan et al., 2007; Wong and Stevens, 2012); however, mechanisms underlying dopaminergic system's role in the control of EFs are not clear yet.

"Peripheral marker hypothesis" revealed that changes in expression level of neurotransmitter receptors in some regions of brain reflected into the peripheral blood lymphocytes (PBLs) (Carlsson et al., 1999a; Czermak et al., 2004). There is some evidence that showed in the schizophrenia (Carlsson et al., 1999b) and drug and behavioral addiction (Goodarzi et al., 2009; Vousooghi et al., 2015), neurotransmitters receptors expressions changed in PBLs.

This survey firstly designed for finding an association between EFs performances and DR mRNA expression as a peripheral marker for EFs status. Because D1 and D2 dopamine receptors are not express in PBL (Ricci et al., 1999), we measured D3RD, D4RD and D5RD expressions. We also evaluated anthropometric factors, body mass index (BMI) and serum testosterone concentration for finding a correlation by EFs function. We used Wisconsin Card Sorting Test (WCST) for evaluating EFs in non-clinical volunteers.

Materials and methods

Participants and study description

This is a double-blind, randomized trial study. As shown in Figure 1, 140 male individuals (age between 21-33 years old) participated in this study (Tehran, Iran). All participants were checked for a drug of abuse using urine test. We used one-step ten drugs screen test panel (Baharafshan Co, Tehran, Iran). This rapid test detected ten different kinds of drugs of abuse in the urine (Cocaine, amphetamine, methamphetamine, marijuana, morphine, phencyclidine, barbiturates, benzodiazepines, methadone and tricyclic antidepressants). All volunteers filled the Depression Anxiety Stress Scales (DASS) questionnaire form (Lovibond and Lovibond, 1995) in the presence of a psychologist. We excluded 32 volunteers with positive results in amphetamine, morphine, phencyclidine and antidepressants drugs. Finally, we evaluated the EFs in the 108 cases using WSCT (Mueller and Piper, 2014) in Psychology Experiment Building Language (PEBL) test battery (Piper et al., 2012). Demographic data was shown in Table 1. Ethical approval was obtained from Tehran University of Medical Sciences ethics committees. Subjects were excluded if they had a history of viral hepatitis or psychological disorders. All participants provided written informed consent before inclusion in the study.

Depression anxiety stress scales (DASS)

DASS is a widely used tool for screening, in both subjects (Lovibond and Lovibond, 1995) and clinical patients (Page et al., 2007). DASS consists of three subscales: depression (DASS-D; with items

Table 1: Demographic data in cases according to the low and high level of executive function.

Groups	Low EFs*	High EFs*
Number of cases	20	20
Age (years)	26.5±6.3	25.1±3.9
Education (years)	15.1±2.2	14.5±1.8

Data were expressed as mean±SEM. *Executive functions: EFs.

concerning dysphoric moods like sadness or worthlessness), anxiety (DASS-A; with items concerning symptoms of physical arousal, panic attack and fear like trembling or faints) and stress (DASS-S; with items concerning tension, irritability). We used DASS-21 Persian translation version with Iran's norms for screening our participants (Asgharipoor et al., 2012).

Psychological test and scoring

EFs were assessed with PEBL's Wisconsin Card-Sorting Test (WCST) (Mueller and Piper, 2014). WCST is a screening test to find individuals with high and low EFs (Grant and Berg, 1948; Piper et al., 2012). Briefly, participants were presented with four piles of cards; each has a different number (one, two, three or four), color (red, green, yellow or blue) and shapes (triangle, star, cross or circle). A series of random cards appear and participants should find the correct pattern for card sorting. After each trial, the participant will get a "correct" or "incorrect" feedback (Piper et al., 2012). Two criteria are important in this test: "category achieved" and "perseverative errors." Category achieved shows the total number of every ten consecutive correct answers. A perseverative error is an incorrect answer that could happen after ten correct answers due to shifting the previous rule (Piper et al., 2012). We chose participants who completed nine categories with the least perseverative error for high EF group and participants who completed 7 or less than seven categories for low EF group.

Blood sampling

Twelve ml of peripheral blood was collected from the cephalic vein. First six ml of blood was used for serum testosterone measurement and biochemical analysis and second six ml of blood was used for qRT-PCR analysis. Serum was separated using centrifuging the blood (3000 g, 3 min) and kept at -80 °C for detecting serum testosterone and biochemical assays. HIV, HBV and HCV tests were performed by rapid screen test kits (ACON Co, San Diego, USA). There was no one with a positive result in HIV, HBV and HCV. For avoiding diurnal heterogeneity of hormones, blood was sampled between 9:00 and 11:00 am.

Anthropometric assessment

Serum Na^+ and K^+ were determined by ion selective electrodes (ParianTeb Co, Tehran, Iran). Serum glucose, creatinine, glutamic-oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) concentrations were assessed following standard laboratory methods (Bahrami Hospital, Tehran, Iran). BMI was defined as the body mass divided by the square of the body height which calculated by an investigator.

Peripheral blood lymphocyte preparation, total RNA extraction and real-time PCR

Using a cell separation medium (Histoprep, BAG, Germany), peripheral blood lymphocytes were collected. Briefly, 6 ml of blood gently was placed in 6 ml cell separation medium and was centrifuged (4 °C in the horizontal rotor for 35 min with 1200 g). Lymphocytes layer was collected carefully, were transferred to another falcon and were washed three times with phosphate buffer saline.

Total RNA was extracted from lymphocytes with the RNeasy mini kit (Qiagen, USA) according to manufacturer's protocol. The quantity of total RNA was determined by spectrophotometer (Picodrop, UK). We performed gel electrophoresis for checking RNA integrity (1% agarose; Merck, Germany). For preparing mRNA to perform real-time PCR, total RNA was converted to complementary DNA (cDNA). We used Prime Script First Strand cDNA Synthesis Kit (Takara, Japan). For all samples, one µg of total RNA reverse transcripted to cDNA. All primers (D3RD,

D4RD, D5RD and beta-actin) were purchased from Qiagen primer bank. To perform quantitative reverse transcription polymerase chain reaction (qRT-PCR), we used Step One Plus Real-Time PCR System (Applied Biosystems). For performing qRT-PCR, two µl of cDNA, two µl of primer were mixed with SYBR Green Master Mix (Takara, Japan) in a total volume of 20 µl according to manufacture protocol. The annealing temperature of all genes adjusted to 60 °C. Specificities of each gene proven by a single peak in melt curve. Each gene product visualized in 2% agarose gel**.**

Serum testosterone level

As described above, blood serum was separated from collecting blood samples and kept at −80 °C. For assessing testosterone level in the serum, we used testosterone ELISA kit (Abcam, USA). The intensity of the color change in each well was measured in a microplate reader (Awareness, USA) at 450 nm.

Statistical analysis

DASS and WCST tests were analyzed by independent sample T-test with SPSS software (version 21). Also, the level of testosterone and other biochemical agents were analyzed using independent sample T-test with SPSS software. We used Relative Expression Software Tool (REST)-XL version 2 for analyzing gene expression data (Pfaffl et al., 2002).

Results

Screening via DASS and testing participants by rapid drug tests

The DASS-21 data are shown in Table 2. None of the subjects had any symptoms of anxiety, depression and stress. After DASS test, their urines were collected for detecting the drugs of abuse. Thirty-two cases were excluded because of illicit drugs or anti-depressant abusing.

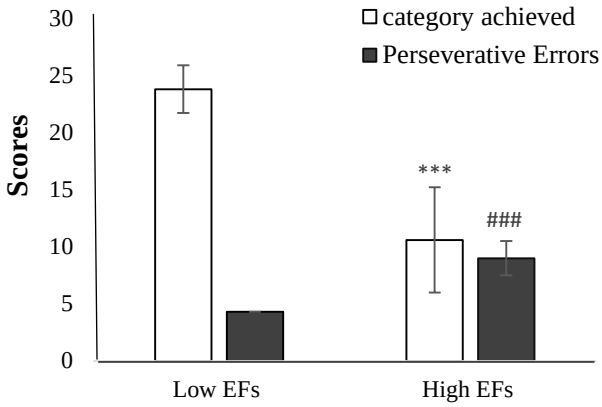

Fig.2. The achieved category and perseverative error in Wisconsin test to divide high (n=20) and low executive function (EFs) (n=20). Data showed as mean±SEM. ****P*<0.001 compared with scores of category achieve in low EFs. ###*P*<0.001 compared with scores of perseverative error in low EFs.

The level of EF was measured through WCST test

WCST widely used for measurement of EFs (Boone et al., 1993). After DASS test, their urines were collected for detecting the drugs of abuse. Thirty-two cases were excluded because of illicit drugs or anti-depressant abusing (Fig. 1). The level of seven or less archived categories and 20-25 perseverativeerrors were presumed as low EFs and level of nine archived categories, and less than 12 preservative errors were considered as high EFs (Fig. 2). There was a statistical difference between two low and high EFs groups (independent sample t-test analysis, *P*=0.000).

Anthropometric data were evaluated in both low and high level of EFs performances

Table 3 showed the level of serum urea, Na^+, K^+, glucose, creatinine, SGOT, SGPT and BMI of participants. The BMI value was increased in low EFs

Table 2: Depression Anxiety Stress Scales (DASS) data in all volunteers.

DASS-21	Mean±S.D (n=140)	Range
Depression	2.8±2.0	0-21
Anxiety	2.6±1.6	0-21
Stress	5.1±2.7	0-21
Total scale	10.6±6.4	0-61

Data were expressed as mean±SD.

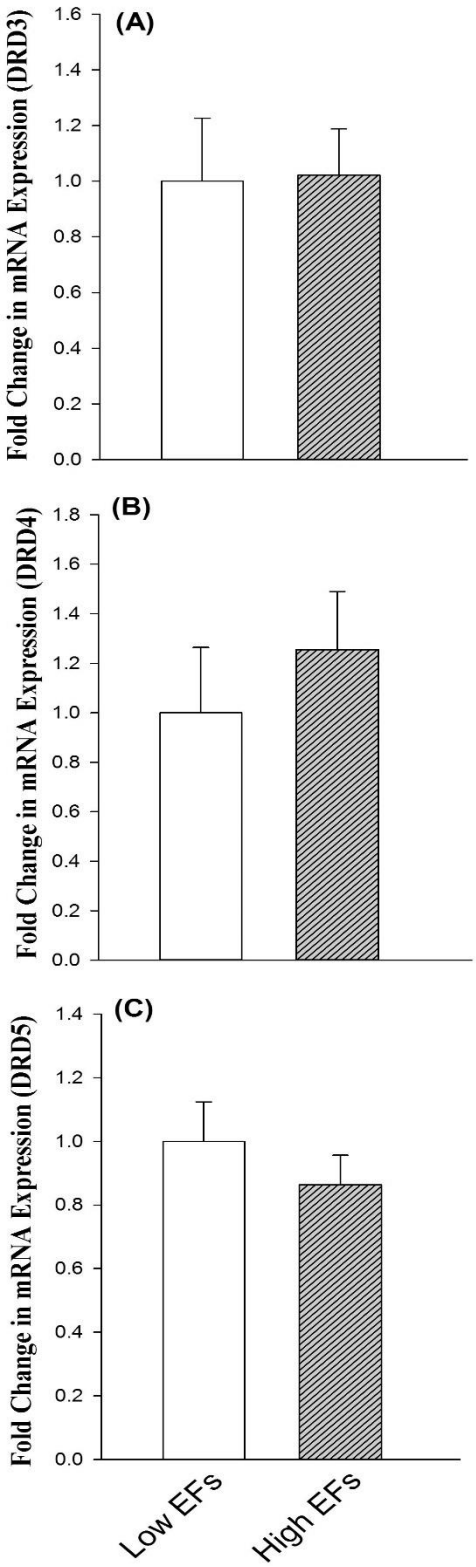

Fig.3. The level of dopamine receptors mRNA expression in low executive function (EFs) (n=20) and high EFs (n=20) performance groups. (A) Changes for DRD-3 mRNA, (B) changes for DRD-4 mRNA and (C) changes for DRD-5 mRNA. Data expressed as mean±SEM.

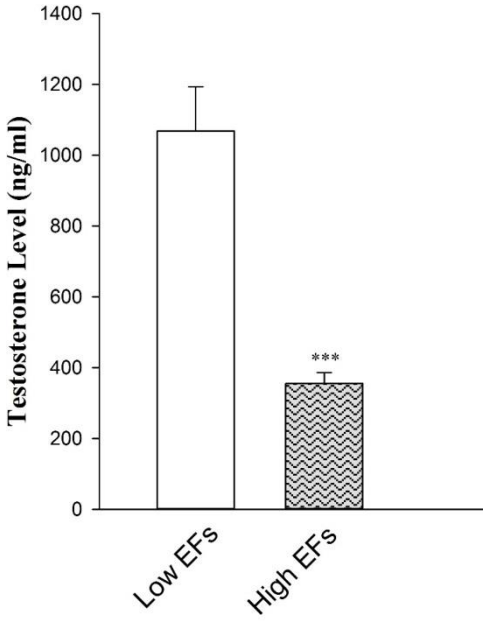

Fig.4. The level of serum testosterone in low executive function (EFs) (n=20) and high EFs (n=20) performance groups. Data expressed as mean±SEM. ****P*<0.001 compared with low EFs.

group compared with high EFs group (*P*=0.04). There was no significant change between two groups in serum urea, Na^+, K^+, glucose, creatinine, SGOT and SGPT (*P*>0.05).

DR subunits not altered in two low and high level of EFs

As shown in Figure 3, there was no significant difference in dopamine receptors (D3RD, D4RD and D5RD) expression level in individuals with high EFs compared with low EFs (*P*= 0.8986, *P*=0.6709 and *P*=0.4708, respectively).

Testosterone level in serum changed in low EFs compared with high EFs

As shown in Figure 4, there was a significant change between individuals with high EFs and low EFs. Individuals with high EFs had low testosterone level. Independent sample T-test showed that the level of serum testosterone was increased in low EFs group compared with high EFs group (*P*=0.000, F=5.004).

Discussion

The present findings established that EFs performances might be related to testosterone level and BMI in healthy males. We observed that in the

Table 3: Anthropometric data in cases according to the low and high level of executive function.

Groups	Low EFs (n=20)	High EFs (n=20)	P value
Serum urea (mg/dL)	30.7±6.8	28.9±8.1	ns
Serum Na^+(mmol/L)	135.9±16.7	140.1±11.3	ns
Serum K^+ (mmol/L)	3.8±0.5	3.6±0.8	ns
Serum glucose (mg/dL)	118.3±12.2	121.9±14.7	ns
Serum creatinine (mg/dL)	1.1±0.7	1.3±0.5	ns
Serum SGOT (U/L)	28.3±4.2	31.6±2.9	ns
Serum SGPT (U/L)	29.8±6.8	31.5±3.7	ns
BMI (kg/m^2)	30.6±2.2	21.4±1.4	0.04*

Data was expressed as mean±SEM. *P<0.05 considered as significant between two groups. Executive functions: EFs, not significant: ns.

healthy men, low or high EFs did not relate to serum urea, creatinine, glucose, SGPT, SGOT, Na^+ and K^+. Likewise, DR expression level in the lymphocyte did not change among individuals with high or low EFs.

EFs are cognitive processes that support working memory, problem-solving and control of attention. Reduction of EFs was seen in many psychological disorders such as schizophrenia, attention deficit hyperactivity disorder, bipolar disorder and dementia. A growing body of evidence supports that EFs were influenced by many biochemical and neurotransmitters, for instance, a recent study indicated that testosterone treatment changed EFs performances in old people (Resnick et al., 2017); another example indicated that balance of body electrolytes influenced EFs (Renneboog et al., 2017). The WCST assessed cognitive function and this test could evaluate working memory, executive function, attention, etc. The executive evaluating is in central of WSCT usage (Mattay et al., 2006). The current study indicated low and high EFs performance had no significant result of depression, anxiety and stress level in healthy males. Our study is in confirmation by Wright et al. (2016) which reported the EFs had no role in depression, anxiety and stress in healthy adult female and male cases. In contrast, many pathological types of research indicated that the level of EFs and cognition might alter in parallel with depression and anxiety in bipolar, schizophrenia, dementia and neurodegenerative disorders (Aparicio et al., 2017; Bollen et al., 2017; Dulau et al., 2017). One must notice that this study followed the role of EFs in normal non-psychotic males and we screened antidepressant and other drugs users.

Accumulating data revealed the role of blood's biochemical factors in EFs (Pesce et al., 2016). The level of serum electrolytes and biochemical's agents were changed in the pathological condition which disturb cognition and EFs (Gropman et al., 2013; Hwang and Kim, 2016; Patt et al., 2003). However, data revealed that there is no correlation between biochemical agents and EFs in the healthy adults (Widaman et al., 2016); our study is in agreement with a report showed that creatine and other metabolically agents did not correlate with cognition performance and working memory (Merege-Filho et al., 2017). However, there is a strong correlation between BMI and EFs (Gettens and Gorin, 2017); as expected, the BMI increased in the low EFs subjects. Weight loss maintenance has a significant role on EFs, and some lines of evidence claimed that obesity might increase cognitive deficits (Sargenius et al., 2017; Smith and Whittingham, 2017) and our data proved mentioned findings in healthy cases (Sargenius et al., 2017; Smith and Whittingham, 2017). In agreement with our result, recent research shows that adolescents with high BMI have slower cognitive processing speed while preserving equivalent performance on EFs compared with healthy peers (Sweat et al., 2017).

Wide ranges of EFs studies have focused on genetic and molecular studies. According to "peripheral marker theory," the changes in receptors in the PBL reflected the brain's receptor alterations, so many neuroscientists evaluated the receptors and proteins in the PBLs (Aquilani et al., 2015; Pinacho et al.,

2015). Our previous studies showed that PBLs are a useful marker for tracking changes which occurred in the brain and reflect some neuronal receptors alteration during pathological and physiological statues (Goodarzi et al., 2009; Roozafzoon et al., 2010; Vousooghi et al., 2015). The dopaminergic system regulates the projections between PFC and mesolimbic system (Roffman et al., 2016). Also, the dopaminergic system has essential roles in some pathologic conditions such as brain trauma, severe depression and neurodegenerative diseases which these disorders target the EFs performances (Mokler et al., 2017; Webb and Willette, 2017). The modulatory role of prefrontal dopamine signaling in working memory -as a key component of EFs- is a well-studied example. Stimulation of prefrontal dopamine receptors facilitates working memory by potentiating responsiveness of pyramidal neurons to task-relevant stimuli and suppressing the response to extraneous ones (Vijayraghavan et al., 2007). Our results presented DRs expression level has no relation with the cognitive performances and EFs in healthy young adults. In contrast to some data which considered the role of dopamine and EFs, an experimental animal study declared that injection of dopaminergic receptors antagonist has no role on EFs in the normal rats (Desai et al., 2017). Moreover, Tombeau and colleagues established that dopamine and EFs have no interaction with each other in the normal female humans (Tombeau Cost et al., 2017). Many investigations revealed that changes in DRs occurred in the pathological conditions such as dementia in elderly people, brain injury and drug addiction (Del Hoyo et al., 2016; McClure and Bickel, 2014; Murakami et al., 2016).

The characteristic of hormones especially androgens, estradiol and testosterone are essential in the cognitive function and testosterone therapy was suggested to diminish dementia and memory loss in the old people (Hua et al., 2016). Bove et al. found that testosterone level was increased in obese people (BMI=37) and consequently testosterone reduction directly reduced the level of EFs in the old people with mild amnesia (Chaves et al., 2006; Bove et al., 2016). Recent evidence demonstrated that testosterone treatment in the older people could improve memory loss, cognitive impairment and enhanced EFs (Holland et al., 2011). In contrary, our data claimed that the scenario was different in the young adult people; while the previous studies indicated that the improvement of serum testosterone enhanced cognition in the old cases but we observed the reverse role of testosterone in the adult samples. In the adult brain, the association of testosterone by age and cognition were cleared in the recent years, but we suggested that optimal level of testosterone has a beneficial role on the EFs and higher than average range could abolish such cognition processes.

Conclusion

Overall, our data presented that EFs performances in healthy adult male cases might depend on BMI and testosterone. DRs alterations in the PBLs had no correlation with EFs in the healthy adult participants. However, the higher level of testosterone observed in the young adults with low EFs which established the dose-dependent role of testosterone in the human. More research need to be done to prove the role of testosterone level in EFs in future work.

Acknowledgments

The authors acknowledge the grant support of the Tehran University of Medical Sciences (92-02-49-22453).

Conflict of interest

The authors declare that they have no competing interest.

References

Aparicio A, Santos JL, Jimenez-Lopez E, Bagney A, Rodriguez-Jimenez R, Sanchez-Morla EM. Emotion processing and psychosocial functioning in euthymic bipolar disorder. Acta Psychiatr Scand 2017; 135: 339-350.

Aquilani R, Emilio B, Dossena M, Baiardi P, Testa A, Boschi F, et al. Correlation of deglutition in subacute ischemic stroke patients with peripheral blood adaptive immunity: essential amino acid improvement. Int J Immunopathol Pharmacol 2015; 28: 576-83.

Asgharipoor N, Asgharnejad Farid A, Arshadi H, Sahebi A. A comparative study on the effectiveness of positive psychotherapy and group cognitive-behavioral therapy for the patients suffering from major depressive disorder. Iran J Psychiatry Behav Sci 2012; 6: 33-41.

Baler RD, Volkow ND. Drug addiction: the neurobiology of disrupted self-control. Trends Mol Med 2006; 12: 559-

66.
Barch DM. The cognitive neuroscience of schizophrenia. Annu Rev Clin Psychol 2005; 1: 321-53.
Bollen J, Trick L, Llewellyn D, Dickens C. The effects of acute inflammation on cognitive functioning and emotional processing in humans: a systematic review of experimental studies. J Psychosom Res 2017; 94: 47-55.
Boone KB, Ghaffarian S, Lesser IM, Hill-Gutierrez E, Berman NG. Wisconsin card sorting test performance in healthy, older adults: relationship to age, sex, education, and iq. J Clin Psychol 1993; 49: 54-60.
Bove RM, Gerweck AV, Mancuso SM, Bredella MA, Sherman JC, Miller KK. Association between adiposity and cognitive function in young men: hormonal mechanisms. Obesity (Silver Spring) 2016; 24: 954-61.
Butini S, Nikolic K, Kassel S, Bruckmann H, Filipic S, Agbaba D, et al. Polypharmacology of dopamine receptor ligands. Prog Neurobiol 2016; 142: 68-103.
Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia--therapeutic implications. Biol Psychiatry 1999a; 46: 1388-95.
Carlsson A, Waters N, Carlsson ML. Neurotransmitter interactions in schizophrenia-therapeutic implications. Eur Arch Psychiatry Clin Neurosci 1999b; 249 Suppl 4: 37-43.
Chaves PH, Carlson MC, Ferrucci L, Guralnik JM, Semba R, Fried LP. Association between mild anemia and executive function impairment in community-dwelling older women: the women's health and aging study ii. J Am Geriatr Soc 2006; 54: 1429-35.
Cools R. Role of dopamine in the motivational and cognitive control of behavior. Neuroscientist 2008; 14: 381-95.
Cools R, Barker RA, Sahakian BJ, Robbins TW. Enhanced or impaired cognitive function in parkinson's disease as a function of dopaminergic medication and task demands. Cereb Cortex 2001; 11: 1136-43.
Cools R, Barker RA, Sahakian BJ, Robbins TW. L-dopa medication remediates cognitive inflexibility, but increases impulsivity in patients with parkinson's disease. Neuropsychologia 2003; 41: 1431-41.
Czermak C, Lehofer M, Wagner EM, Prietl B, Gorkiewicz G, Lemonis L, et al. Reduced dopamine d3 receptor expression in blood lymphocytes of smokers is negatively correlated with daily number of smoked cigarettes: a peripheral correlate of dopaminergic alterations in smokers. Nicotine Tob Res 2004; 6: 49-54.
De Brito SA, Viding E, Kumari V, Blackwood N, Hodgins S. Cool and hot executive function impairments in violent offenders with antisocial personality disorder with and without psychopathy. PLoS One 2013; 8: e65566.
Del Hoyo L, Xicota L, Langohr K, Sanchez-Benavides G, de Sola S, Cuenca-Royo A, et al. Vntr-dat1 and comtval158met genotypes modulate mental flexibility and adaptive behavior skills in down syndrome. Front Behav Neurosci 2016; 10: 193.
Desai SJ, Allman BL, Rajakumar N. Combination of behaviorally sub-effective doses of glutamate nmda and dopamine d1 receptor antagonists impairs executive function. Behav Brain Res 2017; 323: 24-31.
Diamond A. Executive functions. Annu Rev Psychol 2013; 64: 135-68.
Dulau C, Deloire M, Diaz H, Saubusse A, Charre-Morin J, Prouteau A, et al. Social cognition according to cognitive impairment in different clinical phenotypes of multiple sclerosis. J Neurol 2017; 264: 740-748.
Espy KA. Using developmental, cognitive, and neuroscience approaches to understand executive control in young children. Dev Neuropsychol 2004; 26: 379-84.
Fairchild G, van Goozen SH, Stollery SJ, Aitken MR, Savage J, Moore SC, et al. Decision making and executive function in male adolescents with early-onset or adolescence-onset conduct disorder and control subjects. Biol Psychiatry 2009; 66: 162-8.
Gettens KM, Gorin AA. Executive function in weight loss and weight loss maintenance: a conceptual review and novel neuropsychological model of weight control. J Behav Med 2017; 40: 687-701.
Goodarzi A, Vousooghi N, Sedaghati M, Mokri A, Zarrindast MR. Dopamine receptors in human peripheral blood lymphocytes: changes in mRNA expression in opioid addiction. Eur J Pharmacol 2009; 615: 218-22.
Grant DA, Berg EA. A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a weigl-type card-sorting problem. J Exp Psychol 1948; 38: 404-11.
Gropman AL, Prust M, Breeden A, Fricke S, VanMeter J. Urea cycle defects and hyperammonemia: effects on functional imaging. Metab Brain Dis 2013; 28: 269-75.
Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: a review. Maturitas 2011; 69: 322-37.
Hua JT, Hildreth KL, Pelak VS. Effects of testosterone therapy on cognitive function in aging: a systematic review. Cogn Behav Neurol 2016; 29: 122-38.
Hwang SY, Kim J. An examination of the association of cognitive functioning, adherence to sodium restriction and na/k ratios in korean heart failure patients. J Clin Nurs 2016; 25: 1766-76.
Kaplan F, Oudeyer PY. In search of the neural circuits of intrinsic motivation. Front Neurosci 2007; 1: 225-36.
Lewis SJ, Dove A, Robbins TW, Barker RA, Owen AM. Cognitive impairments in early parkinson's disease are accompanied by reductions in activity in frontostriatal neural circuitry. J Neurosci 2003; 23: 6351-6.
Lovibond PF, Lovibond SH. The structure of negative emotional states: comparison of the depression anxiety stress scales (dass) with the beck depression and anxiety inventories. Behav Res Ther 1995; 33: 335-43.
Mattay VS, Fera F, Tessitore A, Hariri AR, Berman KF, Das S, et al. Neurophysiological correlates of age-related changes in working memory capacity. Neurosci Lett 2006; 392: 32-7.
McClure SM, Bickel WK. A dual-systems perspective on addiction: contributions from neuroimaging and cognitive training. Ann N Y Acad Sci 2014; 1327: 62-78.

Merege-Filho CA, Otaduy MC, de Sa-Pinto AL, de Oliveira MO, de Souza Goncalves L, Hayashi AP, et al. Does brain creatine content rely on exogenous creatine in healthy youth? a proof-of-principle study. Appl Physiol Nutr Metab 2017; 42: 128-134.

Miller BT, D'Esposito M. Searching for "the top" in top-down control. Neuron 2005; 48: 535-8.

Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. Annu Rev Neurosci 2001; 24: 167-202.

Mokler DJ, Miller CE, McGaughy JA. Evidence for a role of corticopetal, noradrenergic systems in the development of executive function. Neurobiol Learn Mem 2017; 143: 94-100.

Mueller ST, Piper BJ. The psychology experiment building language (pebl) and pebl test battery. J Neurosci Methods 2014; 222: 250-9.

Murakami H, Momma Y, Nohara T, Mori Y, Futamura A, Sugita T, et al. Improvement in language function correlates with gait improvement in drug-naive parkinson's disease patients taking dopaminergic medication. J Parkinsons Dis 2016; 6: 209-17.

Page AC, Hooke GR, Morrison DL. Psychometric properties of the depression anxiety stress scales (dass) in depressed clinical samples. Br J Clin Psychol 2007; 46: 283-97.

Patt CH, Yoo HY, Dibadj K, Flynn J, Thuluvath PJ. Prevalence of transaminase abnormalities in asymptomatic, healthy subjects participating in an executive health-screening program. Dig Dis Sci 2003; 48: 797-801.

Pesce M, Rizzuto A, La Fratta I, Tatangelo R, Campagna G, Iannasso M, et al. Super-oxide anion production and antioxidant enzymatic activities associated with the executive functions in peripheral blood mononuclear cells of healthy adult samples. Neurosci Res 2016; 106: 23-8.

Pfaffl MW, Horgan GW, Dempfle L. Relative expression software tool (rest) for group-wise comparison and statistical analysis of relative expression results in real-time pcr. Nucleic Acids Res 2002; 30: e36.

Pinacho R, Saia G, Fuste M, Melendez-Perez I, Villalta-Gil V, Haro JM, et al. Phosphorylation of transcription factor specificity protein 4 is increased in peripheral blood mononuclear cells of first-episode psychosis. PLoS One 2015; 10: e0125115.

Piper BJ, Li V, Eiwaz MA, Kobel YV, Benice TS, Chu AM, etal. Executive function on the psychology experiment building language tests. Behav Res Methods 2012;44:110-23.

Renneboog B, Sattar L, Decaux G. Attention and postural balance are much more affected in older than in younger adults with mild or moderate chronic hyponatremia. Eur J Intern Med 2017; 41: e25-e26.

Resnick SM, Matsumoto AM, Stephens-Shields AJ, Ellenberg SS, Gill TM, Shumaker SA, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. JAMA 2017; 317: 717-727.

Ricci A, Bronzetti E, Mignini F, Tayebati SK, Zaccheo D, Amenta F. Dopamine d1-like receptor subtypes in human peripheral blood lymphocytes. J Neuroimmunol 1999; 96: 234-40.

Riggs NR, Spruijt-Metz D, Sakuma KL, Chou CP, Pentz MA. Executive cognitive function and food intake in children. J Nutr Educ Behav 2010; 42: 398-403.

Roffman JL, Tanner AS, Eryilmaz H, Rodriguez-Thompson A, Silverstein NJ, Ho NF, et al. Dopamine d1 signaling organizes network dynamics underlying working memory. Sci Adv 2016; 2: e1501672.

Roozafzoon R, Goodarzi A, Vousooghi N, Sedaghati M, Yaghmaei P, Zarrindast MR. Expression of nmda receptor subunits in human peripheral blood lymphocytes in opioid addiction. Eur J Pharmacol 2010; 638: 29-32.

Sargenius HL, Lydersen S, Hestad K. Neuropsychological function in individuals with morbid obesity: A cross-sectional study. BMC Obes 2017; 4: 6.

Sawaguchi T, Goldman-Rakic PS. The role of d1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. J Neurophysiol 1994; 71: 515-28.

Slifstein M, van de Giessen E, Van Snellenberg J, Thompson JL, Narendran R, Gil R, et al. Deficits in prefrontal cortical and extrastriatal dopamine release in schizophrenia: a positron emission tomographic functional magnetic resonance imaging study. JAMA Psychiatry 2015; 72: 316-24.

Smith E, Whittingham C. Cognitive remediation therapy plus behavioural weight loss compared to behavioural weight loss alone for obesity: study protocol for a randomised controlled trial. Trials 2017; 18: 42.

Sweat V, Yates KF, Migliaccio R, Convit A. Obese adolescents show reduced cognitive processing speed compared with healthy weight peers. Child Obes 2017; 13: 190-196.

Tombeau Cost K, Unternaehrer E, Plamondon A, Steiner M, Meaney M, Atkinson L, et al. Thinking and doing: The effects of dopamine and oxytocin genes and executive function on mothering behaviours. Genes Brain Behav 2017; 16: 285-295.

Vijayraghavan S, Wang M, Birnbaum SG, Williams GV, Arnsten AF. Inverted-u dopamine d1 receptor actions on prefrontal neurons engaged in working memory. Nat Neurosci 2007; 10: 376-84.

Vousooghi N, Zarei SZ, Sadat-Shirazi MS, Eghbali F, Zarrindast MR. Mrna expression of dopamine receptors in peripheral blood lymphocytes of computer game addicts. J Neural Transm (Vienna) 2015; 122: 1391-8.

Webb J, Willette AA. Aging modifies the effect of gch1 rs11158026 on dat uptake and parkinson's disease clinical severity. Neurobiol Aging 2017; 50: 39-46.

Widaman AM, Witbracht MG, Forester SM, Laugero KD, Keim NL. Chronic stress is associated with indicators of diet quality in habitual breakfast skippers. J Acad Nutr Diet 2016; 116: 1776-1784.

Will Crescioni A, Ehrlinger J, Alquist JL, Conlon KE, Baumeister RF, Schatschneider C, et al. High trait self-control predicts positive health behaviors and success

in weight loss. J Health Psychol 2011; 16: 750-9.
Wong CG, Stevens MC. The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder. Biol Psychiatry 2012; 71: 458-66.
Wright BA, Peters ER, Ettinger U, Kuipers E, Kumari V. Moderators of noise-induced cognitive change in healthy adults. Noise Health 2016; 18: 117-32.