AUTONOMIC NERVOUS SYSTEM IN CHILDREN WITH AUTISM SPECTRUM DISORDER

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Abstract

Background. Autism spectrum disorder (ASD) is a neurodevelopmental disorder of unknown etiology, defined by impaired social communication and interaction, and by the presence of restrictive and repetitive behaviour. The autonomic imbalance, in which one branch of the autonomic nervous system (ANS) dominates over the other, is associated with a lack of dynamic flexibility and adaptability. The aim of this article was to summarize the current state of knowledge regarding ANS activity in children with ASD.

Methods and Results. We have collected the latest information on autism and ANS regulation from available medical resources (PubMed). We focused on two main physiological parameters such as heart rate variability (HRV) and electrodermal activity (EDA) as the noninvasive indices of vagal and sympathetic activity, respectively. The studies showed atypical autonomic activity at rest as well as in response to stress.

Conclusion. ASD symptoms are associated with pervasive abnormalities in the central nervous system including structures and networks involved in the complex ANS regulation. Importantly, the autonomic imbalance in a manner of higher sympathetic activity associated with lower vagal activity is associated with increased risk of cardiovascular, and other adverse outcomes in ASD. Therefore, we suggest that detailed complex analysis of physiological parameters may illuminate the pathway linking ASD and autonomic nervous system activity.

Key words: autism spectrum disorder, autonomic nervous system, heart rate variability, cardiac vagal regulation, respiratory sinus arrhythmia, electrodermal activity

INTRODUCTION

Autism spectrum disorder (ASD) as a neurodevelopmental disorder of unknown etiology is defined by impaired social communication and interaction, and by the presence of restrictive and repetitive behaviour.

In 1943, Leo Kanner, an American psychiatrist and physician, described autism as an innate disturbance of affective contact and, nearly at the same time, in 1944, Hans Asperger, an Austrian paediatrician, described a group of children with a psychopathic disturbance of social interaction (Kanner, 1943; Parellada et al., 2014). Kanner autism was included in the chapter on Childhood Schizophrenia of the DSM-I and DSM-II in the fifties and thereafter. Some psychological schools enhanced the hypothesis that autism was a psychological reaction to very disturbed early relationships, put the mother at the core of the etiology (mothers were blamed for their children's illness and branded as "refrigerator mothers") and suggested psychological treatments with a psychoanalytic orientation (Postel et al., 1987). Since 1980 autism has been seceded from other psychotic disorders and classified in a newly created chapter called Pervasive Developmental Disorders (from DSM-III to DSM-IV-TR) (Parellada et al., 2014). The working group DSM-5 in May 2013 established the use of one term Autism Spectrum Disorder (ASD) which covers diagnosis Autistic Disorder, Asperger's disorder and pervasive disorder not otherwise specified. Diagnostic criteria are reduced from 3 to 2, focusing on deficits in social communication and interaction and repetitive behaviour patterns and interests. ASD patients have to show symptoms from early childhood, but these may not occur up to 3 years. Severity of disorder should be specified as level of support for each of the two psychopathological domains. Language and intellectual impairment specifications should be also recorded (American Psychiatric Association, 2013). Recently, reported frequencies for ASD have approached 1% of the population, with similar estimates in child and adult samples (Table 1) (CDC, 2014).

Table 1. Prevalence of Autism Spectrum Disorder (according to CDC, 2014)

In one of 68 children has been identified with autism spectrum disorder (ASD) according to estimates from CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network.
ASD is reported to occur in all racial, ethnic, and socioeconomic groups.
ASD is almost 5 times more common among boys (1 in 42) than among girls (1 in 189).
Studies in Asia, Europe, and North America have identified individuals with ASD with an average of about 1%. A study in South Korea reported a prevalence of 2.6%.
About 1 in 6 children in the United States had a developmental disability in 2006-2008, ranging from mild disabilities such as speech and language impairments to serious developmental disabilities, such as intellectual disabilities, cerebral palsy, and autism.

THE ETIOLOGY OF AUTISM

Autism is a clinically heterogeneous group of disorders and the exact etiology is still unclear (Miles, 2011). It´s a complex disease, probably including both genetic and environmental factors in its etiology. Many new findings clearly show that autism is not a single clinical entity but a behavioural manifestation of tens or perhaps hundreds of genetic and genomic disorders (Betancur, 2011). Identified genetic causes of autism can be classified as the cytogenetically visible chromosomal abnormalities, e.g. m. Down (~5%), copy number variants (CNVs) (i.e. submicroscopic deletions and duplications) (10–20%), and single-gene disorders, e.g. Fragile X syndrome, Rett syndrome, Tuberous Sclerosis Complex (~5%) (Miles, 2011). The apparent overlap between various syndromes with known genetic causes and ASD symptomatology clearly has important influence to understand implications of ASD at both the behavioural and biological level (Moss and Howlin, 2009).

From neurobiological perspective, the autism is caused by disturbances in location of neurons in certain parts of the brain, their subsequent maturation and connecting to the neural circuits. The entire developmental process is complicated by neuromediators, substances affecting transmission of signals between neurons, with subsequent imbalance of excitation (influence of glutamate, serotonin) and inhibition (GABA effect) in neural circuits (Kelemenova, 2010; Ostatnikova et al., 2015). Based on previous studies it is assumed uneven growth of brain with primary rapid growth at an early age and the consequent slowdown and reduction in brain mass in cortical areas in adulthood (Ostatnikova, 2010; Wolf and Piven, 2013; Zielinsky et al., 2014). They suggest that disturbed cortical development in ASD undergoes three distinct phases: accelerated expansion in early childhood, accelerated thinning in later childhood and adolescence, and decelerated thinning in early adulthood (Zielinsky et al., 2014). In the recent study, Parellada et al. have reported about new findings in the neurobiology of autism. Results are briefly summarized in Table 2.

Table 2. Main findings in the neurobiology of autism (according to Parellada et al., 2014).

Genetics	Monozygotic twin concordance is around 60%.
	Recurrence rates of autism in the same family are in the range of 10-18%.
Function of proteins coded by risk candidate genes	Synaptic mechanisms (NRXNs, NLNGs, e.g.).
	Neuronal migration, growth and differentiation.
Neuropathology	Abnormal minicolumnar structure in the neocortex.
Brain structure and function	Brains of around 25-30% of ASD children increase excessively in size between the first and second year of life. Face and object recognition seems to be located in different regions than in controls.
Redox system	Chronic oxidative stress: affects cell function, synaptic plasticity, learning and memory.
Immunology	Pro-inflammatory status in ASD.
	Innate and adaptive peripheral immune abnormalities and autoimmune markers in ASD and relatives.
Oxytocin and social peptides	Low levels of oxytocin and genes coding for oxytocin are altered in autism.

Other biomarkers	Serotonin levels.
	Intrauterine hyperandrogenism.
Environmental factors	Exposure to a number of drugs, viruses or toxins in critical periods of development increases the risk of autism.

CORE AUTISM SYMPTOMS

Autism is defined completely on the basis of its two core behavioural symptoms: impairment in social communication and interactions, and the inclination to repetitive behaviours and restricted interests (Miles, 2011).

People with ASD tend to have communication deficits, such as responding inappropriately in conversations, misreading nonverbal interactions, having difficulty building friendships appropriate to their age, or deficit in understanding verbal and nonverbal communication. In addition, people with ASD are dependent on routines, highly sensitive to changes in their environment, or strongly focused on inappropriate items. Regarding symptoms, some individuals manifest mild symptoms and others have much more severe symptoms. This spectrum will allow clinicians to elucidate the variations in symptoms and behaviours from person to person (American Psychiatric Association – fact sheet, 2013).

ASD is frequently associated with intellectual impairment and structural language disorder, (i.e. inability to comprehend and construct sentences with proper grammar). Many individuals have psychiatric symptoms that do not form part of the diagnostic criteria for the disorder (about 70% of ASD may have one comorbid mental disorder and 40% may have two or more comorbid mental disorders) (American Psychiatric

Association, 2013). Several studies have reported that ASD youth suffering from significantly higher number of comorbid disease than youth with other mental disorders including for example ADHD, oppositional defiant disorder, anxiety, depression and language disorder (Abdallah et al., 2011; Joshi et al., 2010). Neurological diseases including epilepsy, cerebral palsy, Tourette syndrome, etc. are also frequent and severe co-occuring comorbidities (Thorova, 2006).

Mentioned facts emphasize the importance of thorough diagnostic and treatment management and the individual approach to the child´s specific condition. Considering to difficulties in two core domains of ASD and association with various types of comorbidities, including mainly multiple anxiety disorders, many researchers are motivated to investigate and assess the autonomic nervous system and its response to anxiety and stress (Kushki et al., 2014). Anxiety and poor stress management are indeed common in children and adolescents with ASD and they are among the most pressing clinical concerns due to its negative impact on physical and emotional well-being. Therefore, it may be later a source of additional morbidity (Kushki et al., 2014; White et al., 2009). These facts motivate researches to study ANS activity using analysis of autonomic measures, such as heart rate, in ASD. Therefore, this point is discussed in the following section.

AUTONOMIC REGULATION IN AUTISM SPECTRUM DISORDER

The regulatory system of the ANS allows maintaining homeostasis, adaptability and physiological flexibility of the organism. Physiologically, both of the sympathetic and parasympathetic systems work at dynamic balance at rest as well as in response to stress. The autonomic imbalance, in which one branch of the autonomic nervous system dominates over the other, is associated with a lack of dynamic flexibility and health. Therefore, the autonomic imbalance with sympathetic overactivity

associated with lower parasympathetic activity, could represent potential pathomechanism leading to increased risk of cardiovascular disease (Task Force, 1996).

An extensive body of studies and literature outlines that ASD symptoms are associated with pervasive abnormalities in the central nervous system including structures and networks involved in the ANS regulation.

These studies refer to ASD association with abnormalities in the structures involving in the modulation of the ANS activity, such as the amygdala, the anterior cingulate cortex, and the insula (Schumann et al., 2009; Uddin and Menon, 2009). It is argued that the development of face perception and social cognitive skills are supported by the amygdala-fusiform system and that deficits in this network are suggested in autism etiology (Schultz, 2005). Moreover, recent autopsy and/or quantitative magnetic resonance imaging studies of autistic patients have identified abnormal other structures such as agenesis of the superior olive, dysgenesis of the facial nucleus, reduced numbers of Purkinje neurons, hypoplasia of the brainstem and posterior cerebellum (Courchesne, 1997). Thus, these facts intensify the importance to study potential autonomic dysregulation from complex point of view. From this context, the cardiac activity is extremely sensitive to autonomic regulatory inputs, and the interaction between chronotropic regulation of the heart and ASD is extensively studied.

HEART RATE VARIABILITY - AN INDEX OF CARDIAC VAGAL REGULATION

Average value of the heart rate is determined by intrinsic activity as well as by the parasympathetic and sympathetic neurons terminating at sinoatrial node. Parasympathetic nervous control of the heart originates in the dorsal motor nucleus of the vagus and in the ventrolateral part of the nucleus ambiguus in the medulla. Postganglionic fibres synapse with muscarinic receptors in the sinoatrial (SA) and atrioventricular (AV) nodes and activate them by releasing acetylcholine. This action causes negative chronotropic effect by activation of specific potassium channels associated with funny-channels inhibition (Drew and Sinoway, 2012). In contrast, sympathetic nerves originate in cervical and stellate ganglia of paravertebral chains and neurons of these ganglia are controlled by sympathetic preganglionic neurons situated in intermediolateral nucleus in thoracic part of spinal cord. From here, relatively long sympathetic adrenergic efferent fibres extend to the SA and AV nodes in the heart where they release the neurotransmitter noradrenaline at synapses with beta-adrenergic receptors. In contrast to parasympathetic effects, this action causes positive chronotropic and inotropic effect (Drew and Sinoway, 2012).

Cardiac neural control, mediated mainly via sympathetic-parasympathetic interactions, is based on the principle of sympathovagal balance. Physiologically, the activation of either sympathetic or vagal branch is accompanied by the inhibition of the other. This sympathovagal continual dynamic interaction leads to heart rate instantaneous oscillations called heart rate variability (HRV). This physiological phenomenon is characterized by continual "beat-to-beat" oscillations around the heart rate mean value. The HRV is the result of complicated and sophisticated cardiac neural control, providing complex information mainly about parasympathetic activity, central-peripheral interaction, intracardial nervous system and about the end organ – heart, as well. Lower HRV is found in physiological as well as pathological states, e.g. after extreme physical activity, in the elderly, in mental disorders and others (Calkovska and Javorka, 2008). Moreover, the HRV analysis allows diagnosis of early autonomic neuropathy in diabetology, as well as monitoring of therapeutic effects in many other cardiovascular disease (Galuszka, 2007; Metelka, 2014). Importantly, Benarroch (1993) has described the central autonomic network (CAN) as an integral component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, pain, and behavioural responses that are critical for physiological adaptability. It includes the insular cortex, amygdala, hypothalamus, periaqueductal grey matter, parabrachial complex, nucleus of the tractus solitarius, and ventrolateral medulla. Thayer and Lane (2000) suggested that HRV is critical as an index of neurovisceral integration and organism self-regulatory ability. The interplay of sympathetic and parasympathetic (vagal) outputs of CAN at the sinoatrial node produces the complex beat-to-beat variability indicating a healthy and adaptive organism. In addition, several studies using neuroimaging provided evidence that activity of prefrontal cortex is associated with vagal function (Lane et al., 2009). Thus, the HRV analysis could provide important information related to central-peripheral interaction in ASD.

HRV ANALYSIS

The HRV can be analysed by linear (traditional) methods and novel nonlinear methods that describe variability from different aspects. Conventionally used linear methods - time and frequency (spectral) domain analysis – provide the information about the HRV magnitude, mainly information concerning the parasympathetic (vagal) neural outflow. These methods are best suited and recommended to short-term RR interval recordings (5-15min). HRV time analysis is based on the beat-to-beat or NN intervals, which are analysed to give variables such as: SDNN (standard deviation of NN intervals), RMSSD (root mean square of successive differences), pNN50 (the proportion of NN50 divided by total number of NNs), etc. (Table 3) (Task Force, 1996). The spectral analysis provides *information about quantitative characteristics of heart rate beat-to-beat changes*. This method allows to isolate the faster high frequency (HF) respiratory-coupled influences on the HRV (HF-HRV: 0.15-0.40 Hz, i.e. 9-24 cycles per minute) from slower sources of the HRV (LF-HRV: 0.04-0.15 Hz, i.e. 2.4-9 cycles per minute) reflecting mainly sympathetic and parasympathetic activity via baroreflex (Tab. 3) (Task Force, 1996; Visnovcova et al., 2013). HF –HRV gives information primarily about vagally-mediated and respiratory-linked oscillations of heart rate, reflecting in the respiratory sinus arrhythmia (RSA) (Tonhajzerova et al., 2011). This phenomenon is mediated through physiological mechanisms by which the R-R interval in the ECG is shortened during inspiration (heart rate increases) and prolonged during expiration (heart rate decreases). These mechanisms include central medullary generator, reflexes from the lungs, baroreflexes, chemoreflexes, as well as local mechanisms. Generally, the HF-HRV is accepted as an index of cardiac vagal function (Javorka and Javorka, 2005; Tonhajzerova et al., 2008).

Recently, the nonlinear HRV analysis has gained more attention. Nonlinear methods are suitable to detect qualitative characteristics of the analysed signal, e.g. complexity and irreversibility (Porta et al., 2009; Voss et al., 2009). With regard to short-term HRV analysis, symbolic dynamics and time irreversibility are preferred to detect complexity and asymmetry as the qualitative characteristics of HRV. However, this topic requires extensive research.

Table 3. Parameters of linear analysis (according to Task Force, 1996 and Visnovcova et al., 2013).

Parameters	Units	Definition
Time analysis		Information about the magnitude of HRV
Mean HR	ms	Mean of heart rate.
SDNN	ms	Standard deviation of NN = R-R intervals – index of total HRV.
RMSSD	ms	The square root of the mean squared difference of successive NNs – index of parasympathetic activity.
pNN50	%	The proportion of NN50 divided by total number of NNs – index of parasympathetic activity.
Spectral analysis		*Information about individual rhythms amplitude within certain frequencies in HRV – quantitative characteristics of heart rate beat-to-beat changes.*
HF – HRV	ms^2	Index of parasympathetic activity reflecting respiratory sinus arrhythmia.
LF - HRV	**ms^2**	**Baroreflex mediated through sympathetic and parasympathetic activity.**

ELECTRODERMAL ACTIVITY - AN INDEX OF SYMPATHETIC NERVOUS SYSTEM Electrodermal activity (EDA) is considered as a marker of sympathetic cholinergic sudomotor function which induces changes in skin resistance to electrical conduction. Two types of sweating are generally recognized: thermoregulatory sweating, which occurs over the whole body in response to changes in environment, and emotional sweating (palmar and plantar) which is limited to the palms, axillae and soles of the feet (Vertugno et al., 2003). As sweat is an electrolyte solution, the more the skin's sweat ducts and pores are filled with sweat, the more conductive the skin becomes (Figner and Murphy, 2010). However, eccrine sweat glands have predominantly sympathetic cholinergic innervations and their activity increases in sympathetic excitation ("sympathetic arousal"), e.g. in response to stress.

EDA is the umbrella term used for definition of autonomic changes in the electrical properties of the skin. There are two main components to the overall complex referred to as EDA. One component is the general tonic level (skin conductance level: SCL) representing the information about baseline sympathetic activity. Other component is the phasic level reflecting faster changes of discrete stimulus (skin conductance response: SCR) providing information about sympathetic arousal (Braithwaite et al., 2013; Dawson et al., 2000). Tonic SCL can vary between different subjects and within the same subject in different psychological states. The typical range is between 2 μS and 20 μS depending on a type of device. The size of the SCR, quantified as the amount of increase in conductance measured from the onset of the response to its peak, typically ranges between 0.2 μS and 1.0 μS (Dawson et al., 2000). SCR is described as a discrete and short fluctuation in skin conductance that lasts several seconds and usually follows a pattern of an initial, relatively steep rise, a short peak, and then a relatively slower return to baseline. Overall, the parameters evaluated during EDA recording are following: latency (1-3s), rise time (1-3s), amplitude of skin conductance response (SCR), recovery half time of SCR (Fig. 1) (Figner and Murphy, 2010).
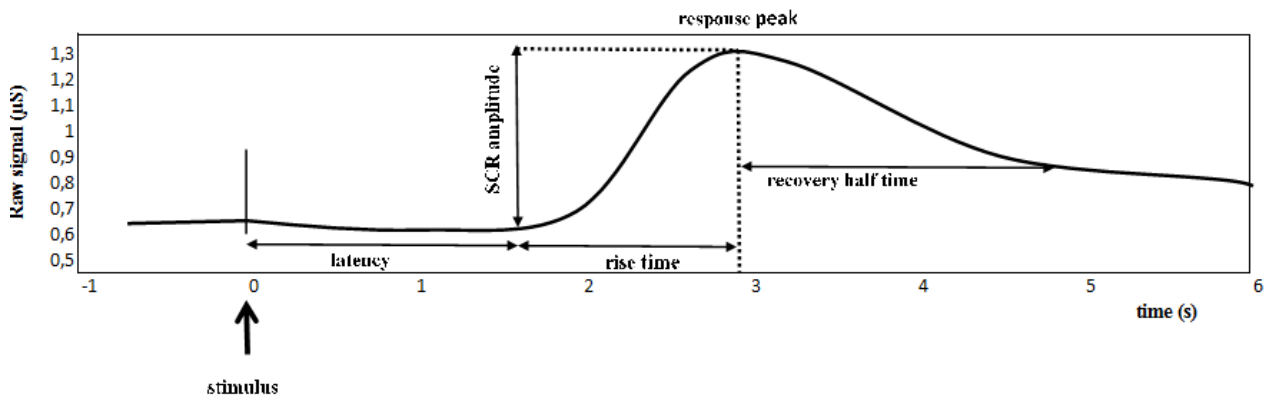

Fig. 1. Electrodermal activity (EDA) in phase level. Detailed explanation of the parameters is discussed in the text (according to Figner and Murphy).

Excitatory and inhibitory influences on the sympathetic nervous system are distributed in various parts of the brain, so the neural mechanisms of EDA are numerous and complex (Dawson et al., 2000). The central origins of EDA involve cortical and subcortical structures. The cortical brain areas that play important role in EDA regulation include premotor cortex (Brodmann area 6), anterior cingulate cortex and prefrontal cortical areas (Boucsein, 1992; Critchley, 2002). Regarding the subcortical structures, the hypothalamic area is a main integrative structure of ANS control system, playing a major role in the elicitation of EDA. Hypothalamic sympathetic activity can be modified by limbic system, especially by amygdala and by the hippocampus. Basal ganglia and reticular formation in the brainstem seem to play an important role in the control of EDA, as well (Boucsein, 1992; Sequeira and Roy, 1993). Importantly, amygdala has extensive connections with the septal area and hypothalamus and with prefrontal cortex, it influences both related behaviour and the related

emotions. The most common emotion following amygdala stimulation is fear, accompanied by its autonomic manifestations (dilation of the pupils, release of adrenalin, and increased heart rate) (Baron–Cohen et al., 2000). Revealed abnormalities in the amygdala (Schultz, 2005; Schumann et al., 2009), the difficulties in

interpreting gaze information (Baron-Cohen et al., 1997), epileptic seizures in temporal lobe, producing autonomic disturbances (Hirstein et al., 2001), impairments in social judgements (Baron–Cohen et al., 2000) and others facts confirm link between damage to the amygdala and autism.

CLINICAL IMPLICATIONS IN AUTISM SPECTRUM DISORDER

As discussed above, the autonomic imbalance - sympathetic overactivity and/or low parasympathetic activity – is associated with the difficulties in social behaviour (Porges, 2003), resulting in potential higher risk of cardiovascular morbidity in ASD children.

With regard the parasympathetic activity, studies concerning the cardiac autonomic regulation in children with ASD emphasize the association with a dampened social engagement system, characterized by lower amplitude of RSA in ASD children compared to age-matched typically developed (TD) children (Porges et al., 2013). Similarly, other studies showed elevated heart rate during both baseline and anxiety conditions (Kushki et al., 2013), decreased baseline vagal tone (Ming et al., 2005) and decreased baseline RSA in association with difficulties in social behaviour (Neuhaus et al., 2014). In contrast, children with ASD characterized by higher magnitude RSA are associated with better social behaviour (Kushki et al., 2013). Moreover, Patriquin et al. (2013) focused on the link between RSA and both social behaviour and cognitive function. This study confirmed that higher baseline RSA magnitude was associated with better social behaviour and receptive language abilities in children with ASD. In addition, Bal et al. (2010) correlated baseline RSA and heart rate with accuracy and latency of recognition of facial emotions in ASD. They found that autistic children with significantly lower RSA and faster HR during baseline period were slower in emotion recognition and selectively made more errors in detecting anger than TD children. ASD children with higher amplitude RSA at baseline recognized emotions more quickly (Bal et al., 2010).

With regard the sympathetic activity, several studies have investigated the physiological responses using

measurement of EDA. Hirstein et al. (2001) compared autonomic responses of autistic children to people (mother's face) and object (paper cup). Although the control group produced larger SCRs to the person than to the cup, the autistic children as a whole showed no difference. This first experiment of the study was based on the fact, that the potential lesion in the amygdala is associated with autism. In addition, amygdala contains group of neurons sensitive to gaze direction and almost every autistic child has difficulties in this field (Baron-Cohen et al., 1997). EDA was monitored also during second experiment ´self-stimulation behaviours´ as the child engaged in sitting quietly, in interaction with parents and self-stimulation activities (watching favourite video, etc.) Most of children had abnormal baseline EDA and during testing activity EDA alternated between hyperarousal and hypoarousal, with a much larger range of EDA than control group. Autistic children tended to use self-stimulation activities (watching a favourite video, arranging toys, immersion of the hand in dry bean) in order to calm hyper-responsive activity of the sympathetic branch of ANS (Hirstein et al., 2001). Another study revealed higher basal EDA without significant response to Stroop task. These findings could indicate sympathetic hyperarousal and decreased stress responsivity (Kushki et al., 2013). In contrast, other study investigating physiological arousal to social stress didn´t find statistically significant differences in EDA at baseline, during the Trier Social Stress Test (TSST), or post-TSST between children with high functioning autism (HFA) and controls (Levine et al., 2012). The discrepancies in the above findings may be related to differences in the degree of anxiety or in other cognitive and performance variables (e.g. IQ, age, task performance) (Kushki et al., 2013). The studies are summarized in Table 4.

Table 4. Changes in parasympathetic and sympathetic activity in ASD children.

Author	Cardiac vagal activity (indexed by RSA)	Sympathetic activity (indexed by EDA)
Porges (2013)	↓ baseline RSA	
Kushki (2013)		↑ baseline EDA, no significant response to Stroop test
Ming	↓baseline cardiac vagal tone	
Neuhaus	↓basal RSA-difficulties in social behaviour	
Patriquin	↑baseline RSA-better social behaviour and receptive language abilities	
Bal	↓baseline RSA-slower emotion recognition	
Hirstein		no differences in EDA response to the person than to the object; ↑baseline EDA and during testing activity with alternating between hyperarousal and hypoarousal
Levine	no differences in vagal tone at baseline and during the TSST between HFA and controls	no differences in EDA at baseline and during the TSST between HFA and controls
Kaartinen		no significant differences in EDA between groups during direct gaze, averted gaze, closed eyes

RSA (respiratory sinus arrhythmia), EDA (electrodermal activity), TSST (Trier Social Stress Test), HFA (high functioning autism)

Case report

As above mentioned, recordings from autistic children showed abnormal results. We focused on EDA as a sensitive marker of sympathetic arousal that has not been studied adequately in children with ASD. We assessed electrodermal response at rest and during physical stressors activating a dynamic sympathovagal balance: orthostatic stress - posture change from standing to lying associated with the sympathetic activation and fall of parasympathetic activity (i.e. vagal withdrawal), and *vice-versa* - clinostasis. Our recording of electrodermal amplitude (µS) revealed increased electrodermal activity during complex orthoclinostatic manoeuvre (lying – standing – lying) indicating a potential higher sympathetic arousal in ASD.

Importantly, the electrodermal activity did not return to baseline level during the clinostatic manoeuvre which is considered as a recovery phase after orthostatic stress associated with decrease of sympathetic activity and raise of parasympathetic activity (i.e. vagal rebound). It seems that sympathetic hyperactivity remains prolonged in recovery phase in ASD (Fig. 2). From this context, it could represent an important pathomechanism leading to cardiovascular adverse outcomes in autistic children. However, this assumption should be validated in a large sample of children suffering from ASD. (Study approved by Ethical Committee JFM CU on 5 November, 2014 under number EK 1529/2014).
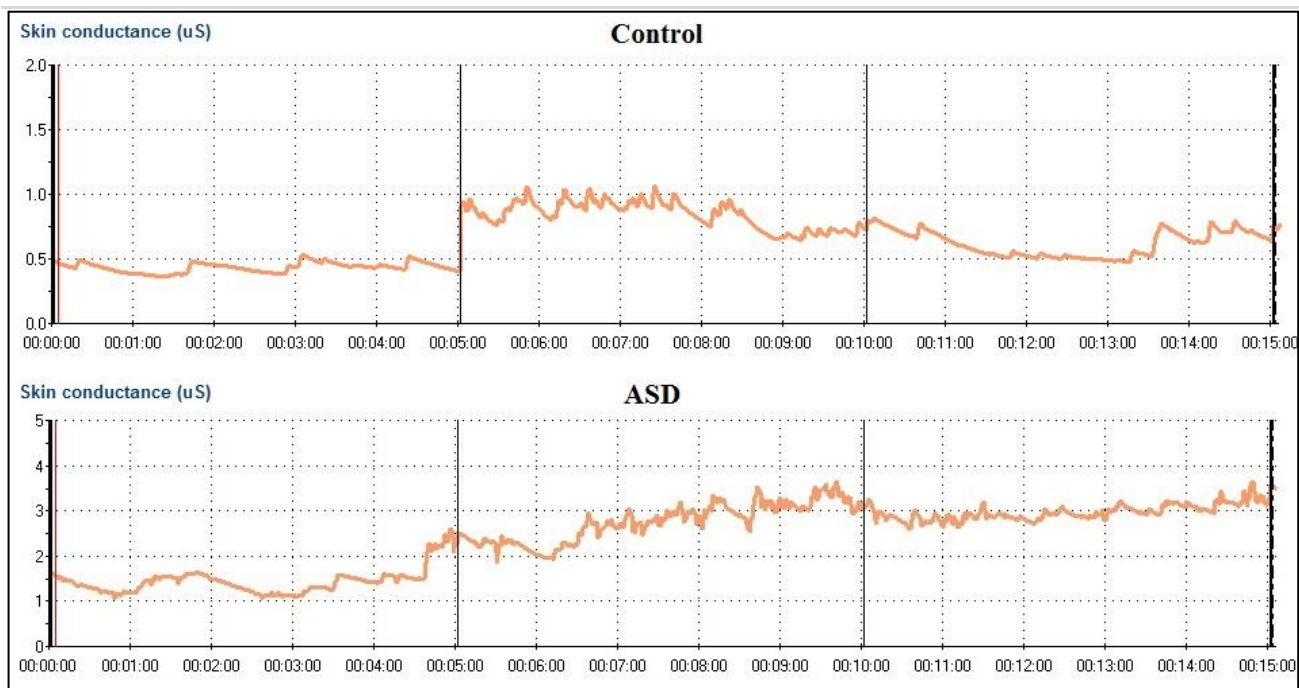
Fig. 2. Continual recording of electrodermal activity during baseline, orthostasis and clinostasis in normally developed child compared with autistic child (ASD) (Department of Physiology and Martin Centre for Biomedicine BioMed Martin, Psychiatric Clinic JFM CU, using device the ProComp Infinity Thought Technology Ltd., Canada,). Detailed explanation is discussed in the text.

OTHER MEASURES OF ANS

Several other studies investigated the feasibility of using other indicators of ANS, such as skin temperature, pupil size and alpha-amylase. Cheshire (2012) summarized recent studies with increasing correlations between autonomic functioning and social behaviour in ASD children. Studies of HRV, pupil size, salivary alpha-amylase and electrodermal responsiveness have shown that autistic children differ from normally developed children in their autonomic responsiveness to visualizing human faces and other mental tasks (Anderson et al., 2013; Bal et al., 2010; Kaartinen et al., 2012; Martineau et al., 2011). Similarly, Daluwatte et al. (2013) demonstrated correlations between pupillary light reflex (PLR) and HRV. PLR is referred as a characteristic process of pupil to constrict and recover when stimulated by a flash of light. The PLR parameters usually calculated from pupilogram are following: the baseline pupil diameter, the relative constriction amplitude, the minimal pupil diameter, the latency, the constriction time, the redilation time, the constriction velocity and the redilation velocity. The neuronal PLR pathway includes the retina, pretectal olivary nucleus, Edinger-Westphal nucleus, and ciliary ganglion. This pathway is mostly under the influence of the parasympathetic system (Neuhuber and Schröder, 2011). Authors found atypical parameters such a greater latency, less constriction amplitude, and shorter constriction/redilation times. They also showed a significant negative correlation between PLR constriction and average heart rate in ASD group indicating potential parasympathetic dysregulation associated with ASD. The ASD group showed a faster average heart rate suggesting an increased sympathetic tone or/and impaired parasympathetic control in children with ASD and also smaller PLR constriction amplitude, indicating lower parasympathetic modulation. These similar atypical findings were observed also in NDD group (non-ASD neurodevelopmental disorder). From this context, abnormal findings encourage PLR differences to be implicated in a wide range of neurodevelopmental disorders. However, this easily accessible and economic

neurological test, PLR may be potentially used for screening of neurodevelopmental disorders in children (Daluwatte et al., 2013). Regarding correlation, Pearson product moment correlation was applied to study correlation between PLR parameters and HRV

parameters. In addition to this processing software, we suggest also apply another procedure, for example Fast Fourier Transform. Further investigation in this field is needed.

CONCLUSION

ASD symptoms are associated with pervasive abnormalities in the central nervous system including structures and networks involved in the regulation of the autonomic nervous system (ANS). Importantly, the autonomic imbalance in a manner of higher sympathetic activity and lower vagal activity is associated with increased risk of cardiovascular, and other adverse outcomes in ASD. Therefore, we suggest that detailed complex analysis of physiological parameters may illuminate the pathway linking ASD and autonomic nervous system activity.

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