Review

Autonomic Dysfunction and Autism: Subtypes and Clinical Perspectives

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Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impaired social communication, restrictive interests and stereotypical repetitive behaviors. It is known that over-activation of the sympathetic branch of the autonomic nerve system (ANS) on a background of deficient parasympathetic tone is related to social, emotional and cognitive behaviors in autistic people. Different autonomic features have been linked to distinct phenotypes of autism. This review demonstrates a novel method to distinguish autism subtypes and comorbidities using autonomic indices combined with neurotransmitters and neuroimaging patterns. The clinical applications and future perspectives of autonomic indices as promising diagnostic and therapeutic biomarkers are also discussed here.
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INTRODUCTION

Autism spectrum disorder (ASD) is considered a complex neurological and developmental disorder characterized by impaired social communication, restrictive interests, as well as stereotypical repetitive behaviors. As a highly prevalent disorder affecting 1 in 68 children in the United States,[1] ASD is considered as a major public health concern not only from medical aspect of view, but also from social and economic perspectives.

Growing evidence has shown the association of ASD with the dysfunction of autonomic nervous system (ANS). ANS is responsible for cognitive, affective and behavioral responses and its dysregulation is found in diverse neuro-psychological disorders, such as anxiety,[2] panic disorder,[3] social phobia,[4] post-traumatic stress disorder,[5] attention-deficit hyperactivity disorder[6] and ASD.[7-10] As an important feature of ASD,[7,8] autonomic dysfunction caught increasing attention by researchers in order to better understand the abnormal clinical behaviors in autistic children. A wide range of studies with variable samples and methodologies have revealed the overall boosted sympathetic nerve system and decreased vagal tone in autistic children.[9] The considerable heterogeneity in ASD linked different clinical symptoms to distinct autonomic features.[7,10] This raised the possibility of the different forms that autonomic dysfunction could take in differentiating ASD phenotypes.

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This review will focus on the role of ANS in autism. First we summarize the neuroanatomic nature of ANS and autism, and the common autonomic indices for autistic children in current literature. Second, we discuss the characteristics of autonomic dysfunction in autistic patients versus typical developed (TD) children in the context of different subtypes and comorbidities, followed by analyses of their clinical significance. Last, we further explore the future application value of autonomic parameters as tools for diagnosing, therapy and disease prevention.

THE NEUROANATOMIC NATURE OF AUTONOMIC DYSFUNCTION AND AUTISM

The Autonomic nervous system (ANS) encompasses two opposing branches, namely the sympathetic and parasympathetic pathways, to maintain body homeostasis in response to physiological changes and environmental stimuli in an involuntary fashion. The sympathetic nervous system (SNS) can be largely characterized as 'fight or flight' defense system in response to 'danger signals'. The arousal response increases the metabolic output and activate internal organ systems leading to responses such as increased heart rate and pupil dilation, muscle vasculature dilation and the inhibition of digestive system.[11,12] The parasympathetic nerve system (PNS) is more complex. According to the well-known Polyvagal Theory brought up by Porges,[13,14] PNS divides into two distinct vagal branches controlling different behavioral responses to threat: 'vegetative vagus' in dorsal vagal complex and 'smart vagus' in ventral vagal complex. Vegetative vagus is the more primitive branch controlled by unmyelinated vagal nerves, originated in the dorsal motor

nucleus, and would elicit 'freezing or fainting' response when threatened to suppress metabolic demands and is potentially lethal to humans. Prolonged activation of this branch could shut off digestion and cause apnea and bradycardia.[15] In contrast, the more evolved branch, the smart vagus, which is unique to mammals and originated from nucleus ambiguous, is controlled by myelinated vagal pathways and is linked to cranial nerves controlling facial expression and vocalization for the regulation of social engagement.[15] This branch would regulate cardiac output rapidly and control the striated muscles of face and head, resulting in social communication, calming and self-soothing.[15,16] Porges further explained the hierarchical organization of ANS. The newest neural structures of PNS, smart vagus, would cope with a stimulus first with social affiliative behaviors, which requires sustained attention and slows down heart rate by inhibiting acceleratory SNS input. If it is ineffective, response strategies shift to fight or flight behaviors, characterized by rage or panic emotions, by withdrawing the vagal brake to release the activities of SNS.[17] If the second strategy also fails, immobilization behaviors, mediated by the oldest response system, would be initiated.[15,17] Functional deficiency of the smart vagus would increase the risk of emotional dysregulation and lead to psychiatric conditions.[18]

From a neuroanatomic aspect of view, the Neurovisceral Integration (NVI) model of ANS suggests that a network of brain areas including prefrontal cortex, cingulate cortex, insula, amygdala and hypothalamus regulates not only the autonomic function, but also social-emotional and cognitive processes.[2,19,20] Dysfunction of this network would lead to many psychiatric diseases including ASD.[9] Studies have shown that the abnormalities of amygdala and other parts of temporal lobe have been related to motor stereotypes of autism such as expressionless faces, spinning and somersaulting.[21,22] Pathological changes of amygdala also contributes to seizure activities, gaze problems and failure of recognition of social emotions in autistic children.[23-25]

Recent studies have found defects of neuronal connectivity within the ANS, as well as between the ANS and other parts of brain region from autistic people. For instance, a whole-brain MRI survey for high-functioning ASD children and those with developmental language disorder has demonstrated reduced functional connection between frontal and parietal-occipital regions as well as lower connectivity between anterior and posterior insula, striatal subregions and limbic cortex.26 Annika et al[27] investigated the socio-emotive circuits of the autistic children, the amygdala-cortical pathways by fMRI and figured out abnormal connectivity of its sensory input.

The shared anatomical brain regions that are important for both autonomic dysfunction and social-emotional dysregulations make autonomic status a good biomarker for ASD and may provide deeper insight into behavioral features in ASD patients.

THE COMMON AUTONOMIC INDICES IN AUTISM

Cardiac Autonomic Measures in ASD Studies

Cardiac autonomic parameters are the most common metrics for scientific research reflecting ANS functions. Heart rate is frequently considered as a measure for autonomic arousal, though it has been variably influenced by both subsystems of the ANS. Heart period (HP) or inter-beat-interval (IBI) has an inverse relation to heart rate, with greater IBIs reflecting a slower heart rate, which is also governed by both SNS and PNS. Pure PNS or SNS metrics are discussed below respectively.

Heart rate variability (HRV) is beat-to-beat variation in heart rate, which is quantified by measuring R-R intervals. It is an important parameter for the assessment of autonomic function. HRV reflects the autonomic function of sinoatrial node, and a major portion of these heart rate changes occur in synchrony with respiration, which is called respiratory sinus arrhythmia (RSA). RSA can be visualized by R-R interval variations on ECG, which is shortened during inspiration and prolonged when exhaling.28 Pharmacological blockade studies proved that RSA changes significantly by blocking vagal parasympathetic activity,[29,30] therefore it serves as a major cardiac PNS index. Though RSA and HRV are not exactly the same, both terms are often used interchangeably as they both reflect changes of the ANS.[31] To evaluate HRV, or the estimated RSA, two approaches are generally applied: frequency and time domain measurements. Frequency domain methods adopt spectral analysis to scrutinize autonomic changes.[32,34] Fast Fourier Transformation is the most common approach for conducting this analysis.[32,35] The HRV is divided into three frequencies: high frequency, low frequency and very low frequency. The high frequency HRV (HF-HRV) is highly correlated with RSA,[36-38] reflecting the parasympathetic activity. The time domain metrics contain root mean successive square difference of normal ECG complex R-R intervals (rMSSD), standard deviation of normal to normal R-R intervals (SDNN) and percentage of the number of pairs of adjacent NN (normal RR) intervals differing by more than 50 ms (pNN50). These all reflect cardiac vagal functions[39] and are measured during short-term (minutes) recordings.[32,35] They are all correlated with RSA[39] and are commonly used in recent literatures.

Sympathetic cardiac control is measured by pre-ejection period (PEP), which is the time interval from heart depolarization to the time when blood enters the aorta. Shorter PEP means greater sympathetic activation. As the measurement of PEP needs echocardiography or MRI, it is rarely used in studies. Other indices of sympathetic activity are controversial, such as low-frequency HRV (LF-HRV), the low-frequency/high-frequency HRV ratio (LF/HF ratio), and so forth.[32,40]

Previously, electrocardiogram (ECG) is the major device for cardiac indices as it could record cardiac signals cleanly and prominently. But as the technology advanced in recent years, various wearable devices focused on peripheral locations have been commercially available. The photoplethysmo-

graphy (PPG) sensor could measure the blood volume pulse (BVP) from peripheral microvasculature, which reflects the heart rate, HRV and other cardiac features. It is convenient and noninvasive, and proved to provide accurate data comparing to ECG.[41] However, PPG is very sensitive to motion artifact[42] and many biosensor companies suggest to wait at least 5 minutes at the beginning of research to calibrate pulse rate variation data with HRV.

Accelerometers (ACM) and gyroscopes are motion detectors that could picking up signals of subtle body motions associated with heart beating, which is known as ballistocardiography. Javier H et al[43] used Google Glass Oculus Rift and Galaxy Gear Apple Watch to investigate the subtle motions of people who stayed 'still', which showed that cardiac motion and person identity/body position were accurately detected if ACM and gyroscopes are combined. The recognition accuracy reaches as high as 94.25% or 93.79% for Glass or Gear, respectively. Besides, ACM is widely used in tracking seizure episodes and other movement disorders.[44] For research purpose, several wrist-worn sensors from different companies such Empatica E4 band has integrated the PPG, ACM and electrodermal activity (EDA) indices together for more sensitive and convenient measurements on autonomic function in autism and epilepsy research.

Skin Autonomic Measures in ASD Studies

The skin conductance response (SCR) is the most popular functional index to interpret sympathetic autonomic function. It is produced by eccrine sweat glands as part of sympathetic (fight or flight) branch of the autonomic nervous system via alpha1-adrenergic receptor by norepinephrine.[3,45] It was also known as Galvanic skin response (GSR), psychogalvanic reflex, sympathetic skin response, skin conductance response (SCR), electrodermal response (EDR) and EDA from different literatures.[46] Currently it is standardized to EDA. EDA could be divided into two types: those related to bodily activity (such as hand gripping) and those to cognitive activity (such as sight of a significant person).[47] The activity of sweating and the change of skin temperature would indicate the psychological or physiological arousal.

The early studies using silver/silver chloride electrodes worn on index and middle fingers tested palm sweating in the 1990's.[45] The dramatic technological advancement in recent two decades has made the recording of EDA more accurate and reproducible. Recent wearable devices prefer wrist sensors rather than palm ones to detect the skin conduction because they have better sensitivity and higher signal peaks.[48]

Other Autonomic Measures in ASD Studies

Pupil size, saliva cortisol level and blood catecholamine levels are also recorded in ASD studies reflecting autonomic status. The neurotransmitters and neuroendocrine biomarkers related to ANS include glutamate, Gamma-aminobutyric acid (GABA), serotonin, dopamine, norepinephrine, acetylcholine and others.[49,50]

Autonomic Dysfunction and Autism: Subtypes and Comorbidities

It is generally believed that autistic children have hyperarousal of sympathetic response and hypofunction of parasympathetic branch.[51] Nevertheless, studies with variable samples, methods, and measures have revealed inconsistent findings.[9]

The controversial results on ANS indicate the possibilities of distinct ANS responses among different subtypes that may confound the results. W. Hirstein et al[27] proposed that there are generally two subtypes of autonomic status in autistic children measured by SCRs. Type A responders have steadily rising above-normal levels of EDA but could be ceased completely by shutdown task. This hyperarousal phenomenon was also accompanied by larger range of EDA variation comparing to that in normal children. Nevertheless, a flat response with complete absence of changing in SCRs when upset, crying or doing normal activities was seen in 4 out of 37 patients, which they called type B response or hypoarousal. These patients tend to be engaged in self-injurious behavior and other extreme behaviors to activate autonomic activity. Interestingly, the constantly-elevated EDA levels in Type A children showed persistent sympathetic alert to every environmental stimulus, which made them tagged everything as significant and chaotic. Thus their behaviors tend to shut the system off such as immersing their hands in a large bowl of dry beans with sharp decrease in EDA. Whereas Type B children, with low sympathetic activity may see nothing as significant, which could explain why they may be engaged in self-injurious behaviors and other extreme activities to produce the sense of significance and activate ANS.

In fact, the diverse phenotypes observed in ASD are more than simply autonomic hypoarousal and hyperarousal. An extensive amount of literatures has been attempted to categorize autism based on their phenotypes, though no uniform classification system is available so far. For example, Wing's subgroups questionnaire divided ASD patients with aloof, passive, and active but odd subtypes.[52] Margot et al[53] differentiated three clusters of autistic-type individuals by clinical experience: Cluster A-autistic-like, B-Asperger-like, and C-mild Pervasive Developmental Disorder (PDD) or Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS). These suggested different levels of social and cognitive impairments. Doshi-Velez F et al[54] conducted a cluster analysis using electronic health records and summarized in three distinct medical trajectories. The three subgroups include: patients with seizures; patients with seizures and multisystem general health problems such as gastrointestinal distress, cardiac and/or auditory problems; patients with psychiatric disorders such as general anxiety, obsessive-compulsive disorder (OCD), depression etc. Lane et al[55] classified ASD children into four distinct sensory subtypes: sensory adaptive, taste smell sensitive, postural inattentive and generalized sensory difference.

Based on the close relationships between neuroanatomy, neurotransmitters and autonomic functions, we divided ASD phenotypes into five distinct psychomotor subgroups according to autonomic indices, neuroimaging patterns and neuro-hormonal changes. We recognize that there may be phenotypic overlaps between these subtypes, such as seizure with catatonia, anxiety with aggression. The subtypes were summarized in **Table 1**.

Subtype 1. ASD with anxiety features

Anxiety is a major feature of ASD and is present in up to 84% of ASD patients. Sakeena Panju et al[56] divided autistic children into high-anxiety group and low-anxiety group and studied their performance in anxiety, attention, response inhibition and social cognition tasks. Besides the fact that ASD children had significantly blunted mean EDA and EDR responses to the anxiety tasks, the high-anxiety ASD subgroup also showed significantly decreased mean EDA compared to both the low-anxiety ASD subgroup and normal controls. More severe symptoms of the high-anxiety ASD subgroup were observed comparing to the low-anxiety ASD group regarding anxiety, depression, attention, aggression, rule breaking, OCD and others. Similar results included a lower heart rate observed in high-anxiety ASD group than low-anxiety group by Hollocks MJ et al.[57] Nevertheless, Chiu et al[58] discovered increased HR in response to anxiogenic stimuli among 80% of autistic participants. The interpretation of decreased EDA is a concern. As EDA arousal and physiological output are thought to follow an inverted U shaped relation, decreased EDA may reflect sympathetic hyper-arousal in this study. And the overall blunted task responses may also be related to compensated down-regulation by chronic exposure to stress.[59] Physical activity wise, a study using ACM in patients with anxiety and/or depression has shown large amounts of sedentary time in anxiety groups.[60]

Besides autonomic patterns, Hollocks MJ et al[59] further investigate the change of HPA-axis and co-morbid anxiety in ASD children. The ASD patients in anxiety subgroup were found to have blunted salivary cortisol level and HR response to psychosocial stress. Furthermore, decreased cortisol level and HR responsiveness were significantly correlated with the severity of anxiety.

Cortical dysconnectivity is another theory for the etiology of ASD. Prater et al[61] investigated the amygdala-frontal cortex connectivity in generalized social anxiety disorder during fearful tasks and demonstrated that patients with anxiety had less connectivity between amygdala, rostral anterior cingulate cortex (RACC) and dorsolateral prefrontal cortex (DLPFC). Interestingly, cardiac autonomic function is also modulated by prefrontal cortex (PFC)-amygdala pathway. The NVI model[9] [9] suggested that the PFC inhibition during threat could over inhibit the vagal mediated response with a depressed HF-HRV and overactive sympathetic tone, which mirrored the EDA results above.

Subtype 2. ASD with aggression features

Many comorbidities of autism, such as ADHD, mood disorders and psychosis had significant aggressive components. Aggression may lead to impulsive outbursts and do harm to patients and their family members. Thus it is very important to recognize it early and treat it properly. Studies have shown that ASD children have more reactive aggression than proactive aggression,[62] which was significantly associated with increased attention deficits and internalizing behaviors. Reactive aggression is controlled by amygdala, central nucleus and periaqueductal gray matter pathway and is closely related to sympathetic activity. Studies from Bink et al[63] exhibited a dampened vagal tone with sympathetic dominance in both ADHD children and autistic patients with co-morbid ADHD. SDNN, rMSSD, pNN50 and HF-HRV were significantly reduced and LF/HF ratio was higher. Methylphenidate (MPH) therapy could improve the vagal tone and has potential cardio-protective effects.[64,65] Besides, studies using ACM to record physical activities of ADHD patients also showed hyperactivities and excessive motor activities.[66]

Several hormones have been shown to play important roles in aggression. Noradrenaline is the key hormone that triggers aggressive behaviors, and it is produced by both SNS and CNS. It targets neurons with postsynaptic alpha2-adrenoceptors to trigger and maintain aggression for prospective fights. In addition, noradrenaline-induced corticosterone secretion may serve as a situation-dependent modulator through neurons with beta-adrenoceptors.[67] Aggression also has close connection with sexual arousal status through medial preoptic area. Testosterone and androgens can participate in neural circuits regulating aggression and produce aggressive behavior. Furthermore, serotonin hypofunction and dopamine hyperfunction in the prefrontal cortex predispose individuals to impulsive aggression.[50]

Subtype 3. ASD with restricted repetitive behaviors and movement disorders

Tics and Tourette syndrome (TS) are common movement disorders in children with ASD. In fact, restricted repetitive behaviors (RRBs) are considered core features of ASD. Brain imaging investigations revealed dysfunction of basal ganglia-thalamo-cortical projection[68] during motor control in autistic people. Cerebellar neuropathy also plays a major role in the development of motor disturbances in ASD children, such as ataxia, repetitive/restrictive behaviors and other motor/cognitive behaviors.[69]

Sympathetic over-activity has been reported in TS patients.[70] GSR, reflecting sympathetic arousal, has been positively correlated with tic frequency during biofeedback study.[71] Suppressing sympathetic tone using Clonidine (alpha-2 adrenoreceptor agonist) could reduce motor tics episodes.[72] On the other hand, the PNS status in tics and TS is unclear. Biofeedback studies showed fewer tics during relaxation with decreased skin conductivity. A case report suggested that Vagus Nerve Stimulation (VNS) can modulate autonomic signals to reduce tic frequency and seizure episodes.[73] Tanner

et al[74] showed that the cholinergic parasympathetic arousal by scopolamine injection decreased motor tics but increased vocal tics in TS patients. The dissociated phenomenon between motor and vocal tics prompt further research.

To monitor tics using ACM, Bernabei M. et al[75] described a study using 3D-acceleration device on the trunk to automatically detect motor tics with 80% sensitivity, specificity and accuracy. The tic events were detected as signal peaks after noise filter with a time-variant threshold.[75]

A large variety of genetic polymorphism and mutations causing changes in neurotransmitters may also contribute to repetitive behaviors and movement disorders. The hormone changes include decreased GABA and dopamine levels, and boosted serotonin and glutamate levels.[76]

Subtype 4. ASD with seizure

About 1/3 of ASD children have coexisting seizure disorders. Epilepsy, especially those occurred at temporal lobe, has a similar neuroanatomic origin with autonomic dysfunction. Ansakorpi et al[77] used 24-h ECG in patients with temporal lobe epilepsy(TLE) with long term follow up, which revealed that well-controlled TLE has no significant HRV changes in normal people. In contrast, reduced HRV seems to be progressive in patients with chronic refractory TLE with recurrent episodes. These reflected a disrupted vagal tone in patients with recurrent epilepsy. Besides, recent studies using wrist sensors have shown a huge sympathetic nerve system surge around an impending seizure event, which is measured by a significant peak of EDA.[78] Poh M.Z. et al[79] examined a total of 34 seizures (22 complex partial and 12 tonic-clonic seizures) from 11 participants and monitored their postictal periods. A surge in EDA and heightened heart rate with coincided persistent suppression of HF-HRV were observed. Both the increased EDA response amplitude and the decrease of HF-HRV are correlated with an increase in the duration of EEG suppression. This study further demonstrated autonomic indices as a predictor for prognosis and sudden unexpected death in epilepsy using wrist biosensor. Wrist biosensor[80] recording of EDA and ACM achieved a high detection rate for grand tonic-clonic seizure with an acceptable false alarm rate of 0.74/24h on average, demonstrating its potential as an automated seizure detector. It could potentially provide caregivers of ASD patients with an alarm system for convulsive seizures and serve as an objective quantification of seizure frequency.

From a hormonal perspective, seizure has been related to sympathoexcitation by increased glutamate level in rostral ventrolateral medulla (RVLM) and increased excitatory neuropeptide pituitary adenylate cyclase activating polypeptide (PACAP).[81]

Subtype 5. ASD with catatonia

Catatonia is another comorbid syndrome of autism, which occur in 12-17% of adolescents and young adults of ASD.[82,83] It is featured by slow motions and strange behaviors such as mutism, stupor, echolalia, stereotypic speech, repetitive behaviors, grimacing, posturing, rigidity, mannerisms and purposeless agitation. It is believed that catatonia could develop after physical or psychological traumatic events, overwhelming stressful experience or extreme fear in children and adolescents with autism.[83-85] 40% of catatonic patients have autonomic symptoms including abnormalities of temperature, perspiration and cardiopulmonary responses.[86,87] 45% of pediatric cases show urinary-fecal incontinence,[86] which is another feature of autonomic dysfunction. Stronger vagal tone as evinced by bradycardia[87,88] and bronchorrhea was found to be associated with catatonia[89] in some studies. Others suggest a tonic immobility governed by the vegetative vagus system, as catatonic patients tend to have diminished HRV, which is the last defense strategy when encountering danger.[90] Currently, there is no ACM data or studies of sympathetic index on catatonic patients, although delayed sympathetic hyperactivity was found in catatonic patients after electroconvulsive therapy.[91] The sympathetic and motor features of catatonia need future research to clarify.

Hormone-wise, studies have shown that catatonia may be caused in part by the dysfunction of GABA type A receptors in the cortico-cortical networks of the frontal lobes, causing hypofunction of the subcortical dopaminergic transmission.[92]

Table 1. The autism subtypes.

Subtypes	Function	HR	PNS indices	SNS indices	ACM	Brain region	Neurotransmitter
Anxiety features	High	Blunted response to task	Depressed HF-HRV	Significantly decreased EDA (sympathetic arousal)	large amounts of sedentary time	Less connectivity between amygdala, RACC and DLPFC	Blunted cortisol response to task
Aggression features	High	Higher baseline	Significantly reduced HF-HRV	Higher LF/HF ratio	Hyperactivity	Amygdala, central nucleus and periaqueductal gray matter pathway; medial preoptic area; PFC	Increased noradrenaline, testosterone and androgens
Movement disorder	High	Tic frequencies were significantly lower during periods of higher HR	None	GSR increased	Peak	Basal ganglia-thalamo-cortical projection; cerebellum	Decreased GABA and dopamine, increased serotonin and glutamate
Seizure features	Both	Heightened HR	Persistent suppression of HF-HRV	Significant peak of EDA before or during attack	Sharp peak during episodes	Temporal lobe and others	Increased glutamate and PACAP
Catatonia features	Low	Bradycardia	Deminished HRV	None	None	Cortico-cortical networks of the frontal lobes	Decreased GABA and dopamine

CLINICAL APPLICATIONS AND FUTURE PERSPECTIVES

The Diagnostic Value of Autonomic Status in Autism

As mentioned above, autonomic indices and its related neurotransmitters could serve as a tool to identify and diagnose different autistic subtypes and comorbidities with unique patterns. The adrenal stress secondary to sympathetic over-arousal and the subsequent adrenal fatigue syndrome is not uncommon in children with ASD. The chronic stress can lead to hypersecretion and depletion of adrenal cortisols, androgens,[93] testerosterones, and thyroid hormones. Thus, testing those hormones would help us to identify adrenal fatigue earlier with appropriate treatment.

Besides, ACM together with autonomic indices could monitor seizure episodes and repetitive motions such as tics with special peaks. As the technology matures, the more sensitive and specific ACM measurements may be able to surveillance seizure and tic episodes in advance to prevent these adverse events.

The Therapeutic Value of Autonomic Status in Autism

Knowing the general autonomic status with hyperarousal of sympathetic nerve system and hypofunction of parasympathetic nerve system, it may be beneficial to use medicines to titrate the imbalance of the whole autonomic system for patients with autism. For instance, to down-regulate sympathetic tone, medications suppressing norepinephrine and glutamate levels were used with significant effects. Propranolol, a beta-adrenergic antagonist, is used to improve the social symptoms and communication skills by inhibiting neural norepinephrine release.[94] The glutamate receptor antagonists, magnesium and other medications are used to inhibit the excitatory effects of glutamate in order to modulate the behaviors of autistic children, though they were off labeled currently (not FDA approved).[95] To upregulate vagal tone, medications aiming to increase the acetylcholine level were used in clinical trials, including acetylcholinesterase inhibitors.[95] Natural alternative supplements such as phostidyl choline, phosphatidyl serine and lecithin may take a promising role in improving parasympathetic nerve system.

Familiarity with the brain regions and specific neurological pathways and circuits could guide transcranial stimulation therapy and neuroendocrine therapy targeting the ANS. For instance, overactivation of the amygdala regions induces anxiety, fear and other social-emotional behaviors in autistic children. Oxytocin could decease amygdala activities,[96] reduce stress-induced heart racing[97] and increase vagal outflow.[98] A number of recent studies have shown the important role of autonomic indices to monitor the influence of repetitive transcranial magnetic stimulation (rTMS) for autistic patients. Wan Y et al[100] found that a course of 12 weekly inhibitory low-frequency rTMS bilaterally applied to the dorsolateral prefrontal cortex (DLPFC) will improve autonomic balance in ASD participants, with increased HF-HRV, decreased LF/HF ratio and decreased SCR indicating increased cardiac vagal tone and reduced sympathetic arousal. These changes could be possibly worked through improved frontal inhibition of the ANS activity. In this study, decreased irritability, hyperactivity, compulsive behavior and stereotype behavior were correlated with these autonomic variables. Similar results were seen in the literature of Casanova et al.[101]

Selective Acronyms

Abbreviation	Full term
HRV	Heart rate variability
RSA	Respiratory sinus arrhythmia
SDNN	Standard deviation of normal to normal R-R intervals
rMMSD	Root mean successive square difference of normal ECG complex R-R intervals
pNN50	Percentage of count of number of pairs of adjacent NN(normal RR) intervals differing by more than 50 ms
PEP	Pre-ejection period
HF-HRV	High frequency heart rate variability
LF-HRV	Low frequency heart rate variability
LF/HF ratio	Low frequency and high frequency heart rate variability ratio
HP	Heart period
IBI	Inter-beat-interval
EDA	Electrodermal activity
GSR	Galvanic skin response
SCR	Skin conductance response
EDR	Electrodermal response
ACM	Accelerometer
PPG	Photoplethysmography
NVI	Neurovisceral integration
RACC	Rostral anterior cingulate cortex
DLPFC	Dorsolateral prefrontal cortex
PFC	Prefrontal cortex
PACAP	Pituitary adenylate cyclase activating polypeptide
ASD	Autism spectrum disorder
TS	Tourette syndrome

In addition, autonomic biomarkers are also applied to monitor therapeutic effects for ASD comorbidities. EDA biofeedback[99] and vagal nerve stimulation[73] have been used to control epilepsy and tic activity by stabilizing autonomic regulation.

Limitations

The current studies on autonomic dysfunction in autistic children have several limitations such as small sample sizes, unmatched age/gender, non-uniform protocols and medication uses that may confound study results. In particular, ANS patterns in different age groups from toddlers to adolescent and adults may be different and require age-specific evaluations. Moreover, future studies should aim to establish standardized reference ranges in order to better quantify the severity of autonomic dysfunction using comprehensive indices. These limitations require further investigations in the future.

CONCLUSION

ASD is a complicated neurodevelopmental disorder with specific psychological, social and behavioral patterns. Autonomic dysregulation was proposed to be a core feature for autism, with distinct patterns in different autism subtypes and comorbidities. The possible roles that the autonomic indices may play in diagnosing, subgrouping, monitoring and preventing ASD make them promising noninvasive biomarkers in the future. Our review demonstrated a novel classification system of autistic subtypes based on ANS dysfunctions including emotional behaviors, autonomic features, neuroanatomic involvement and neurotransmitter changes, which may guide future research in autistic phenotypes.

CONFLICT OF INTEREST

None.

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