Evaluation of sympathetic sudomotor responses to auditory stimuli in children with autism spectrum disorders

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Aim and Objective: Autism spectrum disorder (ASD) being a complex neurological and developmental disorder is also associated with autonomic nervous system dysfunction. Sudomotor nerve function is one highly sensitive index of sympathetic cholinergic activity and can be evaluated by measuring sympathetic skin response (SSR) to various stimuli. Studies reporting SSR to auditory stimulus among ASDs are limited and to the extent of our knowledge not assessed in the Indian scenario. The objective of the study was to assess and compare sympathetic sudomotor activity by evaluating SSR to auditory stimuli in children with and without ASDs.

Materials and Methods: A total of eighty individuals were enrolled in the study, including forty children with ASD and forty typically developing (TD) children. SSR to auditory stimulus was assessed using a digitized data acquisition unit in a soundproof room, maintained at 23°C. SSR indices such as latent period (s), amplitude (mv), and habituation were analyzed and compared using appropriate statistical tests between the groups. \( P < 0.05 \) was considered statistically significant.

Results: Habituation for SSR was statistically significantly lower \( (P < 0.001) \) in children with ASD \( (0.43 [0.21, 0.61]) \) compared to TD children \( (0.78 [0.65, 0.95]) \). Latent period was also statistically significantly higher in children with ASD \( (1.67 [1.37, 2.02]) \) compared to TD children \( (1.41 [1.2, 1.72]) \). However, there was no significant difference in amplitude values between the groups.

Conclusions: Children with ASDs exhibited slower habituation of SSR to auditory stimuli compared to healthy controls. This slower habituation process might be due to the persistent predominant state of sympathetic nerves, which, in turn, contributes to the atypical emotional and behavioral traits prevailing in ASDs.

Key words: Autism spectrum disorders, autonomic nervous system, habituation, sympathetic skin response

INTRODUCTION

Autism spectrum disorders (ASDs) are a group of complicated, rapidly growing neurodevelopmental and behavioral disabilities, which comprise autistic disorder,
Asperger’s syndrome, pervasive developmental disorder, and childhood disintegrative disorder. These disorders are characterized by repetitive and stereotyped behavioral patterns; restricted interests or activities and impairments in social interaction.[1] Many of the pediatric autonomic disorders are apparent at birth or within the 1st year of life. Some of these occur as a result of developmental abnormalities caused by specific genetic mutations, and others as a result of generalized central dysfunction. The onset of ASDs is found early in childhood and lasts throughout a person’s life.[2] ASD prevalence among 4-year-old children in the United States was approximately 1 in 59 children[3] with nearly four times higher incidence in boys than girls, suggesting that these disorders pose “an urgent public health issue.” ASDs are said to be increasing at an alarming rate in the Indian scenario as well with a prevalence of 1 in 100 children as on April, 2018.

Growing evidence from research has shown the association of ASDs with autonomic dysfunction, but the pathomechanism leading to autonomic abnormalities in ASDs is still unclear. Autonomic nervous system (ANS) is responsible for cognitive, affective, and behavioral responses, and its deregulation is found in diverse neuro-psychological disorders such as ASDs. ANS plays an important role in the regulation of the behavioral and physiological state during the dynamic challenges of social interaction.[4] Literature suggests that behavioral and language disabilities as seen in ASDs may arise from abnormalities in cerebral cortex, amygdala, and hypothalamus that interpret sensory input and process language associated with ANS.[2] Autonomic dysfunction is often overlooked as a feature of several pediatric neurodevelopmental disorders. Symptoms of autonomic dysfunction such as mood instability, resistance to change, hyperactivity and inattention, sensory disintegration, sleep disorders, and gastrointestinal dysfunction have been previously recognized in children with ASDs.[3] The common regions of the brain associated with both autonomic dysfunction and socio-emotional deregulations, make autonomic status a good biomarker for ASDs.

Even though the clinical symptoms of autonomic imbalance disorders are often noncharacteristic, autonomic impairment can be assessed by a battery of tests, which includes cardiovascular, sweat function tests, and renal tests.[6] Noninvasive quantitative tests that require minimal participation and cooperation are recommended for pediatric patients. There are a number of clinically useful techniques that test the functional integrity of the sympathetic and parasympathetic nervous system, with the best-known neurophysiological test of sympathetic sudomotor function being the sympathetic skin response (SSR).[7] SSR may be defined as the momentary change in electrical potential of the skin, resulting from the activation of sudomotor sympathetic efferent fibers, due to a transient voltage change across eccrine sweat gland cell membrane. It is reflexly evoked by a variety of internally generated or externally applied arousal stimuli such as deep inspiration; coughing; and electrical, acoustic, and magnetic stimulations applied to peripheral nerves.[8,9] Studies done by Hay et al. establish that auditory stimulus is superior to an inspiratory gasp in evoking SSRs, in terms of consistent appearance as well as reduced variability of SSR indices.[10]

An emerging body of literature suggests the link between ASD symptoms and ANS dysfunction related to sympathetic over-arousal, parasympathetic underactivity, or atypical interaction of both systems.[11] Several research groups studied the sympathetic nervous system (SNS) activity of children with ASDs using measures of skin conductance at rest and skin conductance responses (SCR) following auditory stimulation, but with inconsistent findings. Regarding sympathetic activity quantified by electrodermal activity (EDA), existing findings in ASD are mixed, such as increased activity was found in works done by Kushki et al. 2013, whereas a study by Levine et al. in 2012 found unaltered responses in basal skin conductance, as well as atypical EDA reactivity to faces by Hirstein et al. in 2001 or eye contact by Kylliäinen and Hietanen in 2006.[12-15] Given these contradictory findings, more research is needed in this area to further examine the possible link between autonomic state and socioemotional behavior in children with ASDs.

The prevalence of abnormal behavioral responses to a variety of stimuli among individuals with ASDs led researchers to examine whether physiological reactivity is associated with ANS dysfunction. Occupational therapists generally assume that behavioral responsiveness reflects the degree of underlying sympathetic activation, but research support for this assumption is very limited.[16] Although SNS has a central place in homeostasis in general, and particularly in circulatory adaptation, very little is known about the possible contribution of altered sympathetic nervous function to the development of human diseases.[17] Even though several studies based on EDA have been done on autistic children worldwide, SSR to auditory stimulus is not sufficiently described in ASDs in the Indian scenario, the results of which may provide deeper insight into autonomic dysfunction and the prevailing behavioral features in ASD children. The study assessed and compared sympathetic sudomotor responses to auditory stimuli by evaluating SSR as an index of sympathetic cholinergic activity in ASD and typically developing (TD) children.

METHODS

Study design and setting
This study used a case–control research design to compare SSR to auditory stimuli in children with ASD and TD children. A total of 125 children were recruited to the project between March 2017 and April 2018. The study procedures were performed in the Speech-Language
Pathology Department of K. S Hegde Charitable Hospital, special schools, and speech therapy centers in and around Mangalore. Data analysis was performed in the research lab of the Department of Physiology, K. S. Hegde Medical Academy, Deralakatte, Mangalore.

**Ethical consideration**
Initiation of the study was done after obtaining clearance from the Institutional and Central Ethics Committee of our University with ethical approval number NU/CEC/2017-2018/0104. The study protocol was briefed to the parents/guardians, and written informed consent was obtained from them before recruiting children for the study.

**Participants**
Of the 125 children recruited for the study, 70 were children with ASD and 55 were TD children within the age group of 4–14 years. Children with ASD were recruited from the Psychiatric, Paediatric, and Speech-Language Pathology Departments of K. S Hegde Charitable Hospital, special schools, and speech therapy centers in and around Mangalore. For enrolling children with autism, we identified seven centers in and around Mangalore, of which only four centers granted permission to recruit children for the study. Further, out of the identified seventy children after obtaining parents’ consent, we could perform study only on forty children with autism.

Random sampling method was adopted for the recruitment of TD children. Age- and gender-matched controls were randomly identified from the children of teaching and nonteaching staff of our institute studying in nearby schools. After collecting detailed medical and academic history of the children from their respective parents, children satisfying our study inclusion criteria were recruited. They had no history of mental and neurodevelopmental disorders and had normal school performance. Children with ASD and TD children were all investigated under the same experimental conditions.

ASD diagnosis was assessed by a child and adolescent psychiatrist according to the Diagnostic and Statistical Manual for Mental disorders-5. It was further confirmed by a qualified pediatrician prior to inclusion of the ASD children in this study. The severity of ASD was assessed by administering Childhood Autism Rating Scale-II (CARS-II), which is a 15-item-based questionnaire that helps in rating autism into mild, moderate, and severe categories. This was done by speech language pathologists or a research assistant trained to administer it reliably. Out of the forty children with ASD recruited for the study, based on the severity of autism, 2 children were in minimal-, 28 in mild-to-moderate, and 10 were of severe-grade autism. Majority of the children with ASD recruited for the study fell within the mild-to-moderate category.

Although we recruited 70 children with ASD and 55 TD children, data of only 40 children in each group could be considered for reliable statistical analysis. About 15 children with ASD from the 70 identified were excluded from the study due to the presence of comorbidities such as seizures and severe mental retardation associated with ASD as well as use of medications during the study period. Reasons for dropout were mainly failure to complete the protocol, absence of response to auditory stimuli, excessive movement artifacts, and inability of the software to analyze the obtained data. A flowchart of participant recruitment and the participants included in the present study is presented in Figure 1.

**Inclusion and exclusion criteria**
Inclusion criteria used for enrolling children in the ASD group were as follows: those who underwent primary ASD diagnosis, those who have ability to perform the study, and those with the absence of other comorbid mental disorders (e.g., attention-deficit/hyperactivity disorder, obsessive-compulsive disorder, and seizure disorder), which was confirmed by a specialist child psychiatrist or pediatrician. However, some of the children with autism were on nonpharmacological treatment which included speech and occupational therapy to improve their speech, behavioral, and physical difficulties.

Exclusion criteria for both groups were the following: those with acute infection; those with cardiovascular, endocrine, and respiratory diseases, and those with other disease potentially influencing ANS. Any child with a diagnosis of disruptive behavior disorders and severe intellectual disability (intelligent quotient [IQ] < 70) were also excluded from participating in the study. As per the inclusion/exclusion criteria, children with severe mental retardation (severe

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**Figure 1:** Flowchart of representation of patient recruitment

![Flowchart of representation of patient recruitment](image-url)
intellectual developmental disorder) were excluded from the study. Further, while recruiting the children, we have confirmed that formal IQ assessments were done so that children with severe ID were not included in the study. All control children were healthy, and their history and clinical examination showed no abnormalities. None of the children received any medication at least 1 week before the test procedure.

Data collection
Upon screening children satisfying our study criteria, their demographic and anthropometric data including characteristics such as height (m), weight (kg), basal blood pressure (BP), and heart rate (HR in bpm) were recorded. This was preceded by the evaluation of SSR to auditory stimuli.

Recording of sympathetic skin response
Sudomotor autonomic activity assessed by the evaluation of SSR is considered a sensitive marker of sympathetic cholinergic nervous system, which varies with sweat gland activity due to stress or emotional excitement. The entire experiment was performed by using, a 4-channel data acquisition unit, Power Lab 26T (AD Instruments Ltd., New South Wales, Australia). It was conducted in a soundproof room maintained at a temperature of 23°C–26°C as any external noise produced is found to affect the study parameters.

Once all the preparations were complete, each child was requested to sit in an easy chair and to get accustomed to the room settings. The standard method of obtaining SSR was followed by placing recording electrodes (disposable, pediatric Ag/AgCl) on the palmar (active) and plantar (reference) surfaces of the nondominating hand because these recording sites yield higher amplitudes due to a high density of eccrine sweat glands. The electrodes were placed intact on the skin surface so as to facilitate a smooth and artifact-free recording of SSR. They were connected to a bio-amplifier (Power Lab). On obtaining a stable baseline, ten auditory stimuli (fog horn sound – 95 dB), each of 3 s duration, were delivered at random intervals ranging from a minimum of 13 s to a maximum of 19 s through bilateral headphones connected to the children’s ears and SSR was recorded. The study protocol is explained in Figure 2.

Evaluation of SSR parameters from the obtained response curves

Figure 2: Protocol for sympathetic skin response recording

response. The term “response” is applied when a change in skin conductance that exceeds 0.04 mv occurs within 0.8–4 s after the start of the stimulus. Responses contaminated by children`s body movements were easily distinguished and excluded from the analysis.

Latency is defined as the time lag between the stimulus and the onset of the SSR from the baseline, which was manually measured from the onset of the stimulus artifact to the first deflection of the signal baseline. Amplitude is the voltage change on the surface of the skin due to the movement of ions in the sweat glands, which was measured from the baseline to peak. Habituation is the decrement in responses toward baseline level after repetition of the same stimulus. It was operationalized as the number of trials required before the first of two consecutive nonresponses to a stimulus. The obtained graphical recordings of SSR to auditory stimuli in ASD and TD children are expressed in Figures 3 and 4, respectively.

Statistical analysis
For each quantitative index assessed in this study, the Gaussian/non-Gaussian distribution was ascertained using the Shapiro–Wilk normality test. The Mann–Whitney “U” nonparametric test was used for data with non-Gaussian distribution, and Student’s t-test was used for comparing variables following Gaussian distribution. P < 0.05 was considered statistically significant. Statistical analysis was performed using the SPSS 20.0 (SPSS-Inc., 233 South Wacker Drive, Chicago, IL, USA).

RESULTS

Subject characteristics
The general participant characteristics are summarized in Table 1. The results suggest that children with autism exhibited a statistically significantly higher body mass.
index (BMI) (kg/m²) compared to their nonautistic counterparts with a \( P = 0.01 \). Basal HR (bpm) was also found to be statistically significantly higher (\( P = 0.04 \)) in ASD group compared to TD group. All other characteristics such as age, height, weight, systolic BP (SBP), and diastolic BP (DBP) did not show any significant difference between the groups. SBP and DBP were found to be higher in the autistic group but did not reach a statistically significant level.

Table 2 represents the values of SSR indices such as latent period (s), amplitude (mv), and habituation to auditory stimuli obtained in the study. As the SSR indices were not normally distributed, Mann–Whitney “U” test was used for comparing them between groups. Autistic group exhibits a statistically significantly slower habituation rates (\( P = 0.000 \)) compared to normal children. Latent period (\( P = 0.008 \)) was also statistically significantly prolonged in children with autism compared to TD children. Amplitude values did not show any significant difference between the groups.

The SSR indices were also correlated with severity scores obtained from CARS assessment using Spearman’s correlation which is depicted in Table 3. None of the SSR indices correlated with the severity of autism.

Figure 5 shows amplitude trends to consecutive auditory stimuli applied at pseudorandom intervals in both autistic and TD children. The mean amplitude values to each stimulus are plotted against the stimulus order. There is a sudden fall in amplitude values in normal children compared to their autistic counterparts, which, in turn, leads to a faster habituation than ASD.

### DISCUSSION

The triad of impairments found in communication, imagination, and social interaction in ASD population could be associated with sympathetic autonomic dysfunction. Sympathetic sudomotor activity in a group of autistic and TD children was assessed in this study by evaluating SSR. Being a noninvasive and easily obtainable index of cholinergic sudomotor sympathetic activity, it is the best-known neurophysiological test of sympathetic sudomotor function.\(^{[20]}\) The results of the study point to sudomotor autonomic dysfunction as evident from a significantly high sympathetic nervous activity.

### Table 1: Comparison of patient characteristics

| Characteristics | ASD (n=40) | TD (n=40) | t  | P   |
|-----------------|------------|-----------|----|-----|
| Age (years)     | 10 (5.25-12.00) | 9 (7.25-11.75) | 0.29 | 0.88 |
| Weight (kg)     | 23.5 (19.25-39.5) | 24.5 (19-31) | 0.83 | 0.75 |
| Height (m)      | 1.28±0.22 | 1.3±0.16 | 0.69 | 0.52 |
| BMI             | 16.76 (13.71-18.94) | 14.35 (13.38-15.44) | 2.1  | 0.01* |
| SBP (mmHg)      | 112.6±8.97 | 110.35±6.19 | 1.5  | 0.19 |
| DBP (mmHg)      | 76.93±5.39 | 75.68±4.1 | 1.19 | 0.25 |
| Basal heart rate (bpm) | 84.58±10.11 | 80.5±7.52 | 2.05  | 0.04* |

*Statistical significance (\( P < 0.05 \)). Descriptive: Mean±SD (parametric variables, independent t-test), Median (25th-75th percentile, nonparametric variables, Mann-Whitney U-test); ASD – Autism spectrum disorder; TD – Typically developing; BMI – Body mass index, calculated as weight (kg)/height (m²); SBP – Systolic blood pressure; DBP – Diastolic blood pressure; SD – Standard deviation

### Table 2: Comparison of sympathetic skin response indices in children

| SSR indices | ASD (n=40) | TD (n=40) | U  | P   |
|-------------|------------|-----------|----|-----|
| Latent period (s) | 1.67 (1.37-2.02) | 1.41 (1.2-1.72) | 523.00 | 0.008* |
| Amplitude (mv) | 1.44 (0.5-3.3) | 1.59 (0.97-2.79) | 774.00 | 0.8 |
| Habituation | 0.43 (0.21-0.61) | 0.78 (0.65-0.95) | 326.00 | 0.000* |

*Statistical significance (\( P < 0.05 \)). Descriptive: Median (25th-75th percentile, Mann-Whitney U-test); ASD – Autism spectrum disorder; TD – Typically developing; SSR – Sympathetic skin response
Table 3: Correlation of sympathetic skin response indices with the severity of autism spectrum disorder in children with autism spectrum disorder

| SSR indices            | ASD severity | R     | P    |
|------------------------|--------------|-------|------|
| Latent period (s)      | 0.104        | 0.49  |      |
| Amplitude (mv)         | 0.19         | 0.21  |      |
| Habituation            | 0.01         | 0.93  |      |

R = Spearman’s rho; ASD – Autism spectrum disorder; SSR – Sympathetic skin response

Results from the various anthropometric characteristics assessed in the study show that ASD group exhibited a significantly higher value than TD children in BMI and basal HR [Table 1]. The higher BMI rate in ASDs which might be due to their stereotypical and unhealthy feeding habits, sedentary lifestyle, or rarely due to the underlying genetic causes places them at a greater risk of developing chronic diseases such as heart disease and diabetes at an earlier stage in their life. The increase in basal HR points to an increased sympathetic activity.

SSR occurs due to synchronized activation of sweat glands as a response to a volley discharge in efferent sympathetic nerve fibers during psychological stress. SSR parameters such as latent period, amplitude, and habituation were evaluated in this study. Even though the comparison of habituation pattern of SSR to consecutive auditory stimuli was found to be significantly slower in ASD than TD children, other indices such as latent period and amplitude failed to produce a significant difference between the groups [Table 2]. The study results significantly demonstrate a progressive but irregular amplitude decrease of responses but not to a significant level. The significant difference in latent period between the two groups may be due to difference in nerve conduction, and it does not reflect any relevant sympathetic or psycho-physiological component. A lack of normal habituation in SSR to the same stimulus over time was evident in ASD compared to TD children. This might be because habituation depends on the “excitability level” of the sympathetic neuron pool involved in response production and is highly correlated with the attention state of the child. With repeated unpleasant stimuli, ASD children might have had a persistent predominant state of sympathetic nerves because they were anxiously anticipating the next stimulus.

Previous SCR studies have also revealed that children with ASD do not show normal rate of habituation in the magnitude of their SCR to the same stimulus over time. In studies by Kato et al., children who regularly felt excessive reactions to auditory stimuli tended to have excessive sympathetic responses to repeated loud noises compared with children who did not feel excessive reactions. Chang et al. reported that children with ASD exhibit higher sympathetic activation and strong sympathetic reactivity to auditory stimuli compared to controls. All these are indications of increased sympathetic tone in autism as evidenced in the study. Palkovitz and Wiesenfeld could not, however, find differences in electrodermal responses to auditory stimuli compared to normal controls. Studies also reveal sympathetic underactivity indexed by lower EDA in ASD, which may be associated with potential abnormalities in cortical and subcortical regulatory areas associated with children with autism. These findings are in contrast with most previous studies showing increased or unaltered EDA in ASD. The improvement of atypical behaviors on stimulation of parasympathetic nervous system in children with autism might be due to the suppression of SNS activity, in turn suggesting that chronic hyperactivity of SNS may be a factor contributing to some of the core autistic behaviors.

The slower habituation rate observed in ASDs may reflect their sustained sympathetic excitation due to auditory stimulus and has been proposed to underlie the distinctive social and nonsocial difficulties defined in them. It is also suggested that children with ASDs have difficulty habituating to auditory stimuli due to persistently strong SSRs. Behavioral problems related to auditory and other sensory stimuli are associated with the underlying physiological events that are not under the child’s voluntary control. The altered behavioral response in ASD can thus be associated with their impaired sympathetic nervous activity. Subsequently, this may also contribute to the development of disturbances in social behavior from very early on in ASDs.

A detailed complex analysis of physiological parameters may illuminate the pathway linking ASD and ANS activity. Breakthroughs in the understanding of autism are expected to lead to new approaches for intervention, prevention, or even cure because children with ASD problems should be identified as early as possible for intensive behavioral and educational intervention. ASD continues to be an important public health concern in medical as well as from socioeconomic perspectives; therefore, the findings of this study confirm that tests assessing sympathetic activity could become an important tool in ASD evaluation.

Future studies are needed to pinpoint the underlying mechanisms in the central and peripheral nervous systems that may contribute to this atypical response and to understand the associations between ANS atypicalities and symptomatology. Studies on the challenging issue of SSR waveform and its possible clinical relevance are necessary to explore it in detail.

Limitations of the study

Our findings are based on a cross-sectional study with relatively limited sample size. Further, majority of the children with autism included in the present study were of mild and moderate grades. Data based on an intervention...
study with the training by behavioral therapists, including a larger sample size and all grades of severity of the disease, would help in better understanding of the psychophysiology of ASDs. Therapeutic interventions in autonomic dysfunction will provide a new avenue for both understanding and monitoring the progression of treatment in ASDs.

**Implications of the study**

With the swift increase in the number of children identified with ASD, the need for accurate assessment tools and effective treatment approaches also have increased. There is currently no pharmacological or psychosocial treatment program for the core symptoms of ASD. Development of new neuromodulation and neurotherapy methods aimed at reducing autonomic arousal in children with autism is an important clinical research objective. Considering the increased need for pediatric and specialist services, both for their core functional deficits and concurrent medical conditions in children and adults with ASD, manipulating autonomic function could be a possible treatment avenue for the aggression, anxiety, and irritability, as well as the core symptoms of autism and cognitive functioning. The outcome of the study may play an important role in subgrouping and monitoring of ASD based on this noninvasive test in future.

**CONCLUSIONS**

The study concludes that children with autism exhibited altered sympathetic sudomotor activity, which is evident from their slower habituation to auditory stimulus compared to healthy controls. The slower habituation could be due to sustained sympathetic excitation exhibited in ASDs. The number of pediatric disorders with autonomic dysfunction either primary or secondary is continuing to expand. Therefore, to develop better treatments and to increase our diagnostic acumen in this area, it is essential to have a better understanding of ANS and its normal functioning.

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**Conflicts of interest**

There are no conflicts of interest.

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