Review

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Association between Attention Deficit Hyperactivity Disorder and the Autonomic Nervous System: An Update

Dikkat Eksikliği Hiperaktivite Bozukluğu ile Otonom Sinir Sisteminin İlişkisi: Bir Güncelleme

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ABSTRACT

This article constitutes a review of the research on the relationship between Attention Deficit Hyperactivity Disorder (ADHD) and autonomic nervous system (ANS) functionality. It also explores the possibility of using heart rate variability (HRV) to investigate the link between ADHD and autonomic dysfunction. One line of inquiry that has been the focus of sudies on the pathogensis of ADHD is the dysfunction of the autonomic system. The physiological measurements used to evaluate autonomic dysfunction are concentrated in the cardiovascular system. Databases were searched to identify studies published prior to August 2020. Studies that examined ANS with regard to medication use/treatment were excluded, while those related to ADHD etiopathogenesis were prioritized. In the present article, 52 studies, three of which were systematic reviews and meta-analyses, were evaluated. In general, although the etiopathogenetic association between ADHD and autonomic dysfunction (especially reduced parasympathetic activity) is remarkable, the findings are nonetheless contradictory. Heterogeneity, subtypes, and comorbidities in cases of ADHD appear to complicate the relationship with autonomic dysfunction.

Keywords: Attention Deficit Hyperactivity Disorder, autonomic dysfunciton, heart rate variability, pyschopathology

ÖZ

Bu makale, Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) ile otonom sinir sistemi (OSS) işlevselliği arasındaki ilişki üzerine yapılan araştırmaların bir derlemesini oluşturmaktadır. Ayrıca DEHB ve otonomik işlev bozukluğu arasındaki bağlantıyı araştırmak için kalp hızı değişkenliğini (KHD) kullanma olasılığını ele almaktadır. DEHB'nin patogenezine ilişkin araştırmaların odak noktası olan bir araştırma alanı otonom sistemin işlev bozukluğudur. Otonom disfonksiyonu değerlendirmek için kullanılan fizyolojik ölçümler kardiyovasküler sistemde yoğunlaşmıştır. Ağustos 2020'den önce yayınlanan çalışmaları belirlemek için veri tarandı. OSS'yi ilaç kullanımı/tedavisi açısından inceleyen çalışmalar hariç tutulurken, DEHB etyopatogenezi ile ilgili olanlar önceliklendirildi. . Bu makalede, üçü sistematik derleme ve meta-analiz olan 52 çalışma değerlendirilmiştir. Genel olarak, DEHB ile otonomik disfonksiyon (özellikle azalmış parasempatik aktivite) arasındaki etyopatogenetik ilişki dikkat çekici olsa da, bulgular yine de çelişkilidir. DEHB vakalarında heterojenlik, alt tipler ve komorbiditeler otonomik disfonksiyon ile ilgili yorumları zorlaştırıyor gibi görünmektedir.

Anahtar sözcükler: Dikkat Eksikliği Hiperaktivite Bozukluğu, otonomik işlev bozukluğu, kalp hızı değişkenliği, psikopatoloji

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder emerging in childhood characterized by inattention, hyperactivity, and impulsivity at levels that are incompatible with the child's developmental level (APA 2013). Children with ADHD are easily distracted, hyperactive, and restless, and experience difficulty in paying attention, executing goal-directed behaviors, and suppressing their impulses (Akay and Ercan 2016). On a global scale, ADHD has a prevalence of 5-12% in children and 4.4% in adults (APA 2013).

Although the etiology of ADHD remains unknown, the research supports a multifactorial hypothesis. Recently, attempts have been made to explain the neurobiological basis of ADHD. Over 1800 studies have been performed on the underlying genetics of ADHD, which has a heterogeneous clinical presentation and is a highly heritable psychiatric disorder that damages individuals and their families, thus representing a high cost to society when not properly treated (Banaschewski et al. 2010). The literature on the etiological models of ADHD is very broad, emcompassing functional magnetic resonance imaging (fMRI), magnetic resonance imaging (MRI), and positron emission tomography

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(PET), and has revealed structural and functional differences in ADHD patients (Zametkin et al. 1990, Castellanos et al. 2002, Dickstein et al. 2006, Makris et al. 2006, Seidman et al. 2006, Hart et al. 2013). These differences are more prominent in the forebrain, including the prefrontal cortex.

An important feature of ADHD, with respect to the autonomic nervous system (ANS), is the dysregulation of arousal; in particular, difficulties in regulating arousal when external conditions change may contribute to the behavioral pattern observed in individuals with ADHD. It has recently been argued that ADHD may result from a tonic hypo-aroused state leading to a decrease in alertness and inadequate functioning (such as in screening, selection, and focus), such that hyperactive and impulsive behavior patterns may be considered an autoregulatory strategy to increase stimulation (Silverman 1993). Emotional dysregulation, sleep disorders, and appetite-regulating problems have all been observed in cases of ADHD, suggesting difficulty in regulating arousal levels (Hanć and Cortese 2018, Faraone et al. 2019). Since performance fluctuation is the clinical reflection of difficulties in maintaining an optimal level of alertness, it has been evaluated as a possible marker of difficulty in arousal regulation in ADHD. Brainstem regions that mediate between nervous systems that support cognition and ANS and behavior in cases of ADHD have yet to be studied in detail.

At present, understanding the functioning of ANS is vital to increasing our knowledge about ADHD and its underlying mechanisms, and new treatment strategies should be investigated and developed to improve the clinical pattern associated with ADHD. This review aims to gather studies on the relation between ADHD and ANS functionality. In addition, it aims to create an idea in the mind of the reader about the relationship between ADHD and autonomic dysfunction and heart rate variability measurement method.

Autonomic Nervous System

The autonomic nervous system is the part of the peripheral nervous system that helps control arterial blood pressure, sweating, body temperature, motility and secretions of the digestive system, bladder emptying, and many other visceral functions (Guyton et al. 2003). One of the most striking features of the autonomic nervous system is its ability to rapidly and powerfully alter visceral functions. The ANS is activated primarily by several centers located in the hypothalamus, brainstem, and spinal cord. In addition, signals are transmitted to lower centers by the cerebral cortex (particularly the limbic cortex), thereby affecting autonomic control. Autonomic efferent signals are transmitted to various regions of the body by two main subsections, the sympathetic and parasympathetic nervous systems; many regions of the body and visceral functions are under the control predominantly of one of these two systems. The sympathetic and parasympathetic systems are constantly active, and their base levels of activity are known as the sympathetic and parasympathetic tones. The former is found in systemic arterioles while the latter is located in the intestines. While parasympathetic activity (the parasympathetic tone) is dominant in the heart at rest, sympathetic activity increases with effort (Guyton et al. 2003). Many of the parasympathetic nerve fibers and almost all of the sympathetic fibers form sac-like enlargements called varicosities as they pass through the organs they innervate. These varicosities contain numerous mitochondria that produce adenosine triphosphate, providing the energy required for the synthesis of acetylcholine (ACh) and norepinephrine (NE). When an action potential propagates to axon termination, the depolarization process increases the permeability of the fiber membrane to Ca^{2+} ions, which cause nerve endings/varicosities to discharge their contents. ACh synthesis occurs in the axoplasm, with the exception of most vesicles. A few seconds after ACh is secreted from the nerve endings, it is broken down into acetate and choline by the enzyme acetylcholinesterase, which is bound to collagen and glycosaminoglycans in the local connective tissue. Choline then undergoes reuptake into the nerve endings. Levodopa (L-DOPA) is produced from L-tyrosine and is subsequently converted into dopamine, which is transported into the vesicles. NE is synthesized from dopamine in the vesicles and is taken back up into the nerve terminals by active transport (80% is removed thusly), passing into the blood and surrounding bodily fluids, and then degraded by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (Guyton et al. 2003).

Concept of the “Central Autonomic Network”

Signals from the hypothalamus may alter the activities of all autonomic control centers in the brainstem. Therefore, autonomic centers in the brainstem serve as an intermediate station for control activities that originate in the higher brain centers (Guyton et al. 2003, Taner 2013). The brain regions regulating the autonomic functions of organs and systems are called *the central autonomic network*. This includes the insular and medial prefrontal cortices, central nucleus of the amygdala, bed nucleus of the stria terminalis, hypothalamus, midbrain periaqueductal gray, parabrachial pontine region, nucleus tractus solitarius, medullary reticular formation, and the ventrolateral medulla (Thayer and Lane 2009).

The caudal ventrolateral medulla (CVLM) and nucleus tractus solitarius (NTS), located in the brainstem and parts of the central autonomic network, as well as the nucleus ambiguus (NA) and dorsal vagal nucleus (DVN) stimulate the vagus nerve. These brain regions are also collectively known as *the cardioinhibitory center*. The rostral ventrolateral medulla (RVLM) in the brainstem contains the sympathoexcitatory neurons and produces sympathetic effects on the heart by stimulating sympathetic fibers in the intermediolateral column, also known as *the cardioaccelerator center*. The central nucleus of the amygdala increases cardiac sympathetic activity (Saha 2005). However, the anterior cingulate and insular and prefrontal cortices tonically inhibit the amygdala, providing cardiac autonomic balance. These regions play an indirect role in the maintenance of vagal functions (Thayer and Lane 2009).

On the basis of complex mechanisms in the central autonomic network, sympathetic effects are associated with the activity of subcortical structures (e.g., amygdala, hypothalamus), while parasympathetic effects are associated with the activity of cortical structures (prefrontal, insular and cingulate cortices). Autonomic dysfunction develops due to the pathologies in these brain centers where autonomic functions are regulated.

Studies utilizing brain imaging methods showed that some brain regions (the anterior cingulate cortex, dorsolateral prefrontal cortex, inferior frontal cortex, and subcortical structures) which execute autonomic functions and are parts of the central autonomic network, were affected by ADHD (Zametkin et al. 1990, Castellanos et al. 2002, Dickstein et al. 2006, Makris et al. 2006, Seidman et al. 2006, Hart et al. 2013). Therefore, ADHD is considered a disease of autonomic dysfunction (Guideri et al. 1999, Ming et al. 2005, Bienias et al. 2017).

Polyvagal Theory

Benarroch (1993) stated that the central autonomic network regulated the relationship between the brain and the heart. Porges (1995) reported that brain functions such as attention maintenance, task management, and emotional regulation were associated with cardiac vagal control based on the principles of the polyvagal theory.

Polyvagal theory (Porges 1995) maintains that the parasympathetic nervous system manages the arrangement of facial and head muscle movements necessary for social communication. Therefore, maintaining the vagal brake (less respiratory sinus arrhythmia (RSA) suppression) to achieve a calmer visceral state visceral promotes social engagement. This theory proposes two branches of the vagus nerve: the smart vagus and vegetative vagus. The former modulates sympathetic response in emotional regulation and social affiliative behavior and is unique to mammals. It inhibits sympathetic input that accelerates the heart rate in situations consistent with constant attention and/or social engagement and withdraws its inhibitory effect on the sympathetic nervous system when the flight-or-fight response is required (Beauchaine 2001, Beauchaine et al. 2007, Hastings et al. 2008, Whedon et al. 2018). In contrast, the vegetative vagus plays a vital role in the primal survival strategies of primitive vertebrates, reptiles, and amphibians, which display a freeze response to threat. According to polyvagal theory, the functional defect of the smart vagus increases the risk of emotional lability accompanying psychopathology. In individuals with ADHD, the functions of the smart vagus (e.g., attention and emotional regulation) are impaired (Rukmani et al. 2016). This suggests the possibility of a functional defect of the vagus nerve in cases of ADHD. NE dysregulation and prefrontal hypofunction seen in ADHD and the potential functional defect of the smart vagus indicate the possibility of autonomic dysfunction (Rukmani et al. 2016).

Polyvagal theory has contributed special insights into the role of emotion dysregulation in psychopathology and into the development of aberrant patterns of autonomic nervous system functioning in numerous clinical syndromes (both the internalizing and externalizing spectra). It is hoped that this theory will continue to improve our understanding of psychopathology and its development. Polyvagal Theory offers an approach to autonomic regulation as part of the mind/body connection. This approach has been studied in various contexts with proven efficacy as a means of self-regulation, positively affecting physiological and emotional outcomes in various settings. Self-regulation promotes better, more lucid thinking and improved problem-solving abilities and communication as a means to manage distress and anxiety (Bailey et al. 2020).

Methods used in the evaluation of autonomic nervous system dysfunction have included *the measurement of changes in blood pressure and heart rate, the measurement of electrocardiographic changes* (prolongation of the QT-QTc interval due to changes in the durations of depolarization and repolarization, atrial and ventricular arrhythmias, tachycardia-bradycardia and ventricular hypertrophy findings (Maeda et al. 2014, Ng 2016, Agarwal et al. 2017)), *the measurement of respiratory sinus arrhythmia (RSA), heart rate variability (HRV) and the pre-ejection period* (PEP) (Guideri et al. 1999, Axelrod 2002, Ming et al. 2005, Trang et al. 2005, Maeda et al. 2014, Ng 2016, Goodman 2016, Agarwal et al. 2017, Bienias et al. 2017), the *measurement of skin conductance* (Herpertz et al. 2001, El-Sheikh et al. 2013, Beauchaine et al. 2015), and *the measurement of pupillary diameter by pupillometry* (Kara et al. 2013). Autonomic dysfunction also affects the arterial vascular system due to high blood pressure, leading to arterial stiffness (Kim et al. 2017). Although these autonomic indicators are measured during rest, reactivity measures such as HRV and RSA reactivities, which evaluate responses to a stressor, are thought to represent a valid means of monitory autonomic function.

Holter Monitoring: Heart Rate Variability (HRV)

Heart Rate Variability (HRV) expresses the fluctuations in heart rate around an average rate. In healthy subjects, the heart rate is neither strictly regular nor periodic. HRV, which is also a biomarker of cardiac vagal control and a non-invasive electrocardiographic (ECG) method, can be measured using long-term Holter recordings or short-term ECG recordings. A decrease in HRV is indicative of increased sympathetic tone and decreased vagal tone. It has been suggested that HRV constitutes a reliable test to confirm a finding of dysautonomia. Previous studies have reported a decrease in HRV in individuals with autonomic dysfunction and that this decrease was associated with mortality risk (Thomas et al. 2011, Ward et al. 2015, Akay and Ercan 2016).

Measurement of HRV is performed by means of two main parameters. In **Time Measurements (Time Domain),** calculated according to an analysis of the intervals between consecutıve beats in ECG recordings, the interval between two consecutive normal beats leaving the sinoatrial (SA) node (referred to as NN intervals) is evaluated. The most commonly used indices are mean HR, standard deviation of NN intervals (SDNN), standard deviation of the average NN intervals for each 5 min segment (SDANN), percentage of successive beat-to-beat (RR) intervals that differ by more than 50 ms (pNN50), and root mean square of successive RR interval differences of a 24 h HRV recording (rMSSD). While mean heart rate and SDNN reflect 24-hour heart rate variability, rMSSD and pNN50 reflect the parasympathetic component of autonomic tone. In the other main parameter, **Frequency Measurements (Frequency**

Domain), heart rate signals are separated based on their frequency and intensity. High frequency (HF), low frequency (LF), medium frequency (MF), ultra low frequency (ULF), and very low frequency (VLF) parameters are evaluated. With regard to autonomic tone, LF reflects the sympathetic and HF reflects the parasympathetic component; thus, the LF/HF ratio reflects the sympathetic/parasympathetic balance (Silverman 1993).

Respiratory Sinus Arrhythmia (RSA)

RSA is defined as high frequency rhythmic variability in the heart rate occurring within the respiratory cycle, evaluated as a non-invasive parasympathetic cardiac effect index. The change that occurs in response to environmental factors is termed RSA reactivity. The suppression of RSA (RSA withdrawal) is considered a sign of self-regulation process during challenging tasks. The functional relationship between behavioral compatibility (compliance) and RSA suppression has been discussed in the literature (Wang et al. 2013).

Cardiac Pre-Ejection Period (PEP)

PEP is evaluated as an index of sympathetic control of the heart via the beta-adrenergic system, represented by the time between the depolarization of the left ventrical and the onset of the ejection of blood into the aorta. Lower PEP values have been associated with increased sympathetic activation (Beauchaine et al. 2001, Musser et al. 2011).

Studies on the Autonomic Nervous System and ADHD

Databases (including PsycInfo, ASSIA, Medline, Embase, Scopus, and Google scholar) were thoroughly searched to identify relevant published studies. Following the removal of duplicates, an further search and preliminary analysis were conducted of the medical subject headings (MeSH) and keywords related to ADHD contained in the abstract and title. The search strategy consisted of a combination of keywords (e.g., 'ADHD', 'autonomic dysfunction', 'heart rate variability', 'pyschopathology', 'respiratory sinus arrhythmia', 'pre-ejection period', 'skin conductance level', 'RSA withdrawal'). The search was performed in August of 2020; date and language limits were not applied.

Most of the studies in the literature investigating cardiac influences in ADHD patients have been aimed at examining the side effects of treatment (Newcorn et al. 2008, Bélanger et al. 2009, Hammerness et al. 2009, Negrao et al. 2009, Sert et al. 2012, Mick et al. 2013, Kelly et al. 2014). There are a limited number of studies comparing children with ADHD and healthy controls wth respect to cardiac effects related to ADHD (Castellanos et al. 2002, Makris et al. 2006, Seidman et al. 2006, Millichap 2008, Wilens 2008, Banaschewski et al. 2010, Cortese 2012, Thapar et al. 2013). Few studies have investigated whether ADHD-related cardiac effects differ according to ADHD subtypes (Kim et al. 2015, Griffiths et al. 2017). In this review, studies that examined the ANS with regard to medication use/treatment were not included, while those relating to ADHD etiopathogenesis have been prioritized.

Fifty-two studies, three of which represent meta-analysis/systematic review studies, were evaluated with a focus on the latest findings regarding the relationship between autonomic nervous system functioning and ADHD. The research presented herein is comprised mainly of HRV studies, while also examining markers such as blood pressure, skin conductivity level, PEP, and RSA. The most recent meta-analysis study on this subject is that of Robe et al. (2019).

Studies Evaluating Blood Pressure

One study investigating blood pressure in ADHD patients found no significant difference between patients (whether or not treated with stimulants) compared to healthy controls (Hailpern et al. 2014). Meyer et al. (2017) observed that both systolic and diastolic blood pressures were lower in subjects with ADHD than in healthy controls, and determined this to be associated with vitamin D deficiency in the former. Psychostimulants, frequently used in the treatment of ADHD, may increase blood pressure due to their catecholaminergic effects (Herpertz et al. 2001, Beauchaine et al. 2015), however, those diagnosed with ADHD had significantly lower mean blood pressure readings than the controls. Data linking reduced blood pressure to the diagnosis of ADHD cannot be explained by the pharmacological effects of medication. Fuemmeler et al. (2011) found that both systolic and diastolic blood pressures were higher in patients with ADHD, suggesting that elevated blood pressure in ADHD patients may be associated with obesity as their body mass index was higher compared to healthy controls. In a cross-sectional study, mean systolic and diastolic blood pressure values were statistically considerably higher in the ADHD group receiving MPH than in the ADHD group not receiving MPH and the control group (Karpuz et al. 2017).

Studies Evaluating Heart Rate

While most studies on ADHD patients found that their heart rate was higher (Imeraj et al. 2011, Buchhorn et al. 2012, Tonhajzerová et al. 2014), others reported no significant difference (Altay 2018). One study determined that the mean heart rate was significantly lower due to increased parasympathetic activity in the ADHD group not receiving medication than in the control group, and that this difference disappeared following stimulant treatment (Negrao et al. 2011). Tonhajzerova et al. (2014) evaluated heart rates in the supine position and standing up from the supine position (orthostatic stress) in healthy children and children with ADHD in order to investigate autonomic functions in ADHD patients. They found that ADHD patients showed smaller changes in orthostatic stress and heart rate.

Studies with ECG

There has been only a limited number of studies evaluating ECG in ADHD patients not receiving medication (Mahle et al. 2009, Nahshoni et al. 2009, Thomas et al. 2011, Shahani et al. 2014). Mahle et al. (2009) cross-sectionally evaluated the ECG recordings of 1470 ADHD patients. They determined that the most common pathological ECG findings were left ventricular hypertrophy (28.2%), right ventricular hypertrophy (20.5%), and QT interval prolongation (18.5%). A similar study was conducted by Thomas et al. (2011), in which 372 ADHD patients underwent ECG screening before drug treatment. Pathological ECG findings, including QTc prolongation, ventricular hypertrophy, and atrial/ventricular premature beats, were detected in 24 patients. Shahani et al. (2014) cross-sectionally evaluated 341 ADHD patients not taking medication, detecting pathological ECG findings in 17 of them. The most common pathological ECG findings were right ventricular hypertrophy, left ventricular hypertrophy, QTc prolongation, atrial dilation, abnormal axis, and premature atrial beats. Nahshoni et al. (2009) showed that early repolarization (an elevation of the QRS-ST-segment junction) existed on ECG recordings of patients with ADHD, but observed no notable difference between QT and QTc. All of these studies have emphasized that performing ECG assessments prior to drug treatment is important for detecting long QT syndrome, hypertrophic cardiomyopathy, Wolff-Parkinson-White syndrome, and arrhythmias in ADHD patients. In a study involving 40 children receiving atomoxetine for ADHD, heart rate, mean systolic and diastolic blood pressure, QT dispersion, QTc interval, and left ventricular systolic function were recorded at baseline and five weeks following treatment with atomoxetine. Short-term atomoxetine treatment was shown not to lead to clinically significant changes in these functions (Sert et al. 2012). In a study by Altay et al. (2018), ECG characteristics of drug naive ADHD patients were compared to those of a control group. The researchers found that high QTd, QTc, max Tp-e, and Tp-ed intervals in ADHD patients may be indicators of cardiac arrhythmia.

Studies Evaluating HRV

Numerous studies have investigated HRV in ADHD patients (Crowell et al. 2006, Luman et al. 2007, Lackschewitz et al. 2008, Buchhorn et al. 2012, Oliver et al. 2012, Wang et al. 2013, de Carvalho et al. 2014, Karalunas et al. 2014, Kim et al. 2015, Rukmani et al. 2016, Koenig et al. 2017). In a study in which the Korean ADHD Rating Scale (K-ARS) rating and HRV measurements were repeated before and after 12 weeks of stimulant treatment, there were significant correlations between certain HRV parameters and the K-ARS inattention score. HF and rMSSD, both associated with parasympathetic vagal tone, were significantly lower compared to baseline values, suggesting that parasympathetic predominance in ADHD may be changed when patients are treated with methylphenidate. In addition, the researchers concluded that HRV parameters can be used as psychophysiological markers in the treatment of ADHD (Kim et al. 2015).

In a study examining autonomic activity and autonomic reactivity by evaluating heart rate variability during a continuous performance test (TOVA) and at rest in a group of unmedicated children with ADHD compared to healthy controls, the LF/HF ratio was higher under both circumstances in boys with ADHD. A higher LF/HF ratio during the continuous performance test was correlated with poor performance for both groups (Griffiths et al. 2017). Since the LF/HF ratio reflects the sympathetic/parasympathetic activity ratio, a difference in favor of sympathetic activity in individuals with ADHD would be expected; on a related note, a correlation was found between a higher sympathetic/parasympathetic activity ratio and a low level of sustainable attention. In another study comparing HRV measurements in 77 children during a continuous performance test, no significant relationship was observed between attention scores and HRV parameters. However, good performance during test was associated with a higher vagal tone (Eisenberg 2011).

Buchhorn et al. (2012) conducted a study on ADHD children treated with methylphenidate (MPH), children with ADHD not receiving MPH, and healthy controls. They found that mean heart rates were significantly higher in the ADHD children both with and without MPH treatment, while pNN50 and rMSSD were highest in controls, middle in ADHD children with MPH, and lowest in ADHD children without MPH. These findings indicated a lower vagal tone manifested by significantly higher heart rates and reduced HRV in unmedicated ADHD children. Treatment with MPH thus improved the test results for ADHD children, offering a potential cardioprotective effect. Rukmani et al. (2016) reported that significantly decreased pNN50, SDNN, and rMSSD values in drug-naive ADHD patients in study involving 20 patients employing short-term HRV assessment. A decrease in the parasympathetic activity in patients with ADHD was also observed. Wang et al. (2013) determined that HRV was not affected by gender in ADHD patients. Various studies have shown that effects on the brain vary according to ADHD subtypes in patients with ADHD (Castellanos 1997, Schrimsher et al. 2002, Solanto et al. 2009, Semrud-Clikeman et al. 2014, Ercan et al. 2016, Park et al. 2016, Qureshi et al. 2016). There are only two studies in the literature on the question of whether these different effects lead to a difference in autonomic influence (Kim et al. 2015, Griffiths et al. 2017). Kim et al. (2015) compared HRV parameters between ADHD patients with inattentive type and those with hyperactive-impulsive type, finding that HF and parasympathetic activity were lower in the latter group. Griffiths et al. (2017) reported that, with regard to HRV parameters, there were no significant difference between patients with inattentive type and those with combined type ADHD.

In their study involving 56 children with ADHD and controls, Bunford et al. (2017) focused on emotion regulation and autonomic nervous system flexibility in their study involving, examining the correspondence between HRV and parent-reported emotional dysregulation. Baseline HRV recordings were taken from participants while sitting and watching two short movies for 5 minutes. The results indicated that parent-reported emotion regulation was associated with HRV and that this index was predicted by HRV in addition to ADHD. Children with lower HRV values exhibited higher levels of parent-reported emotion dysregulation.

In a case-control study evaluating HRV parameters using Holter monitors, in which ADHD patients were classified into mild and severe groups based on the clinical global assessment scale for ADHD, no significant difference was found between the ADHD and control groups in terms of HRV parameters (Yüksel and Özcan 2018). The results showed that as the severity of ADHD increased, autonomic nervous system dysfunction also increased. With the knowledge that pNN50 and minSPH values reflect parasympathetic activity in the heart, the researchers concluded that parasympathetic tone was reduced in the severe ADHD group compared to the control group. In another study, SDNN and rMSSD were lower in both ADHD groups (untreated and treated with methylphenidate) than in the control group but were lowest (to a stasticially significant degree) in the methylphenidate group. LF was observed at higher levels in both ADHD groups than in the control group but was significantly higher in the methylphenidate group than in the latter. Children with ADHD displayed low parasympathetic activity, indicating autonomic dysfunction; this reduced level was pronounced in patients receiving methylphenidate (Karpuz et al. 2017).

Studies Evaluating PEP and RSA

In a study by Beauchaine et al. (2013), RSA and PEP (indicators of cardiac parasympathetic and cardiac sympathetic activity, respectively) were measured both in response to behavioral challenges and at rest, prior to participants and their parents completing one of two versions of the Incredible Years parent and child interventions. PEP and RSA values were averaged across 30-sec periods under different conditions (e.g., baseline, block building, reward task). Reactivity was computed by subtracting baseline averages from block building and reward task averages. Children who exhibited lengthened cardiac PEP at rest and reduced PEP reactivity to incentives scored higher on measures of aggression and conduct problems both before and after treatment. However children who exhibited lower baseline RSA and greater RSA withdrawal had lower scores on prosocial behavior both prior to and following treatment (RSA withdrawal = RSA Reactivity = task RSA – baseline RSA). Finally, children who exhibited greater RSA withdrawal had lower scores on emotion regulation. In other words, increased sympathetic activity was correlated with aggression and conduct problems, while decreased parasympathetic activity was correlated with lower emotion regulation and lower prosocial behavior scores.

In a study investigating the physiological mechanism of emotion regulation in ADHD, RSA and PEP reactivity were examined using four emotional tasks in ADHD and control groups. Both groups showed strong task-response changes in RSA. However, a pattern of elevated parasympathetic activity (RSA) was observed under all task conditions compared to the baseline in children with ADHD. With respect to sympathetic activity (PEP), no differences were observed difference between the groups. The researchers concluded that abnormal parasympathetic mechanisms involved in emotion regulation are associated with ADHD in childhood (Musser et al. 2011). In another study, children with ADHD were divided into two groups, those with typical and those with low prosocial behavior, and compared with a control group. RSA and PEP were evaluated to infer autonomic nervous system functioning during emotional induction suppression tasks. In addition to being clinically heterogeneous, the researchers emphasized that ADHD is also heterogeneous with regard to physiological indices of the autonomic nervous system (Musser et al. 2013). Ward et al. (2015) worked with ADHD and control groups analyzing cardiac-derived indices of the parasympathetic reactivity (RSA) baseline and during short-term memory (STM) storage and rehearsal tasks. The researchers determined that RSA reactivity moderated the relationship between STM and ADHD and that variations in parasympathetic reactivity may help explain neuropsychological heterogeneity in ADHD.

Studies Evaluating a Combination of PEP/RSA Values, Electrodermal Activity (EDA), Carotid Artery Stiffness Index, or Evaluating EDA Only

ADHD and oppositional defiant discorder (ODD) symptoms, internalizing problems, parent-rated emotion regulation and physiological reactivity were evalueted in a sample of 61 children, with and without clinical elevations in ADHD symptoms (McQuade and Breaux 2017). Participants taking stimulant medication refrained from taking their medication only on the day of the assessment. In the results obtained cross-sectionally, ADHD symptoms were associated with higher emotional negativity/lability and with blunted RSAwithdrawal in response to social rejection. No similar effects were observed in response to other non-social tasks. Internalizing problems were found to be associated with poor emotion regulation and increased skin conductance level activity in response to social rejection. In this study, high rates of negative and labile emotional reactions in youths with elevated ADHD symptoms were understood to result, in part, from a failure to exhibit adaptive RSA withdrawal in response to social challenges, such failure being an indicator of parasympathetic system dominance. However, the expected situation in challenging tasks is parasymphatic nervous system withdrawal and increasing sympathetic nervous system activity (McQuade and Breaux 2017). In a study investigating the possibility that electrodermal activity (EDA) may constitute a biological determinant of treatment response in ADHD, non-specific fluctuations (NSFs) in skin conductance indicating sympathetic nervous system activity were measured before and after behavioral intervention in preschool-age ADHD and control groups. No significant difference was found in NSFs between the two groups prior to treatment, indicating no difference in sympathetic activity between the two groups. However, fewer pretest NSFs predicted worse treatment response in ADHD patients, leading the researchers to conclude that preschool children with ADHD who exhibited lower EDA were more resistant to treatment (Beauchaine et al. 2015). Furthermore, in the group with ADHD, low sympathetic tone was associated with resistance to behavioral intervention therapy. In a study by Beauchaine et al. (2001), electrodermal response and cardiac PEP/RSA measurements for ADHD, ADHD/DB and control groups were obtained at rest, during the performance of a repetitive motor task, and while watching a video about a peer conflict. Participants with ADHD and ADHD/DB displayed lower electrodermal responses compared to the controls and reduced sympathetic activity. The ADHD/DB group was differentiated from the ADHD and control groups through PEP and from the control group through RSA. A study conducted by Kelly et al. (2014) in children with ADHD receiving stimulant treatment reported an increase in the carotid artery stiffness index. Children and adolescents diagnosed with ADHD treated with stimulants and their siblings without ADHD were included in this cross-sectional study. The participants with ADHD exhibited signs of altered cardiac autonomic function, characterized by increased sympathetic tone and/or reduced parasympathetic tone, and showed evidence of arterial stiffening. The researchers noted the effect on cardiovascular health related to elevated sympathetic

Table 1. Characteristics of studies assessing heart rate variability and attention-deficit hyperactivity disorder arranged by year of publication

Study	Population characteristics	Diagnostics	Exclusionary criteria	Outcomes measured	Findings
Yüksel et al. (2018)	51 ADHD (new diagnosis, untreated) and 51 healthy controls, 8-11 years	DSM-IV, K-SADS, CPRS-L, CGI-ADHD Severity Scale	chronic medical illnesses (such as neurological and/or cardiologic diseases), diffuse developmental disorders, intellectual disability, psychotic disorder, using drugs or substances affecting sympathetic-parasympathetic nervous system activity	24-h Holter recording, HRV	pNN50 and minSPH values were lower and maxHRH and mean HR values were higher in severe ADHD group. As the severity of ADHD increased, ANS dysfunction became more pronounced.
Karpuz et al. (2017)	99 ADHD (untreated, new diagnosis) and 100 ADHD (MPH-treated for last three months) and 125 healthy controls, 7-14 years	DSM-V	not taking medication for more than two consecutive days, cardiovascular, pulmonary and/or endocrine disorders, using drugs affecting the sympathetic parasympathetic nervous system activity, psychotic disorder, autistic disorder, intellectual disability	ECG recording of 200 heartbeats in the supine position, systolic and diastolic blood pressure, mean heart rate, HRV	Mean systolic and diastolic blood pressure were found to be statistically significantly higher in the MPH group than in the other groups. Mean heart rate was highest in the MPH-treated group. SDNN and RMSSD were lower and LF values were higher in MPH group than in the control group. Parasympathetic activity was lower in children with ADHD, this was more marked in patients on methylphenidate.
Griffiths et al. (2017)	229 ADHD (stimulants 48 h washout) and 244 controls, 6-19 years	DSM-IV, CPRS-L	medical condition that might interfere with assessments; heavy alcohol, drug, caffeine use; inability to comprehend and follow instructions	during rest and sustained attention tasks (CPT) RMSSD, LF, HF, LF/HF	No group differences in LF, HF, RMSSD during sustained attention tasks. No differences in degree of reactivity between groups. LF/HF however was higher in ADHD during both rest and sustained attention conditions.
Bunford et al. (2016)	48 with ADHD and 56 without (resembling a healthy control sample), 8-10 years	P-ChIPS, DBD, two clinical psychologists, IRS, ERC	pervasive developmental disorder, severe hearing/visual impairment, and taking psychiatric medication other than stimulants to treat ADHD	resting HRV 5 min, RMSSD	Index of parent-reported emotion regulation was associated with HRV; this index was predicted by HRV above and beyond ADHD.
Rukmani et al. (2016)	10 drug-naive ADHD and 10 controls, 7-12 years	DSM-IV, child and adolescent psychiatrist	comorbid psychiatric/neurological/medical disorders	short-term ECG	Reduced SDNN, RMSSD, pNN50, LF, HF in ADHD compared to control group. LF/HF ratio significantly higher in ADHD group compared to controls.
Kim et al. (2015)	37 participants with ADHD initially drug free who completed the 12-week treatment and HRV measurements, 6-12 years	K-ARS, DSM-IVTR	medical problems requiring special attention, such as cardiovascular disorders, learning disabilities or intellectual disability, psychiatric comorbidities	short-term ECG recording, SDNN, RMSSD, VLF, LF, HF and LF/HF	HF and RMSSD showed significant decreases from baseline to endpoint.

Table 1. Continued

Study	Population characteristics	Diagnostics	Exclusionary criteria	Outcomes measured	Findings
Carvalho et al. (2014)	28 ADHD and 28 controls, 9-11 years	DSM-IV-R	congenital anomalies, central nervous system malformations, metabolic disorders, taking medication that influences cardiac autonomic modulation (eg, methylphinedite)	RMSSD, pNN50, SDNN, LF, HF, LF/HF	Indices which indicate parasympathetic activity were higher in children with ADHD.
Wang et al. (2013)	88 preschool-age children	SNAP-IV	a history of congenital heart disease, neuropathy, cardiac arrhythmia, other cardiovascular diseases, taking any medication within the previous week	the short-term ECG, VLF, LF, HF and LF/HF	The scores for inattention, hyperactivity/impulsivity and oppositional defiant disorder were negatively associated with LF and LF/HF.
Buchhorn et al. (2012)	31 ADHD (12 unmedicated) and 19 controls, 10.5 ± 2.2 years	Child and adolescent psychiatrist	cardiac complications, respiratory disease	24 h Holter ECG recording, HRV, HR	Children with ADHD had higher HR than controls regardless of medication. pNN50 and rMSSD were lowest in ADHD children without MPH, middle in ADHD children with MPH, and highest in controls. No significant difference in SDNN. Results suggested decreased vagal tone with diminished HRV and higher HRs in unmedicated ADHD children.
Eisenberg et al. (2011)	77 subjects suspected of having attention difficulties, 7-14 years	Conners		ECG baseline and during a Continuous Performance Test (TOVA test), HRV	No individual correlations were found between attention scores and HRV. Good performers had a higher "vagal" tone than poor performers.
Negrao et al. (2011)	19 ADHD (stimulant-free and during use stimulants) and 18 controls, 6-15 years	DSM-IV-R, psychiatrist	comorbidities, medication other than methylphenidate, malnourished children, intellectually disabled children, those unable to understand and give informed consent	baseline and during focused attention SDNN, RMSSD, LF, HF, LF/HF	Stimulant-free children with ADHD showed parasympathetic overarousal, methylphenidate shifted the autonomic balance of children with ADHD towards normal levels. No group differences in HRV reductions during sustained attention.
Tonhajzerova et al. (2009)	20 ADHD (medication-naive) and 20 controls, 8-12 years	DSM-IV-TR, child psychiatrist	psychopharmacological treatment, smoking, hypertension, diabetes mellitus, obesity, underweight, other diseases	short-term ECG in a supine position and during postural change from lying to standing (orthostasis) RMSSD, LF, HF, LF/HF	RMSSD, HF-HRV, significantly lower in children with ADHD.

ADHD = Attention Deficit/Hyperactivity Disorder; KSADS-E = Kiddie Schedule for Affective Disorders and Schizophrenia; CPRS-L = Conner's Parent Rating Scale Long Version; CGI = Clinical Global Impressions; ECG = Electrocardiogram; HRV = Heart Rate Variability; DSM = Diagnostic and Istatistical Manual of Mental Disorders; HF = High Frequency; LF = Low Frequency; RMSSD = Root Mean Square of Successive Rhythm to Rhythm Differences; SDNN = Standard Deviation of Normal to Normal Beats; pNN50 = Percentage of Adjacent RR or NN Intervals That Differ by More Than 50 Milliseconds; minSPH = minimum Spectral Power per Hour; maxHRH = maximum 1-Hour Heart Rate Holter; HR = Heart Rate; ANS = Autonomic Nervous System; P-ChIPS = Children's Interview for Psychiatric Syndromes-Parent Version; DBD = Disruptive Behavior Disorders Rating Scale; IRS = Impairment Rating Scale-Parent and Teacher Versions; ERC = Emotion Regulation Checklist ; K-ARS = Korean ADHD Rating Scale; SNAP-IV = The Swanson, Nolan and Pelham-IV Rating Scale

Table 2. Characteristics of meta-analysis/systematic review studies assessing cardiac vagal control and attention-deficit hyperactivity disorder

Study	Population characteristics of studies evaluated	Outcomes measured	Findings
Robe et al. 2019	13 studies, 869 ADHD and 909 healthy controls	during the task, HRV, RSA	ADHD patients had reduced vagally mediated HRV.
Koenig et al. 2016	8 studies, 317 ADHD and 270 healthy controls	during resting state, short-term measurement of HRV	No significant effect on individuals with ADHD compared to healthy controls.
Rash et al. 2012	6 studies, 155 ADHD and 160 controls	24 h holter ECG recording and short-term measurement of HRV, PEP, RSA	Children with unmedicated ADHD had lower levels of CVC. Children with ADHD experienced reduced CVC reactivity during tasks.

ADHD = Attention Deficit/Hyperactivity Disorder; ECG = Electrocardiogram; HRV = Heart Rate Variability; RSA = Respiratory Sinus Arrhythmia; PEP = Pre-Ejection Period; CVC = Cardiac Vagal Control

activity associated with stimulant treatment. This represents a promising method of evaluating sympathetic activation.

In a recent study, skin conductance level and non-specific fluctuations were measured during four different resting-state and cognitive conditions. Lower arousal was observed in individuals with ADHD only while undertaking a slow, low-demanding task, while more fluctuating arousal was observed towards the end of the assessment. Both inattentive and hyperactive impulsive symptoms were associated with arousal levels and fluctuations, independently from ODD/CD. Under-arousal and fluctuating arousal were both determined to be context-specific rather than stable impairments in ADHD (du Rietz et al. 2018).

The authors of another article aimed to summarize the latest findings in the neurobiology of ADHD. They noted that pupillometric evaluation and eye-tracking can be used to assess the functioning of both branches of the autonomic nervous system and that certain parameters of pupil responsivity may represent a useful tool for diagnosis and treatment. Although there have been studies on this topic examining autonomic regulation/dysregulation based on HRV and EDA, there is a dearth of studies utilizing the measurement of pupil diameter, which may constitute a promising method of assessing the autonomic nervous system (Sekaninova et al. 2019).

Meta-Analysis and Systematic Review Studies

Rash and Aguirre-Camacho (2012) performed a systematic review of six studies that met their inclusion criteria investigating the relationship between cardiac vagal control (CVC) and ADHD without comorbidities. All of the studies assessed healthy controls together with children diagnosed with ADHD. Four studies examined ADHD populations without comorbidities and one study involved long-term assessment of HRV. The findings of the studies were not unanimous, although children with unmedicated ADHD were observed to have lower levels of CVC compared to the controls. While CVC reactivity depended on the task, children with ADHD experienced reduced CVC reactivity during tasks. The authors reported that medication acted to correct the autonomic imbalance in ADHD, but found it difficult to reach any definite conclusion due to so few studies having been published on this topic (Rash and Aguirre-Camacho 2012).

In a meta-analysis by Koenig et al. (2017), eight studies published prior to January 2015 were reviewed and discussed. Two of these studies were conducted with adults (Lackschewitz et al. 2008, Oliver et al. 2012) while six involved children (Crowell et al. 2006, Luman et al. 2007, Negrao et al. 2011, de Carvalho et al. 2014, Karalunas et al. 2014, Tonhajzerová et al. 2014). A total of 587 cases (317 patients, 270 controls) were evaluated in these studies. The studies reviewed in this meta-analysis all measured HRV, taken under varying conditions as follows: at rest (Crowell et al. 2006), during an attention test (Negrao et al. 2011), during a stress test (Lackschewitz et al. 2008), during a task performance test (Luman et al. 2007), during a driving test (Oliver et al. 2012), and during an emotional stimulation test (Karalunas et al. 2014). Two studies (de Carvalho et al. 2014, Tonhajzerová et al. 2014) evaluated HRV at different positions (lying and standing). The authors of one of the latter studies (Carvalho et al. 2014) found that NN50 from time domain parameters was higher in children with ADHD and concluded that this result was related to increased parasympathetic activity in patients with ADHD. In another study, that of Negrao et al. (2011), time domain parameters and LF from frequency domain parameters were higher in ADHD patients; the researchers believed these findings to be related to decreased sympathetic activity/increased parasympathetic activity in patients with ADHD. Tonhajzerova et al. (2009) observed that ADHD patients had lower rMSSD and HF, a higher LF/HF ratio, and showed decreased parasympathetic activity. The other studies reviewed in this meta-analysis (Crowell et al. 2006, Luman et al. 2007, Lackschewitz et al. 2008, Oliver et al. 2012, Karalunas et al. 2014) found no significant change in HRV parameters among ADHD patients.

Another recent meta-analysis study (Robe et al. 2019) reviewed the results of 13 articles published between 1997 and 2017 involving 869 ADHD patients and 909 healthy participants. Case-control or cohort studies reporting vagally-mediated HRV measurements following a task request were evaluated. A total of 1778 participants were included in the analysis, which compared the results of healthy controls to those of individuals with ADHD. This meta-analysis found that vagally-mediated HRV was lower in ADHD patients than in healthy controls, but the authors concluded that it corresponded to a small effect size. In all 13 of the studies, short-term recordings were performed. Autonomic functions were evaluated using RSA measures in nine studies and HRV parameters in four studies. In order to reveal changes in autonomic functions, three of the studies involved an attention task, one study was based on a memory task, seven studies incorporated an emotion regulation paradigm, and two studies employed a physical activity task that included a postural change or a behavior modification technique. While most of the studies involved both male and female participants, one study included only males (Beauchaine et al. 2001). Four of the studies evaluated ADHD patients without psychiatric comorbidity, while nine studies evaluated ADHD patients with psychiatric comorbidity. A majority of the studies (11) reported one or more ADHD subtypes, while two did not report any ADHD subtypes. The participants in all studies remained drug-free during the test tasks. All 13 studies examined cardiac vagal control in response to a physical, emotional, or cognitive task. Vagally-mediated HRV was observed to be lower in ADHD patients compared to healthy controls in five of the studies (low vagally-mediated HRV indicates that the parasympathetic tone on the heart is reduced), studies reported no significant difference between the two groups, and one found that HF-HRV was higher in ADHD patients than in the controls (since the HF parameter expresses parasympathetic activity, the findings of this last study supported the dominance of parasympathetic activity in ADHD). The authors determined that psychiatric comorbidity and task type showed moderator effects and that the physical activity task had the largest effect size; drug status, ADHD subtypes, and different recording devices or systems for measuring HRV had no moderator effect. Although this meta-analysis had a small effect size, the authors emphasized that the wide range of inconsistent findings related to autonomic dysfunction in ADHD patients nonetheless represent the first quantitative synthesis of the data.

Conclusion

Examining the nature of cardiac autonomic dysfunction in ADHD facilitates an understanding of the neurobiology of ADHD, allowing us to better assess whether these children are at high risk of cardiovascular disease. To date, studies on this subject have confirmed possible ANS dysfunction in ADHD patients, a topic that should remain a research question on the agenda of child and adolescent psychiatrists. Researchers investigating this subject can help in planning treatment, providing follow-up care, and improving the quality of life of children with ADHD. HRV and its relation to behavior and cognition have been increasingly studied in the last two decades. There is mounting evidence to suggest that ADHD is associated with altered resting-state vagal tone, indexed by high frequency HRV (HF-HRV), although the findings have been inconsistent. In the context of arousal dysregulation, the relationship between ADHD and ANS opens a number of novel lines of inquiry. Among the main issues to be examined regarding ANS dysfunction in ADHD are possible roles played by clinical differences between ADHD subtypes, the contribution of ANS dysfunction to the presence of comorbidities, how this dysfunction is affected in the presence of a comorbid diagnosis, and whether it is a cause of treatment-resistant ADHD. Moreover, in accordance with the results of the research questions, the subject of whether ANS dysfunction constitutes an objective biomarker candidate in combination with neuroimaging, electrophysiology, and /or biochemical parameters should be investigated.

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