DOI: 10.5455/bcp.20121130085850

Investigation of Autonomic Nervous System Functions by Pupillometry in Children with Attention-Deficit/ Hyperactivity Disorder

Koray Kara[1], Dursun Karaman[1], Uzeyir Erdem[2], Mehmet Ayhan Congologlu[3], Ibrahim Durukan[1], Abdullah Ilhan[4]

ÖZET:

Dikkat Eksikliği Hiperaktivite Bozukluğu olan çocuklarda pupillometri ile otonom sinir sistemi işlevlerinin araştırılması

Amaç: Dikkat eksikliği hiperaktivite bozukluğu (DEHB) okul çağındaki çocuklarda en sık görülen nörogelişimsel bozukluklardan birisidir. DEHB'nun ortaya çıkış nedeni tam olarak bilinmemekle birlikte genetik, biyolojik ve psikososyal faktörlerin etiyolojide yer aldıkları düşünülmektedir. Bu araştırmada polikliniğe başvuran ve DSM-IV'e göre DEHB tanısı konulan 6-11 yaş arası erkek çocukların otonom sinir sistemi işlevlerinin pupillometrik ölçümler yapılarak, sağlıklı kontrol grubu ile karşılaştırılması amaçlanmıştır.

Yöntem: Araştırma grubu DEHB tanısı ile takip edilen 32 erkek çocuktan, kontrol grubu ise 24 sağlıklı erkek çocuktan oluşmuştur. DEHB olgularında tanı Okul Çağı Çocukları İçin Duygulanım Bozuklukları ve Şizofreni Görüşme Çizelgesi ile konulmuştur. Karşıt olma-karşı gelme bozukluğu (KO-KGB) haricinde diğer psikiyatrik tanısı olanlar çalışmadan dışlanmıştır. Araştırma ve kontrol grubunun otonom sinir sistemi işlevleri fotopik ve mezopik koşullarda pupil boyutlarındaki değişiklikler ölçülerek incelenmiştir.

Bulgular: DEHB olan çocukların fotopik ve mezopik koşullarda ölçülen pupil çaplarının sağlıklı kontrollerden anlamlı farklılık göstermediği bulunmuştur. KO-KGB birişikliği olan ve olmayan DEHB olguları karşılaştırıldığında; mezopik ve fotopik pupil çapları benzer bulunmuştur.

Sonuç: Araştırma bulguları DEHB olan erkek çocukların mezopik ve fotopik pupil çapları yönünden sağlıklı çocuklardan farklılık göstermediğini düşündürmektedir. Bu durum DEHB'nda pupillometri yöntemi ile ölçülen otonom sinir sistemi işlevlerinde farklılık olmadığına işaret etmektedir. Ancak, sonuçların kapsamlı araştırmalarla desteklenmesi gerekmektedir.

Anahtar sözcükler: Dikkat eksikliği hiperaktivite bozukluğu, çocuklar, otonom sinir sistemi, göz merceği

Klinik Psikofarmakoloji Bülteni 2013;23(1):49-56

ABSTRACT:

Investigation of autonomic nervous system functions by pupillometry in children with Attention-Deficit/Hyperactivity Disorder

Objective: Attention deficit hyperactivity disorder (ADHD) is one of the most frequently seen neurodevelopmental disorders among school-aged children. Although the main cause of ADHD is unknown, combinations of genetic, biological and psychosocial factors are thought to play a part in the etiology of ADHD. This study aims to compare the autonomic nervous system functions of 6-11 year-old males diagnosed with ADHD against healthy controls by measuring pupil diameters.

Methods: Thirty-two males with ADHD and 24 healthy controls participated in this study. Any other psychiatric disorders except oppositional defiant disorder (ODD) were excluded from this study. The autonomic nervous system functions of participants were evaluated by measuring pupil diameter changes in photopic and mesopic conditions.

Results: There were no statistically significant difference on photopic and mesopic pupil diameters between the ADHD and healthy control groups. Moreover, the ADHD subgroup with ODD did not differ from the ADHD subgroup without ODD with respect to the same parameters.

Conclusion: In conclusion, these findings suggest that males with ADHD show no differences in pupil diameters compared to typically developing children. This might indicate no difference in autonomic nervous system functions measured by pupillometry. However, it is recommended that the results of our study need to be confirmed by more detailed studies.

Key words: Attention deficit hyperactivity disorder, children, autonomic nervous system, pupil

Bulletin of Clinical Psychopharmacology 2013;23(1):49-56

[1]MD, Gulhane Military Academy, School of Medicine Department of Child and Adolescent Psychiatry, Ankara - Turkey
[2]Associate Professor, Gulhane Military Academy, School of Medicine Department of Ophthalmology, Ankara - Turkey
[3]Associate Professor, Gulhane Military Academy, School of Medicine Department of Child and Adolescent Psychiatry, Ankara - Turkey
[4]Assistant Dr., Gulhane Military Academy, School of Medicine Department of Ophthalmology, Ankara - Turkey

Yazışma Adresi / Address reprint requests to:
MD, Koray Kara, Gulhane Military Academy, School of Medicine Department of Child and Adolescent Psychiatry, Etlik, Keçiören, Ankara - Turkey

Telefon / Phone: +90-312-304-3796/4567

Elektronik posta adresi / E-mail address: drkoraykara@yahoo.com

Gönderme tarihi / Date of submission:
11 Ağustos 2012 / August 11, 2012

Kabul tarihi / Date of acceptance:
30 Kasım 2012 / November 30, 2012

Bağıntı beyanı:
K.K., D.K., U.E., M.A.C., I.D., A.I.: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Declaration of interest:
K.K., D.K., U.E., M.A.C., I.D., A.I.: The authors reported no conflict of interest related to this article.

INTRODUCTION

Attention-deficit hyperactivity disorder (ADHD) is a common childhood behavioral disorder of inattention, impulsivity, and hyperactivity that affects 8-12% of children worldwide (1). Children with ADHD often have more social, emotional and cognitive problems than other children (2).

The autonomic nervous system (ANS) is the part of the peripheral nervous system that acts as a control system for visceral functions, functioning largely below the level of consciousness. The ANS works to achieve homeostasis between the organism and the external environment and has a critical role in balancing physiological stimulation and inhibition under stress. In addition, it is known that the ANS is a prerequisite for regulating emotional and cognitive functions, particularly attention (3). It has been suggested that school age children with psychiatric symptoms might show a pattern of autonomic dimorphism in their reactivity to standardized challenges (4).

Previous studies examining the relationship between the ANS and psychiatric disorders have measured various physiological parameters like blood pressure, skin conductivity, heart rate variability and pupil light reflex (5-10). Pupil size is under the control of both sympathetic and parasympathetic autonomic fibers and is responsive to a range of excitatory stimuli. Therefore, pupillometric measurements can provide valuable data concerning the functioning of both branches of the autonomic nervous system. Furthermore, the pupillometric approach is a simple noninvasive technique to obtain relevant information on the autonomic nervous system (11,12). It has even been proposed that for some disorders pupillometry may be a more sensitive test of automatic nerve dysfunction than assessment of cardiovascular reflexes (13). The size of the pupil is determined by the tone in two opposing smooth muscles; pupillary constriction or "myosis" is brought about by the action of the sphincter muscle under parasympathetic control, whereas pupillary dilation or "mydriasis" is brought about by the action of the dilator muscle under sympathetic control. At any point in time, the balance of activity in parasympathetic and sympathetic supplies depends on a number of factors, including genetic influences, age, wakefulness, accommodative state and ambient lighting conditions. When these are standardized or controlled, measurement of pupil size can be used to identify parasympathetic or sympathetic deficits (14).

There are a number of studies examining the functionality of the ANS in ADHD and oppositional defiant disorder (ODD) (4). Most of these studies which are based on heart rate variability (15,16) and skin conductivity (17,18), asserted that in the neurobiology of ADHD, ANS regulation problems may have an important role. Although pupil diameter measurement has been used in conditions like enuresis, diabetes mellitus and Parkinson's disease to evaluate the ANS (19), ANS activity has not previously been studied through pupil diameter measurement in ADHD. There is, however, an interesting study by Zahn and colleagues, in which 32 children with minimal brain dysfunction were found to have smaller pupil dilatation to visual stimulus when compared with controls (20).

This study aims to compare the ANS functions of 6-11 year old males diagnosed with ADHD against healthy controls comparable in age and sex by using pupillometry, a simple non-invasive technique measuring pupil size under mesopic and photopic conditions.

MATERIALS AND METHODS

Subjects

A total of 32 males between 6 and 11 years old were recruited to this study. The subjects were children with ADHD, who had been followed up and treated at least for one year (range from 1 year to 5 years) in the outpatient clinic of child and adolescent psychiatry at Gülhane Military Faculty of Medicine. The diagnosis was made by a pediatric psychiatrist based on the criteria from the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) by seeking clinical information from multiple informants including parents, the

child, and teachers. Measurement tools included the Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version, Turkish Version (K-SADS-PL-T) and the DSM-IV Based Behavior Disorders Screening and Rating Scale. Consecutive children, who presented for evaluation to the outpatient clinic of child and adolescent psychiatry were screened for inclusion in this study.

Only children with the combined subtype of ADHD were included to maintain homogeneity of the sample. Children, who met these additional criteria were included into the study: 1- males aged 6-11 years (prepubertal); 2- at least one year of MPH use and being drug-responsive; 3- no history of other psychiatric disorders (conduct disorder, any anxiety disorder, depressive disorder, learning disorder etc.) except oppositional defiant disorder, 4-no history of mental retardation, neurological disorders, sensorimotor handicaps, 5-no history of chronic medical illness (respiratory diseases etc.). [ANS symptoms like excessive fatigue, syncope and dizziness and ophthalmic pathology may effect pupillary reaction including corneal leukoma, cataract, macular pathologies, optic atrophy], and 6- not being within the 25th percentile for the Raven's Colored Progressive Matrices. Twenty-four healthy children of similar age and gender were recruited for the control group.

The ADHD group was drug free for at least 48 hours to prevent drug effects on psychometric and pupillometric measurements. The study was approved by the Gülhane Military Faculty of Medicine Local Ethical Committee. Informed consent was obtained from both parents or legal guardian after the standard information about the study conducted and the nature of the procedures was explained.

Procedures and Assessment Measures

A. Demographic Information Form: A semi-structured interview including age, gender, stages of development, educational and medical history of the child and the educational history of the parents.

B. Schedule for Affective Disorders and Schizophrenia for School Age Children-Present and Lifetime Version, Turkish Version (K-SADS-PL-T): The K-SADS-PL-T is a semi-structured interview form that was developed by Kaufman and colleagues (1997) and is capable of generating 32 DSM-III-R and DSM-IV Axis I child psychiatric diagnoses. Diagnoses are scored as definite, probable (greater or equal to 75% of symptom criteria met) or not present (21).

C. The DSM-IV Based Behavior Disorders Screening and Rating Scale: The scale was prepared by Turgay. The validity and reliability of the Turkish Version were done by Ercan and colleagues. The scale has three subscales for ADHD, ODD and conduct disorder (CD) based on the DSM-IV criteria. These subscales have 41 items, including 9 inattention items, 6 hyperactivity items, 3 impulsivity items, 8 items related to ODD, and 15 items related to CD. Informants describe the severity of each symptom as "not at all", "just a little", "pretty much", and "very much". To diagnose ADHD, at least six of the criteria on either the inattention subscale or the hyperactivity-impulsivity subscale should be met; to diagnose ODD at least four of the criteria on the ODD subscale should be met (22).

D. Raven's Progressive Matrices Test (RPMT): The RPMT is a non-verbal multiple choice tool that measures the reasoning (or "meaning-making") component, which is often referred to as general intelligence. The RPMT was originally developed by John C. Raven in 1936. In each test item, the subject is asked to identify the missing element that completes a pattern. Many patterns are presented in the form of 4x4, 3x3, or 2x2 matrices, giving the test its name. The matrices are available in three different forms for participants of different ability: Standard Progressive Matrices, Colored Progressive Matrices and Advanced Progressive Matrices. The Colored Progressive Matrices Test is designed for children aged 5 through 11 years-of-age, the elderly, and mentally and physically impaired individuals. This test contains sets A and B from the standard matrices, with a further set of 12 items inserted between the two, as set AB. Most items are presented

Table 1: Comparison of pupil diameters of study and control groups*

Pupillometric measurements (mm)	ADHD group (n=32)	Control group (n=24)	t	P
Photopic				
right	3.90 ± 0.76	4.01 ± 0.85	0.51	0.61
left	3.85 ± 0.62	4.04 ± 0.85	1.03	0.33
Mesopic				
right	6.80 ± 0.67	6.67 ± 0.76	0.63	0.54
left	6.76 ± 0.67	6.62 ± 0.74	0.70	0.49
Right mesopic-photopic difference	2.96 ± 0.64	2.65 ± 0.89	1.45	0.17
Left mesopic-photopic difference	2.90 ± 0.62	2.57 ±0.92	1.56	0.15

*Expressed as mean ± SD; compared with Student's t test

Table 2: Comparison of pupil diameters of ADHD and ADHD/ODD subgroups*

Pupillometric measurements (mm)	ADHD only (n=19)	ADHD/ODD (n=13)	Z	P
Photopic				
right	3.86 (2.67-6.20)	3.54 (3.33-5.07)	0.41	0.68
left	3.66 (2.68-5.33)	4.11 (2.97-4.84)	1.44	0.15
Mesopic				
right	6.62 (5.18-8.64)	6.94 (6.23-7.52)	1.14	0.25
left	6.72 (5.01-8.01)	6.79 (6.13-7.32)	0.53	0.60
Right mesopic-photopic difference	2.58 (2.04-3.89)	3.10 (2.30-4.06)	1.39	0.16
Left mesopic-photopic difference	2.90 (1.58-3.95)	2.61(1.66-3.96)	0.95	0.34

*Expressed as median (min-max); compared with Mann-Whitney U test

on a colored background to make the test visually stimulating for participants. However the very last few items in set B are presented as black-on-white; in this way, if a subject exceeds the tester's expectations, transition to sets C, D, and E of the standard matrices is eased (23).

E. Pupillometric Measurements: Pupil diameter measurements were performed using the pupillometer incorporated in the NIDEK OPDScan (NIDEK Co Ltd, Gamagori, Japan). It uses an infrared detector to capture an image and provides pupillometry measurements. The OPD-Scan automatically performs three measurements (first under mesopic conditions followed by one scan under photopic conditions) and yields the mean of these three measurements as an output. There is an automatic quality check, which rejects bad measurements. The pupil camera was used to capture images of each eye in a closed and darkened room with the illumination of B0.07 lux in the afternoon (3:00 PM to 5:00 PM) under two natural undilated illumination conditions (mesopic: 10 lux; photopic: 100 lux). For this study, all OPD measurements were performed after 15 min of dark adaptation for each eye. The pupillometric measures are done by an ophthalmologist at the Department of Ophthalmology of GATA (24,25).

STATISTICS

Differences between both groups were determined using Student's t test for normally distributed data and continuous variables and compared with the Mann-Whitney U test for data that was not normally distributed. Data correlations were tested by using Pearson's correlation analysis. The SPSS (Statistical Package for Social Sciences) v.15.0 program was used in all analyses, and the level of significance was accepted as $p<0.05$.

RESULTS

Both the subjects of the study and the control

group were from the middle socioeconomic class. The mean age of the ADHD group was 9.31±1.28 years and that of the controls was 9.71±1.60 years with (p=0.325).

There were no significant statistical differences between the means of the subscale scores of the DSM-IV Based Behavior Disorders Screening and Rating Scale filled out by parents and teachers (p>0.05). These data show that the interpreting ability of the parents agrees with that of the teachers about the ADHD symptoms of the children.

There were no statistically significant differences in photopic and mesopic pupil diameters between the ADHD and healthy control groups (p>0.05, Student t test) (Table 1). There were no correlations between the scale points and the pupillometric data (p>0.05, Pearson correlation analysis).

Thirteen subjects of the study group (40.6%) had ODD comorbidity. The ADHD group with ODD did not differ from the ADHD group without ODD on photopic and mesopic pupil diameters (p>0.05, Mann Whitney U test) (Table 2).

DISCUSSION

In the present study, we found no statistically significant difference on photopic and mesopic pupil diameters between the ADHD and healthy control groups. Moreover, the ADHD subgroup with ODD did not differ from the ADHD subgroup without ODD with respect to the same variables. The previous studies that have evaluated ANS in ADHD mostly used heart rate variability and electrodermal activity (EDA). The studies using the heart rate variability procedure suggests that there is a significant difference in ANS regulation in children with ADHD (15,16). One of these two studies indicated high vagal activity in ADHD (16). The studies using EDA measurement showed decreased electrodermal response to a task relevant stimulus in ADHD (17,18). These findings have suggested that ADHD may be related to decreased sympathetic activity. With regard to the findings of these studies, decreased pupil responses can be anticipated when either increased parasympathetic reactivity or decreased sympathetic activity are taken into account. In spite of that, in our study there were no statistically significant differences on photopic and mesopic pupil diameters between ADHD and healthy control groups.

Although pupillometric assessment had been used in some psychiatric disorders for researching ANS functions (26-29), there are not any studies of ANS functionality in ADHD using pupillometry. There is only one study of children with minimal brain dysfunction that was carried out by Zahn and colleagues (20) that can be indirectly associated with ADHD. In that study decreased pupil dilatation to visual stimulus was found but there were a number of limitations. Even if decreased pupil diameter indicated an ANS imbalance on behalf of sympathetic stimulation, this result should be confirmed by other procedures that evaluate ANS. Contrary to Zahn and colleagues, we didn't find any statistically significant difference on photopic and mesopic pupil diameters between ADHD and healthy control groups.

Previous findings from autonomic stimulation studies have produced contradictory results for ADHD subjects. Although in some of these studies subjects with ADHD had a tendency to show lower autonomic stimulation either during rest or during cognitive or stress tasks (17,30-34), other studies found there were children with ADHD who didn't present decreased autonomic stimulation (35,36). The authors tried to explain the reason of this contradiction as a result of not taking into account comorbidities like ODD and conduct disorder. Herpertz and colleagues (6,37) have suggested that decreased ANS functions may be related to conduct disorder more than ADHD and Raine and colleagues (36) found supporting data. Also Ortiz and colleagues (38) suggested that lower stimulation and decreased autonomic responses are more related to ODD than ADHD. In our study 40% of the ADHD subjects had ODD comorbidity and there were no statistically significant differences on photopic and mesopic pupil diameters between the ADHD subgroup with ODD and the ADHD subgroup without ODD. This result can be interpreted to mean that even comorbidity of ODD does not affect ANS functionality.

It is known that norepinephrine and

acetylcholine are peripheral components of the ANS, but also neurotransmitters of the central nervous system. In addition, the locus coeruleus (LS) has a critical role in the regulation of the ANS beside the hypothalamic-pituitary axis. LS dysfunction has been suggested as an etiological factor for ADHD and psychiatric disorders related with stress and narcolepsy (39). Animal studies aiming to identify neural projections from the forebrain to the kidney, using the virus pseudorabies, have found multi synaptic connections between the LS and subcoerulear structures and the bladder, urethral sphincter and kidney via autonomic (sympathetic and parasympathetic) pathways (40,41). This data indicates that the LS regulates autonomic functions. Therefore one reason for dysfunction of the ANS may originate from a deficiency of the regulatory function of the LS. LS deficits that are assumed to be relevant to ADHD may be the reason for ANS dysregulation which has been identified in previous studies; however, speculation about central nervous system function is difficult since no statistically significant difference in pupil diameters between ADHD and healthy control groups were found in our study.

One of the most interesting features of eye is its reaction to light. Acetylcholine via muscarinic receptors (parasympathetic system) causes contraction of the iris sphincter pupillary muscle and a decrease in pupil diameter. Norepinephrine (sympathetic system), which is secreted from the neuromuscular junction causes mydriasis. Therefore, as a response to a light stimulus pupil diameter size changes are based on the balance of the sympathetic and parasympathetic nervous systems (12). In regard to this, pupillometry has been used occasionally to evaluate ANS functions, but there is no study in the literature using pupillometry for searching ANS functions in ADHD. Our study is the first one in this context and should be accepted as a preliminary study.

In our study we only included children with the combined subtype of ADHD and excluded subjects who had a history of any other psychiatric disorder (except ODD), chronic medical illness or ANS symptoms like excessive fatigue, syncope and dizziness, ophthalmic deficits like refraction error, cornea or macular pathologies, and those were were not within the 25th percentile for the Raven's Colored Progressive Matrices to maintain homogeneity of the sample with respect to ANS functionality. However, our study has some limitations: 1) pupillometry is an indirect method to evaluate the ANS imbalance; therefore, it might be supported by other methods which evaluate ANS functionality, like measuring heart rate variability for 24 hours, skin conductance responses, tilt table test, measurement of urinary catecholamine levels and pseudomotor axon reflex; 2) our findings can only be generalized for only males and for a definite age range; for females and different age ranges there is need for more comprehensive studies; 3) the study examined a limited number of subjects; 4) pupillometric measures reflect a short period of time; therefore, extending the recording time of the pupillometric measures as long as possible might be more helpful for more accurate results; and 5) pupillometry is a procedure which is used for estimating ANS functions by measuring the light reflex based pupil size changes, but doesn't indicate the effects on the ANS and pupil size of cognitive and emotional processes. Therefore pupil diameter measures under the influence of cognitive and emotional tasks should be added. In addition real time pupil diameter measures that are conducted during the daily routine via an apparatus like eye tracking equipment will strengthen these findings.

In conclusion, these findings suggest that males with ADHD show no differences in pupil diameters compared to typically developing children. This might indicate no difference in autonomic nervous system functions measured by pupillometry. However, it is recommended that the results of our study need to be supported by more detailed studies.

References:

1. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. Lancet 2005; 366(9481):237-48.

2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition (Text Revision) (Çev. ed.: E. Köroğlu). Ankara: Hekimler Yayın Birliği; 2000. (Turkish)

3. Garralda ME, Connell J, Taylor DC. Psychophysiological anomalies in children with emotional and conduct disorders. Psychol Med 1991; 21(4):947-57.

4. Boyce WT, Quas J, Alkon A, Smider NA, Essex MJ, Kupfer DJ. Autonomic reactivity and psychopathology in middle childhood. Br J Psychiatry 2001; 179:144-50.

5. Beauchaine TP, Katkin ES, Strassberg Z, Snarr J. Disinhibitory psychopathology in male adolescents: discriminating conduct disorder from attention-deficit/hyperactivity disorder through concurrent assessment of multiple autonomic states. J Abnorm Psychol 2001; 110(4):610-24.

6. Herpertz SC, Mueller B, Wenning B, Qunaibi M, Lichterfeld C, Herpertz- Dahlmann B. Autonomic responses in males with externalizing disorders. J Neural Transm 2003; 110(10):1181-95.

7. Van Goozen SH, Matthys W, Cohen Kettenis PT, Gispen-de Wied C, Wiegant VM, van Engeland H. Salivary cortisol and cardiovascular activity during stress in oppositional-defiant disorder males and normal controls. Biol Psychiatry 1998; 43(7):531-9.

8. Rogeness GA, Cepeda C, Macedo CA, Fischer C, Harris WR. Differences in heart rate and blood pressure in children with conduct disorder, major depression and separation anxiety. Psychiatry Res 1990; 33(2):199-206.

9. Mezzacappa E, Tremblay RE, Kindlon D, Saul JP, Arseneault L, Seguin J, et al. Anxiety, antisocial behavior and heart rate regulation in adolescent males. J Child Psychol Psychiatry 1997; 38(4):457-69.

10. Kawasaki A. Physiology, assessment and disorders of the pupil. Curr Opin Ophthalmol 1999; 10(6):394-400.

11. Piha SJ, Halonen JP. Infrared pupillometry in the assessment of autonomic function. Diabetes Res Clin Pract 1994; 26(1): 61-6.

12. Fotiou F, Fountoulakis KN, Goulas A, Alexopoulos L, Palikaras A. Automated standardized pupillometry with optical method for purposes of clinical practice and research. Clin Physiol 2000; 20(5):336-47.

13. Pena MM, Donaghue KC, Fung AT, Bonney M, Schwingshandl J, Howard NJ, et al. The prospective assessment of autonomic nerve function by pupillometry in adolescents with type 1 diabetes mellitus. Diabet Med 1995; 12(10): 868-73.

14. Bremner F. Pupil evaluation as a test for autonomic disorder. Clin Auton Res 2009; 19(2):88-101.

15. Crowell SE, Beauchaine TP, Gatzke-Kopp L, Sylvers P, Mead H, Chipman-Chacon J. Autonomic correlates of attention-deficit/hyperactivity disorder and oppositional defiant disorder in preschool children. J Abnorm Psychol 2006; 115(1):174-8.

16. Tonhajzerova I, Ondrejka I, Adamik P, Hruby R, Javorka M, Trunkvalterova Z, et al. Changes in the cardiac autonomic regulation in children with attention deficit hyperactivity disorder (ADHD). Indian J Med Res 2009; 130(1):44-50.

17. Shibagaki M, Yamanaka T, Furuya T. Attention state in electrodermal activity during auditory stimulation of children with attention-deficit hyperactivity disorder. Percept Mot Skills 1993; 77(1): 331-8.

18. Zahn TP, Kruesi MJ. Autonomic activity in boys with disruptive behavior disorders. Psychophysiology 1993; 30(6):605-14.

19. Piha SJ, Halonen JP. Infrared pupillometry in the assessment of autonomic function. Diabetes Res Clin Pract 1994; 26(1):61-6.

20. Zahn TP, Little BC, Wender PH. Pupillary and heart rate reactivity in children with minimal brain dysfunction. J Abnorm Child Psychol 1978; 6(1):135-47.

21. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for Affective Disorders and Schizophrenia for Schoolage Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997; 36(7):980-8.

22. Turgay A. Disruptive Behavior Disorders Child and Adolescent Screening and Rating Scales for Children, Adolescent, Parents and Teachers. Toronto, Canada: Integrative Therapy Institute; 1995.

23. Raven JC. Guide to the Standart Proggressive Matrices, London: Lewis HK, 1960.

24. Gavriysky VS. Human pupillary light reflex during and after two-fold Valsalva maneuver. J Auton Nerv Syst 1995; 54(3):247-52.

25. Fotiou F, Fountoulakis KN, Goulas A, Alexopoulos L, Palikaras A. Automated standardized pupillometry with optical method for purposes of clinical practice and research. Clin Physiol 2000; 20(5):336-47.

26. Steinhauer SR, Hakerem G. The pupillary response in cognitive psychophysiology and schizophrenia. Ann NY Acad Sci 1992; 658:182-204.

27. Dundaroz, R, Turkbay T, Erdem U, Congologlu A, Sakallioglu O, Tascilar E. Pupillometric assessment of autonomic nervous system in children with functional enuresis. Int Urol Nephrol 2009; 41(2):231-5.

28. Bakes A, Bradshaw CM, Szabadi E. Attenuation of the pupillary light reflex in anxious patients. Br J Clin Pharmacol 1990; 30(3):377-81.

29. Sokolski KN, DeMet EM. Cholinergic sensitivity predicts severity of mania. Psychiatry Res 2000; 95(3):195-200.

30. Hermens DF, Williams LM, Lazzaro I, Whitmont S, Melkonian D, Gordon E. Sex differences in adult ADHD: a double dissociation in brain activity and autonomic arousal. Biol Psychol 2004; 66(3):221-33.

31. Iaboni F, Douglas VI, Ditto B. Psychophysiological response of ADHD children to reward and extinction. Psychophysiology 1997; 34(1):116-23.

32. Lazzaro I, Gordon E, Li W, Lim CL, Plahn M, Whitmont S. Clarke S, et al. Simultaneous EEG and EDA measures in adolescent attention deficit hyperactivity disorder. Int J Psychophysiol 1999; 34(2):123-34.

33. Satterfield JH, Cantwell DP, Lesser LI, Podosin RL. Physiological studies of the hyperkinetic child. Am J Psychiatry 1972; 128(11):1418-24.

34. Satterfield JH, Dawson ME. Electrodermal correlates of hyperactivity in children. Psychophysiology 1971; 8(2):191-7.

35. Delamater AM, Lahey BB, Drake L. Towards an empirical subclassifiacation of ''learning disabilities'': a psychophysiological comparison of ''hyperactive'' and ''nonhyperactive'' subgroups. J Abnorm Child Psychol 1981; 9(1):65-77.

36. Raine A, Jones F. Attention, autonomic arousal, and personality in behaviorally disordered children. J Abnorm Child Psychol 1987; 15(4):583-99.

37. Herpertz SC, Wenning B, Mueller B, Qunaibi M, Sass H, Herpertz-Dahlmann B. Psychophysiological responses in ADHD boys with and without conduct disorder: implications for adult antisocial behavior. J Am Acad Child Adolesc Psychiatry 2001; 40(10):1222-30.

38. Ortiz J, Raine A. Heart rate level and antisocial behavior in children and adolescents: a meta-analysis. J Am Acad Child Adolesc Psychiatry 2004; 43(2):154-62.

39. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Rev 2003; 42(1):33-84.

40. Marson L. Identification of central nervous system neurons that innervate the bladder body, bladder base, or external urethral sphincter of female rats: a transneuronal tracing study using pseudorabies virus. J Comp Neurol 1997; 389(4):584-602.

41. Sly JD, Colvill L, McKinley JM, Oldfield JB. Identification of neural projections from the forebrain to the kidney, using the virus pseudorabies. J Auton Nerv Syst 1999; 77(2-3):73-82.