Evaluation of the Relationship between Brain-Derived Neurotrophic Factor Levels and the Stroop Interference Effect in Children with Attention-Deficit Hyperactivity Disorder

Şeref ŞİMŞEK¹, Salih GENÇOĞLAN², Tuğba YÜKSEL¹, İbrahim KAPLAN³, Hüseyin AKTAŞ¹, Rumeysa ALACA¹

¹Department of Child Psychiatry, Dicle University School of Medicine, Diyarbakır, Turkey

²Department of Child Psychiatry, Yüzüncü Yıl University School of Medicine, Van, Turkey

³Department of Biochemistry, Dicle University School of Medicine, Diyarbakır, Turkey

ABSTRACT

Introduction: Brain-derived neurotrophic factor (BDNF) has been suggested to play a role in the pathogenesis of attention-deficit hyperactivity disorder (ADHD). In addition, impairment in executive functions has been reported in children with ADHD. This study investigated the presence of a relationship between Stroop test scores and BDNF levels in children with ADHD.

Methods: The study was conducted in the Department of Child Psychiatry at Dicle University. The study included 49 children between 6 and 15 years of age (M/F: 42/7), who were diagnosed with ADHD according to DSM-IV, and who did not receive previous therapy. Similar in terms of age and gender to the ADHD group, 40 children were selected in the control group. The Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version was administered to all participants. Parents and teachers were administered Turgay DSM-IV-based Child and Adolescent Behavior

Disorders Screening and Rating Scale to measure symptom severity in children with ADHD. Children with ADHD underwent the Stroop test. BDNF levels were evaluated in serum by ELISA.

Results: The ADHD and control groups did not differ in terms of BDNF levels. BDNF levels did not differ between ADHD subtypes. There was also no relationship between the Stroop test interference scores and BDNF levels.

Conclusion: The findings of the present study are in line with those in studies that demonstrated no significant role of BDNF in the pathogenesis of ADHD.

Keywords: Attention-deficit hyperactivity disorder; brain-derived neurotrophic factor; Stroop; pathophysiology; executive functions

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder that develops during childhood and persists during adulthood; it is characterized by motor activity inconsistent with developmental level, attention deficit, and impulsivity (1). The worldwide prevalence of ADHD is approximately 5.3% among children and adolescents (2), and the prevalence has been reported to be 8.1% among Turkish school-age children (3).

The pathogenesis of ADHD has not been fully elucidated; however, the dopaminergic system is considered to be primarily responsible (4). Molecular genetic studies have suggested that genetic polymorphisms in the dopaminergic system, such as in dopamine D4, D5, and dopamine transporter, are associated with ADHD (5). Neuroimaging, neurophysiologic, neurochemical, and genetic studies in patients with ADHD have demonstrated evidence for structural and functional alterations in certain areas of the brain (6). The molecules responsible for changes in plasticity in these areas of the brain may contribute to pathogenic mechanisms (7).

Brain-derived neurotrophic factor (BDNF) is the most abundantly produced and the most extensively studied neurotrophin in the nervous system. BDNF plays a role in the regulation of neurogenesis, development of neuronal pathways, growth of dendrites, and modulation of synaptic plasticity (8,9,10,11). In previous studies, BDNF has been shown to play a role in the pathophysiology of many mental disorders (12,13,14,15,16). Evidence from recent studies suggests that BDNF plays a role in the etiology of ADHD. In particular, low central BDNF activity in the midbrain has been reported to play a role in the pathogenesis of ADHD (4). Low BDNF activity in the midbrain has been shown to cause dopaminergic dysfunction, which in turn results in the development of ADHD (17). A decrease in BDNF gene expression has been observed in the frontal cortex of dopamine transporter knockout mice (18), and these mice exhibit behaviors mimicking the basic behavior pattern in ADHD such as learning difficulties, aggressiveness, anxiety, and hyperactive locomotor behavior (19,20).

Correspondence Address: Şeref Şimşek, Dicle Üniversitesi Tıp Fakültesi, Çocuk Psikiyatri Anabilim Dalı, Diyarbakır, Türkiye
E-mail: drserefsimsek@gmail.com

Received: 13.02.2015 **Accepted:** 05.09.2015

©Copyright 2016 by Turkish Association of Neuropsychiatry - Available online at www.noropsikiyatriarsivi.com

From two studies that were conducted on treatment-naïve children with ADHD, one found higher plasma BDNF levels and the other found comparable BDNF levels in the control group than in the ADHD group (7,17). Serum BDNF levels have been found to be lower in adult patients with ADHD than in the control group. Low BDNF levels in patients with ADHD have been suggested to cause neurodevelopmental insufficiency and thereby result in the persistence of this disorder during adulthood (21).

The current study aimed to investigate whether serum BDNF levels differed between children and adolescents with ADHD and healthy controls and whether there is a relationship between BDNF levels and Stroop test scores.

METHODS

Study Sample

The study was conducted in the Department of Child Psychiatry at Dicle University Training and Research Hospital. Study data were collected between November 2012 and June 2013. The study included 49 children between 6 and 15 years of age [7 girls (14%) and 42 boys (86%)], who were diagnosed with ADHD according to DSM-IV, and who did not receive previous therapy. Patients with clinically diagnosed mental retardation, history of seizures, loss of consciousness, head trauma, and encephalitis and those with Tourette's syndrome, pervasive developmental disorders, bipolar mood disorders, psychotic disorders, and any chronic systemic disease that could affect biochemical parameters were excluded. Patients with oppositional defiant disorder and conduct disorder were included in the study. The control group comprised children with similar age and gender distribution, who were residing at addresses similar to children in the ADHD group but who were not siblings, and who did not have a history of medical problems and psychiatric disorders. Approval was obtained from the Non-interventional Clinical Research Ethics Committee at Dicle University Faculty of Medicine. The parents of the participants provided written volunteer informed consent.

Study Procedures

The sociodemographic features of the participants were obtained, and a clinical data form was completed. A structured psychiatric interview was conducted with the patients (K-SADS-PL). Parents and teachers completed the DSM-IV-based behavior disorders screening form and rating scale for attention deficit and disruptive behavior disorders. This was followed by the Stroop test, which is a neuropsychological test reflecting the activity of the prefrontal area of the brain. The Stroop test was administered to only the ADHD group. Finally, a 2-ml sample of venous blood was obtained for biochemical tests.

Forms and Scales

Sociodemographic Data and Clinical Data Form: This form included questions about age, gender, educational status, ages and occupations of the parents, consanguinity between parents, number of siblings, history of psychiatric disorders or criminal background among family members and relatives, family history of substance abuse, height, and weight.

Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL): The schedule (K-SADS-PL) was originally developed by Kaufman et al. (22) It was adapted to Turkish by Gökler et al. in 2004 (23). K-SADS-PL is administered during an interview with parents and their children, and the final evaluation is performed using input from all data sources. This scale evaluates

the presence of common psychopathologies, primarily ADHD, in children and adolescents.

Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S): This scale was developed by Turgay based on the DSM-IV criteria, and it contains 41 items: nine probe attention deficit, six probe hyperactivity, three probe impulsivity, eight probe oppositional defiant disorder, and 15 probe behavioral disorder (24). The validity and reliability of this scale was evaluated by Ercan et al. (25).

Stroop Test TBAG Form: The Stroop test is a neuropsychological test reflecting the activity of the prefrontal area of the brain. It involves the use of four white cards measuring 14.0×21.5 cm. Each card contains an array of six lines comprising four items. These cards are the "stimuli" of the test, and the reactions that the participant must give to these stimuli or the tasks that the participant must perform constitute the sections of the test. The scores in each test are calculated by separately rating each section. The test evaluates the ability of parallel distributed processing for recognized and unrecognized stimuli, processing speed, and the ability to resist against interference effects of automatic processes (26). The validity and reliability of the Turkish version of this scale was evaluated by Karakaş et al. (27,28). Considering the fact that completing the tasks on the card would be affected by variables such as perceptual problems and psychomotor speed, the interference effect score was calculated by subtracting the time to recognize colors from the time to complete the interference effect card.

Measurement of BDNF Levels

Blood samples were collected into gel tubes between 09:00 and 12:00. After collecting, they were left at room temperature for 15 min to facilitate clotting. The blood samples were centrifuged at 5000 rpm for 6 min. The serum was transferred to 1.5-ml polypropylene tubes that were stored at -80°C for further analysis. Mature BDNF levels were measured using a human BDNF ELISA Kit (Hangzhou Eastbiopharm CO. LTD, China). To minimize assay variance, all BDNF measurements were conducted on the same day. All experiments were performed in duplicate. The tests were performed according to the manufacturer's instructions. The optical density of each well was measured using an automated microplate reader.

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc; Chicago, IL, USA) 15. The chi-square test was used to evaluate the presence of a difference between the groups in terms of gender, consanguinity between parents, history of psychiatric disorders or criminal background among family members and relatives, family history of substance abuse, and domestic violence. Student's t-test was used to compare normally distributed variables in independent groups, and the Mann-Whitney test was used to compare not normally distributed categorical variables. BDNF levels were compared between the ADHD, ADHD plus ODD, and ADHD plus CD groups using the Kruskal-Wallis test as this parameter did not show normal distribution. Pearson's test was used to evaluate correlation coefficients and statistical significance of normally distributed variables, and Spearman's test was used to evaluate variables not without a normal distribution. A p-value below 0.05 was considered to be statistically significant.

RESULTS

The mean age of the children was 8.6±2.4 years in the ADHD group (M/F: 42/7) and 8.7±2.2 years in the control group (M/F: 32/8). There was no difference between the groups in terms of age and gender. There

was also no difference between the groups in terms of the occupation of parents and consanguinity between parents. The rates of psychiatric illness among family members and relatives and domestic violence were higher in the ADHD group than in the control group ($p=0.01$ and $p<0.01$, respectively). The groups did not differ in terms of criminal background and substance abuse among family members. Sociodemographic data are presented in Table 1.

T-DSM-IV-S scores in the ADHD group as completed by the parents and teachers are presented in Table 2, and the Stroop test scores are presented in Table 3. There was no difference in BDNF levels between the groups. No relationship was found between symptom severity in ADHD and BDNF levels. We could not detect a significant relationship between the interference effect score and BDNF levels. There was also no relationship between the interference effect score and T-DSM-IV-S (inattentive, hyperactive, and opposition) scores ($r=-0.19$, $p=0.65$; $r=0.31$, $p=0.45$; and $r=0.17$, $p=0.69$; respectively).

Among children with ADHD, 34.7% ($n=17$) had the predominantly inattentive type and 65.3% ($n=32$) had the combined type. There was no patient with the predominantly hyperactive-impulsive type. BDNF levels did not differ between the subtypes ($p=0.54$). Among these patients, 51% ($n=25$) were only diagnosed with ADHD, 28.6% ($n=14$) were diagnosed with ADHD plus ODD, and 20.4% ($n=10$) were diagnosed with ADHD plus CD. The groups did not differ in terms of BDNF levels.

DISCUSSION

One of the most important findings in the present study is that there was no difference in BDNF levels between the ADHD and control groups. Studies have yielded controversial results on BDNF levels in ADHD. Some studies found higher plasma and serum BDNF levels in treatment-naïve patients with ADHD than in the control group (17,29,30), while others showed no difference (7,31,32). Serum BDNF levels were lower in adult patients with ADHD than in the control group (21).

Another important finding of the present study is that there was no relationship between ADHD symptom severity and BDNF levels. In addition, BDNF levels did not differ between the subtypes of ADHD. Shim et al. reported a positive correlation between plasma BDNF levels and symptom severity of attention deficit (17). No difference in BDNF levels was reported between disease subtypes (7,21,32,33). Plasma BDNF levels are more affected by environmental factors, e.g., storage conditions, elapsed time between the blood samples (34). It has been reported that serum BDNF measurement gives more stable results than plasma (35). Furthermore, the BDNF gene is not present among ADHD-related genes (36).

Oppositional defiant disorder/conduct disorder is a common comorbidity reported in patients with ADHD (37). The difference in BDNF levels among the three disease groups was investigated (ADHD, ADHD plus ODD, and ADHD plus CD). No difference was found among these groups. To our knowledge, there are no studies in the literature that evaluate such a relationship.

Attention-deficit hyperactivity disorder is associated with a range of cognitive disorders, mainly those related to the impairment of executive functions. Common symptoms of impaired executive functions in ADHD include motor inhibition, working memory, and planning and organizing deficits associated with attention (38). Other cognitive disorders include sustained attention, vigilance, motor timing, and data processing (39,40). Studies that evaluated the relationship between BDNF levels and executive functions have shown that low BDNF levels affect the anatomical development and executive functions of the prefrontal cortex (41,42).

Table 1. Sociodemographic data

	ADHD group (n=49)	Control group (n=40)	z value	p
Age (years)	8.6±2.4	8.7±2.2	-0.37	0.71
Education duration (years)	3.2±2.1	4.0±2.2	-1.67	0.09
Mother's age (years)	33.2±6.6	34.5±6.2	-1.53	0.13
Mother's education duration (years)	5.7±4.3	6.5±4.3	-1.08	0.28
Father's age (years)	38.6±6.4	40.4±7.0	-1.40	0.17
Father's education duration (years)	9.1±4.7	9.4±4.5	-0.06	0.95
Number of siblings	3.5±2.1	3.1±1.3	-0.43	0.66
BMI (kg/m ²)	16.4±1.7	17.6±2.5	-1.95	0.05
BDNF (ng/mL)	11.1±16.8	8.7±12.3	-0.08	0.94

ADHD: attention-deficit hyperactivity disorder; BMI: body mass index; BDNF: brain-derived neurotrophic factor

Table 2. T-DSM-IV-S scores of the participants with ADHD

	Parents (mean±SD)	Teachers (mean±SD)
Attention	16.9±5.1	15.7±5.4
Hyperactivity-impulsivity	12.0±8.9	12.8±7.7
Opposition defiance	8.7±7.7	7.1±6.8

T-DSM-IV-S: Turgay DSM-IV-based Child and Adolescent Behavior Disorders Screening and Rating Scale; SD: standard deviation

Table 3. Stroop test scores

	Time (s) (mean±SD)	Number of errors (mean±SD)	Number correction (mean±SD)
1 st card (word reading)	16.8±13.9	0.2±0.4	0.1±0.3
2 nd card (word reading)	17.5±15.0	0.1±0.2	0.1±0.2
3 rd card (tell the color)	21.9±8.5	1.6±2.0	1.1±1.5
4 th card (tell the color)	34.7±15.2	1.2±2.5	0.7±0.9
5 th card (interference effect card)	47.1±13.0	3.2±3.6	1.7±1.5
Interference score (5 th card-3 rd card)	25.2±10.7		

There was also no relationship between the interference effect score and BDNF levels in patients with ADHD.

The present study has several limitations. The subjects in the control group did not undergo the Stroop test. Physical activity was not measured in patients with ADHD. Physical activity can affect BDNF levels. Depression is more frequently observed in patients with ADHD than in those without ADHD (43). BDNF levels are lower in patients with depression (44). However, depression was not measured in the present study.

In conclusion, there was no difference in BDNF levels between the ADHD and control groups. There was no relationship between ADHD symptom severity and BDNF levels. No difference was reported between the subtypes of ADHD in terms of BDNF levels. There was no difference in BDNF levels between patients with ADHD and those with comorbid

ODD/CD. In the ADHD group, there was no relationship between the Stroop test interference effect score and BDNF levels. The results of the present study are consistent with those of previous studies that demonstrated no relationship between BDNF levels and ADHD.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Dicle University School of Medicine.

Informed Consent: Written informed consent was obtained from the parents of the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Ş.Ş.; Design – Ş.Ş.; Supervision – Ş.Ş.; Resources – T.Y.; Materials – T.Y.; Data Collection and/or Processing – R.A., H.A.; Analysis and/or Interpretation – İ.K., Ş.Ş., T.Y.; Literature Search – H.A., R.A.; Writing Manuscript – Ş.Ş.; Critical Review – T.Y.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, Sklar P. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2005; 57:1313-1323. [CrossRef]
2. Polanczyk G, de Lima M, Horta B, Biederman J, Rohde L. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry* 2007; 164:942-948. [CrossRef]
3. Erşan EE, Doğan O, Doğan S, Sümer H. The distribution of symptoms of attention-deficit/hyperactivity disorder and oppositional defiant disorder in school age children in Turkey. *Eur Child Adolesc Psychiatry* 2004; 13:354-361. [CrossRef]
4. Tsai SJ. Attention-deficit hyperactivity disorder may be associated with decreased central brain-derived neurotrophic factor activity: Clinical and therapeutic implications. *Med Hypotheses* 2007; 68:896-899. [CrossRef]
5. Bobb AJ, Castellanos FX, Addington AM, Rapoport JL. Molecular genetic studies of ADHD: 1991 to 2004. *Am J Med Genet B Neuropsychiatr Genet* 2006; 141:551-565. [CrossRef]
6. Cortese S. The neurobiology and genetics of Attention-Deficit/Hyperactivity Disorder (ADHD): What every clinician should know. *Eur J Paediatr Neurol* 2012; 16:422-433. [CrossRef]
7. Scassellati C, Zanardini R, Tiberti A, Pezzani M, Valenti V, Effedri P, Filippini E, Conte S, Ottolini A, Gennarelli M, Bocchio-Chiavetto L. Serum brain-derived neurotrophic factor (BDNF) levels in attention deficit-hyperactivity disorder (ADHD). *Eur Child Adolesc Psychiatry* 2014; 23:173-177. [CrossRef]
8. Black IB. Trophic regulation of synaptic plasticity. *J Neurobiol* 1999;41:108-118.
9. Tyler WJ, Alonso M, Bramham CR, Pozzo-Miller LD. From acquisition to consolidation: on the role of brain-derived neurotrophic factor signaling in hippocampal-dependent learning. *Learn Mem* 2002; 9:224-237. [CrossRef]
10. Vicario-Abejón C, Owens D, McKay R, Segal M. Role of neurotrophins in central synapse formation and stabilization. *Nat Rev Neurosci* 2002; 3:965-974. [CrossRef]
11. Chappelle CA, Pozzo-Miller L. Activity-dependent structural plasticity of dendritic spines. *Concise Learn Mem Ed Sel Oxf Elsevier* 2007; 281-305.
12. Bocchio-Chiavetto L, Bagnardi V, Zanardini R, Molteni R, Nielsen MG, Placentino A, Giovannini C, Rilloi L, Ventriglia M, Riva MA, Gennarelli M. Serum and plasma BDNF levels in major depression: a replication study and meta-analysis. *World J Biol Psychiatry* 2010; 11:763-773. [CrossRef]
13. Fernandes BS, Gama CS, Ceresér KM, Yatham LN, Fries GR, Colpo G, de Lucena D, Kunz M, Gomes FA, Kapczinski F. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. *J Psychiatr Res* 2011; 45:995-1004. [CrossRef]
14. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. *Mol Psychiatry* 2011; 16:960-972. [CrossRef]
15. Nakazato M, Hashimoto K, Shimizu E, Niitsu T, Iyo M. Possible involvement of brain-derived neurotrophic factor in eating disorders. *IUBMB Life* 2012; 64:355-361. [CrossRef]
16. Maina G, Rosso G, Zanardini R, Bogetto F, Gennarelli M, Bocchio-Chiavetto L. Serum levels of brain-derived neurotrophic factor in drug-naïve obsessive-compulsive patients: a case-control study. *J Affect Disord* 2010; 122:174-178. [CrossRef]
17. Shim SH, Hwangbo Y, Kwon YJ, Jeong HY, Lee BH, Lee HJ, Kim YK. Increased levels of plasma brain-derived neurotrophic factor (BDNF) in children with attention deficit-hyperactivity disorder (ADHD). *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32:1824-1828. [CrossRef]
18. Fumagalli F, Racagni G, Colombo E, Riva MA. BDNF gene expression is reduced in the frontal cortex of dopamine transporter knockout mice. *Mol Psychiatry* 2003; 8:898-899. [CrossRef]
19. Chourbaji S, Hellweg R, Brandis D, Zörner B, Zacher C, Lang UE, Henn FA, Hörtnagl H, Gass P. Mice with reduced brain-derived neurotrophic factor expression show decreased choline acetyltransferase activity, but regular brain monoamine levels and unaltered emotional behavior. *Brain Res Mol Brain Res* 2004; 121:28-36. [CrossRef]
20. Rios M, Fan G, Fekete C, Kelly J, Bates B, Kuehn R, Lechan RM, Jaenisch R. Conditional deletion of brain-derived neurotrophic factor in the postnatal brain leads to obesity and hyperactivity. *Mol Endocrinol* 2001; 15:1748-1757. [CrossRef]
21. Corominas-Roso M, Ramos-Quiroga JA, Ribases M, Sanchez-Mora C, Palomar G, Valero S, Bosch R, Casas M. Decreased serum levels of brain-derived neurotrophic factor in adults with attention-deficit hyperactivity disorder. *Int J Neuropsychopharmacol* 2013; 1-9. [CrossRef]
22. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, Williamson D, Ryan N. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry* 1997; 36:980-8. [CrossRef]
23. Gökler B, Ünal F, Pehlivanlı B, Kültür EÇ, Akdemir D, Taner Y. Reliability and validity of schedule for affective disorders and schizophrenia for school age children-present and lifetime version-Turkish version (K-SADS-PL-T). *Turk J Child Adolesc Ment Health* 2004; 11:109-116.
24. Turgay A. Disruptive behavior disorders child and adolescent screening and rating scale for children, adolescents, parents, and teachers. West Blomfield (Michigan): Integrative Therapy Institute Publication; 1994.
25. Ercan ES, Amado S, Somer O, Çikoğlu S. Development of a test battery for the assessment of attention deficit hyperactivity disorder. *Turk J Child Adolesc Ment Health* 2001; 8:132-144.
26. Stroop JR. Studies of interference in serial verbal reaction. *J Exp Psychol* 1935; 18:643-662. [CrossRef]
27. Karakaş S. Bilnot Bataryası El Kitabı: Nöropsikolojik Testler için araştırma ve geliştirme çalışmaları. Ankara: Dizayn Ofset; 2004.
28. Kılıç B., Koçkar A., Irak. Stroop testi TBAG formunun 6-11 yaş grubu çocuklarda standardizasyon çalışması. *Çocuk ve Genç Ruh Sağlığı Derg* 2002; 9:86-99.
29. Fu-Qiang Y, Xue-xiang Y, Miao P, Zhen-Wu M, Wei-Na G, Hui Y. Relationship between serum brain-derived neurotrophic factor and 5-HT in children with attention deficit hyperactivity disorder plus learning disabilities. *Chin J Neuromedicine* 2012; 11:294-296.
30. Li H, Liu L, Tang Y, Ji N, Yang L, Qian Q, Wang Y. Sex-specific association of brain-derived neurotrophic factor (BDNF) Val66Met polymorphism and plasma BDNF with attention-deficit/hyperactivity disorder in a drug-naïve Han Chinese sample. *Psychiatry Res* 2014; 217:191-197. [CrossRef]
31. Sahin S, Yuce M, Alacam H, Karabekiroğlu K, Say GN, Salis O. Effect of methylphenidate treatment on appetite and levels of leptin, ghrelin, adiponectin, and brain-derived neurotrophic factor in children and adolescents with attention deficit and hyperactivity disorder. *Int J Psychiatry Clin Pract* 2014; 1-8. [CrossRef]
32. Sargin E, Akay A, Resmi H, Cengizhan S, Özek H, Ellidokuz H, Miral S, Orçin E. Evaluation of serum brain-derived neurotrophic factor levels in children with

- attention deficit hyperactivity disorder: preliminary data. *Arch Neuropsychiatry* 2012; 49:96-101.
33. Amiri A, Torabi Parizi G, Kousha M, Saadat F, Modabbernia MJ, Najafi K, Atrkar Roushan Z. Changes in plasma Brain-derived neurotrophic factor (BDNF) levels induced by methylphenidate in children with Attention deficit-hyperactivity disorder (ADHD). *Prog Neuropsychopharmacol Biol Psychiatry* 2013; 47:20-24. [\[CrossRef\]](#)
 34. Elfving B, Plougmann PH, Wegener G. Detection of brain-derived neurotrophic factor (BDNF) in rat blood and brain preparations using ELISA: pitfalls and solutions. *J Neurosci Methods* 2010; 187:73-77. [\[CrossRef\]](#)
 35. D'Sa C, Dileone RJ, Anderson GM, Sinha R. Serum and plasma brain-derived neurotrophic factor (BDNF) in abstinent alcoholics and social drinkers. *Alcohol* 2012; 46:253-259. [\[CrossRef\]](#)
 36. Zhang L, Chang S, Li Z, Zhang K, Du Y, Ott J, Wang J. ADHD gene: a genetic database for attention deficit hyperactivity disorder. *Nucleic Acids Res* 2012; 40:D1003-9. [\[CrossRef\]](#)
 37. Biederman J, Petty CR, Dolan C, Hughes S, Mick E, Monuteaux MC, Faraone SV. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. *Psychol Med* 2008; 38:1027-1036. [\[CrossRef\]](#)
 38. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. *Biol Psychiatry* 2005; 57:1336-1346. [\[CrossRef\]](#)
 39. Toplak ME, Rucklidge JJ, Hetherington R, John SCF, Tannock R. Time perception deficits in attention-deficit/hyperactivity disorder and comorbid reading difficulties in child and adolescent samples. *J Child Psychol Psychiatry* 2003; 44:888-903. [\[CrossRef\]](#)
 40. Shanahan MA, Pennington BF, Yerys BE, Scott A, Boada R, Willcutt EG, Olson RK, DeFries JC. Processing speed deficits in attention deficit/hyperactivity disorder and reading disability. *J Abnorm Child Psychol* 2006; 34:584-601. [\[CrossRef\]](#)
 41. Egan MF, Kojima M, Callicott JH, Goldberg TE, Kolachana BS, Bertolino A, Zaitsev E, Gold B, Goldman D, Dean M, Lu B, Weinberger DR. The BDNF val66met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. *Cell* 2003; 112:257-269. [\[CrossRef\]](#)
 42. Rybakowski JK, Borkowska A, Czerski PM, Skibińska M, Hauser J. Polymorphism of the brain-derived neurotrophic factor gene and performance on a cognitive prefrontal test in bipolar patients. *Bipolar Disord* 2003; 5:468-472. [\[CrossRef\]](#)
 43. Daviss WB. A review of co-morbid depression in pediatric ADHD: etiologies, phenomenology, and treatment. *J Child Adolesc Psychopharmacol* 2008; 18:565-571. [\[CrossRef\]](#)
 44. Molendijk ML, Spinhoven P, Polak M, Bus BA, Penninx BW, Elzinga BM. Serum BDNF concentrations as peripheral manifestations of depression: evidence from a systematic review and meta-analyses on 179 associations (n=9484). *Mol Psychiatry* 2014; 19:791-800. [\[CrossRef\]](#)