Auditory Brainstem Development in Autism: From Childhood Hypo-Responsivity to Adult Hyper-Reactivity

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Abstract

Background: Autism spectrum disorder (ASD) is characterized by sensory disruptions, including auditory processing differences, which can significantly impact social, emotional, and cognitive development. This study investigates auditory brainstem development in Autistic children and adults using auditory brainstem responses (ABRs) and acoustic startle responses (ASRs), two key measures of auditory processing. We hypothesize that early hypo-responsivity in children, measured with ABRs, may lead to compensatory neural adaptations, resulting in hyper-reactivity in adulthood, measured by ASRs.

Methods: The study included 40 Autistic children, 57 non-Autistic children, 20 Autistic adults, and 21 non-Autistic adults. Participants underwent peripheral hearing screening, ABR testing at slow and fast click-rates, and ASR measurements. ABR wave and ASR latencies and amplitudes were analyzed. Statistical analyses included mixed-model ANOVAs and Spearman's correlations to examine group differences and associations with age.

Results: Autistic children exhibited increased ABR wave latencies and reduced amplitudes, indicating slower neurotransmission and reduced neural responsivity in the ascending auditory pathway. In contrast, Autistic adults showed normalized ABR latencies but increased ASR magnitude, suggesting hyper-reactivity to auditory stimuli. Age-related correlations revealed that ABR latencies increased with age in non-Autistic participants, while ASR magnitude was negatively correlated with age in non-Autistic participants. The associations were significantly different between groups.

Conclusion: The findings support the hypothesis that Autistic children experience auditory brainstem hypo-responsivity, which may normalize in adulthood but lead to maladaptive hyper-reactivity. These results highlight the role of early auditory disruptions in shaping long-term sensory processing and reactivity in Autism, emphasizing the need for further research into the neural mechanisms underlying these differences.

Introduction

Autism is a neurodevelopmental condition characterised by challenges in social interaction, communication, and the presence of restricted and/or repetitive behaviors and interests. Sensory disruptions, such as hyper- and hypo- sensitivities, were only included in the most recent version of the diagnostic criteria under the umbrella of restricted and repetitive behaviors[12]. Sensory disruptions are well-documented in clinical[3,4] and experimental measures[3,5]. Moreover, difficulties in sensory processing can cascade to affect social communication and interactions[6–9], education[10–13], and everyday activities[10,14]. Moreover, they are associated with higher rates of social-emotional dysregulation[15,16], anxiety[16–18], and other mental health difficulties[19,20]. Sensory disruptions are often categorized into three subcategories, hyper-responsiveness, hypo-responsiveness, and sensory seeking[19]. They are reported in multiple modalities[21] such as olfactory[22,23], tactile[24–26], auditory[27], visual[28], as well as in the interplay of those modalities[29–34].

Auditory processing plays a crucial role in cognitive development[35], impacting how individuals interpret, understand, and respond to sound stimuli in their environment. Disruptions in auditory processing during early development and critical periods is especially impactful[36–38]. These periods close after structural consolidation, reducing future plasticity as the brain reaches adulthood. Although critical periods provide an exceptional time window for learning and consolidation, they also represent a period of great vulnerability for the developing brain[39]. This study focused on the auditory sensory disruptions at the level of the brainstem across development. There are multiple studies reporting alterations in the ascending auditory brainstems in Autistic individuals, including slower neurotransmission[40–43] and atypical cell structures[44–46]. In addition, there is evidence from animal models of Autism indicating reduced responsivity of the ascending auditory pathway[47,48].

The functionality of the auditory brainstem pathway is commonly measured through the auditory brainstem response (ABR) a well-characterized auditory evoked potential of the brainstem. The ABR output is a waveform with five major wave peaks that have well-established bio generators. Wave I is linked to the distal portion of the auditory nerve with an absolute latency of 1.5 msec[52,53]. While wave II is associated with the proximal portion of the auditory nerve and cochlear nucleus with an absolute latency of 2.5 msec[53,54]. Wave III is generated by the cochlear nucleus and superior olivary complex with an absolute latency of 3.5 msec[55]. Wave IV is associated with the superior olivary complex and ascending auditory fibers of the lateral lemniscus with an absolute latency of 4.5 msec[55]. Wave V corresponds to the lateral lemniscus and inferior colliculus with an absolute latency of 5.5 msec [56–58] (Figure 1). The latency of the wave is indictive to the speed of neurotransmission while the amplitude of the waves is indictive of neural responsivity[56].

ABRs are measured as a common newborn hearing test to provide information about brainstem maturation. Given this, is has been possible to detect differences in ABRs in infants later diagnosed with Autism[49–51]. The ABR reports in Autism, however, have been inconsistent, with some reporting no group differences and others reporting delayed and/or muted ABR waves for

Autistic individuals[59]. The inconsistency could be owed to the heterogeneity of Autism, the variation in the ABR parameters, or the participant ages in the studies. Studies that looked at ABRs in younger samples such as newborns[49–51], toddlers[60,61], or school-aged[62,63] children report increased ABR peak latencies. However adult study results are less consistent[64–66]. This could be due to a delay in the development of the ascending auditory pathway.

There is also bulk of evidence supporting increased behavioral responses to sound associated with Autism, including brainstem-mediated reflexive responses. These responses are commonly measured by the acoustic startle response (ASR), which is an evolutionary conserved protective response to sudden auditory stimuli[4,67–69]. The primary startle pathway includes spiral ganglion cells innervating the cochlea and synapsing on secondary auditory neurons in the cochlear nucleus which innervate the ventrolateral caudal pontine reticular nucleus (PnC)[70]. PnC giant neurons project to the spinal cord where they ipsilaterally innervate motor neurons[70] (Figure 1). The startle response is a measure of acoustic reactivity and is typically quantified in humans using electromyography (EMG) of the eyeblink, in which electrodes measure orbicularis oculi muscle activity. Autistic individuals are reported to have increased startle reactivity. According to the literature, Autistic individuals have been reported to express acoustic hyper-reactivity[3] and hyposensitivity to complex stimuli in the ascending auditory pathway[71], measured by the auditory brainstem response. It is unclear if these two seemingly contradicting constructs are explained by the heterogeneity of Autism.

This study focused on the auditory brainstem development by investigating the auditory brainstem response and the acoustic startle response in a sample of Autistic children and Autistic adults. According to previous report, we expect that Autistic children will have hypo-responsivity to sounds quantified by muted and delayed ABR wave peaks compared to non-Autistic children, while Autistic adults will have normalized ABR. We hypothesize that this hypo-responsivity in Autistic children will lead to the development of an adaptive compensatory gain of auditory signals downstream of the ABR. As the hypo-responsivity of the ABR gets resolved with age, the adaptive compensatory gain would become maladaptive. Therefore, we predict that the Autistic adults will have increased behavioral reactivity measured by startle response compared to non-Autistic adults. Finally, we hypothesize that ABR parameters will negatively correlate with age while behavioural reactivity will positively correlate with age for the Autistic participants.

Methodology

Participants

This study includes 40 Autistic children and 57 non-Autistic children. It also included 20 Autistic adults and 21 non-Autistic adults (Tables 1 and 2). All participants had normal hearing (confirmed in the study, details below) and absence of neurological disorders, history of seizures, or past head injury. Participants' cognitive ability was assessed by the Wechsler Abbreviated Scales of Intelligence, second edition[72] or Kaufman Brief Intelligence Test, Second Edition[73]. The study was a fully passive study therefore allowing us to include 3 Autistic participants that could not sit through the IQ test due to communication difficulties. Participants in the Autism group had a clinical diagnosis of Autism by a professional including medical doctors such as

family physicians, pediatricians and psychiatrists, psychologists and psychological associates, or nurse practitioners. The diagnosis was confirmed by an Autism Diagnostic Observation Schedule, Second Edition[74] conducted by a research-reliable administer, or a clinically reliable administer supervised by a research-reliable administer. Participants in the non-Autism group had no family history of Autism in first-degree relatives. An additional 2 participants were excluded due to ADOS-2 not confirming the Autism diagnosis. Final groups did not differ on hearing screening and age. Participants aged eighteen or more or the parents of younger participants gave informed assent, and children gave assent.

Periphery Hearing Screening

A periphery hearing screening was conducted before being included in the study. The screening consists of a visual otoscope inspection, an audiometric assessment (Midimate 602), and a tympanometry test (MT10 by interacoustics). The evaluation criteria are (1) no perforation in the eardrum, (2) pass an audiometer screen for frequencies (250 Hz, 500 Hz, 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz) < 25 dB, and (3) have a detected tympanogram peak with compliance(ml) = 0.30-1.5, pressure (dapa)= -/+ 100 and ear canal volume (ECV)= 0.5-1.35. All assessments were completed for both ears and the participants were included if they passed 2 out of the 3 assessments for every ear.

Auditory Brainstem Response

The ABR was measured ABR Integrity™ V500 System. The acoustic stimuli were presented via ER-2 insert earphones. Presentations were made monoaurally and click pulses were repeated until a total of 2000 accepted evoked potential sweeps had been collected and accepted. The acoustic stimuli were presented at a slow click-rate (19.1 clicks/sec) and a fast click-rate (59.1 clicks/sec) at sound pressure level of 80 dB HL. Two trials were recorded for every condition from each ear. The peaks were marked by two trained personnels. The ABR variables were averaged across both trials and ears for every participant.

Acoustic Startle Response

The acoustic startle response was recorded using SR-HLAB™ EMG. All auditory stimuli and background white noise were delivered binaurally to participants through stereophonic headphones. Startle eyeblink electromyographic responses were recorded from the left orbicularis oculi muscle. The eyeblink magnitude of every startle response was defined as the voltage of the peak electromyographic activity within a latency window of 20 to 160 msec following startle-eliciting stimulus onset. The startle onset was defined as the point of positive inflection of the volts before startle peak and the startle latency is the latency of the peak voltage. The peaks were marked automatically by the software. The paradigm consisted of a 5-minute acclimation period and consistent 60 dB white noise background. The acoustic reactivity trials consisted of white noise pulse ranging from 65db to 105db for 40 msec with 10db increments and all trial conditions were repeated 10 time. All trials were presented in a fixed pseudorandom order, separated by intertrial intervals of 10 to 20 s (15 s on average). Startle magnitude was averaged for every condition.

Statistical Analysis

The main objective of the study was to investigate functional and behavioral measures of the auditory brainstem across development in Autism. To compare group differences, we used a four-way, mixed-model ANOVA with between-subjects factors of diagnostic group (Autistic, non-Autistic), sex (females, males), and age (kids, adults) and a within-subjects factors of click rate for ABR (slow, fast) and sound-level intensity for ASR (65dB, 75dB, 85dB, 95dB, 105dB). In cases when the parametric assumptions were not met, a rank-based ANOVA was completed. The Mauchly test was used to determine whether the data violated the sphericity assumption. In the case of a violation, the degrees of freedom were corrected using the Greenhouse–Geisser correction. Main effects and interactions were assessed, followed by post hoc simple main effect analysis for the overall effect of diagnostic group and t-tests using a Bonferroni correction to further investigate specific differences between Autistic and non-Autistic at a given age. Differences were considered statistically significant when adjusted p-values were smaller than 0.05. In all experiments, interactions involving diagnostic group or a main effect of diagnostic group were of utmost interest. Spearman's rank correlation was used to assess the relationship between ABR and reactivity features, and Age in both the Autistic and Non-Autistic groups. Bootstrapping with 1,000 resamples was applied to estimate 95% confidence intervals (CIs) for the correlation coefficients and the difference in correlations between groups. Data analyses were performed with Microsoft Excel office 365 and graphical display was completed with GraphPad Prism 6.01. R was used for statistical analysis. The study was pre-registered in Open Science Foundation osf.io/hg6b2.

Results

Periphery Hearing Screening

There were 10 participants excluded from the study based on their periphery hearing screening (Tables 3 and 4). They are not included in the study's total number of participants.

ABR: Absolute and Interpeak latencies

We analyzed absolute latency of ABR (figure 2; figure 3) wave I, negative wave 1, wave II, wave III, wave V and negative wave V and interpeak latencies (IPLs; Figure 4) between waves I and III (I–III IPL) as well as waves III and V (III-V IPL) and overall waveform of wave I and V (I-V IPL; sex X click-rate X diagnostic group X Age group). Overall, the diagnosis group differences are summarized with increased absolute latencies for Autistic children compared to non-Autistic children. The main effects of sex (Table 5), age (Table 6), and ABR click-rate (Table 7) are summarized in the tables.

ABR: Wave amplitudes

The amplitudes of waves I, III, and V were analyzed and there was a main effect of group for all waves (Figures 2 & 5). There were no interactions with group. In addition, there was no main

effect of group on central gain which is the ratio of wave V to wave I. The Autistic participants had reduced neural responsivity across the ascending auditory pathway.

ASR: Startle Magnitude

Startle magnitude was higher for the Autistic participants with a main effect of group (Figure 6) on acoustic reactivity. There was also a 3-way interaction of group by age by sex. When probing the interaction, we found a simple main effect of diagnostic group on reactivity for adults and a simple main effect of diagnostic group on female children. The Autistic participants presented with hyper-reactivity to auditory stimuli.

ASR: Startle latency

There was a three-way interaction of group by age by sex on startle latency ($F_{(1,615)} = 5.86$, $p = 0.016$) and startle onset ($F_{(1,620)} = 9.62$, $p = 0.002$) but when probing for simple main effects there was no simple main effect of group.

Associations with age

The ASR reactivity was only negatively correlated with age for the non-Autistic participants (Table 6).The ABR wave latencies were positively correlated with age, while amplitudes were negatively correlated (Figure 7). When splitting the groups by diagnosis some associations were only significant for one of the groups (Table 8), for example wave I latency was positively correlated with age for the non-autistic participants, a relation not established for the autistic participants. There were no significant associations of age and startle latency or startle onset.

ABR and acoustic reactivity associations

ABR amplitudes and reactivity associations are in opposite directions for Autistic and non-Autistic participants (Table 9). Wave I and wave V amplitudes were positively correlated with reactivity for the non-autistic participants while they were negatively correlated with reactivity for the autistic participants. The associations were significantly different from each other.

Discussion

We investigated whether Autistic children and adults experienced a combination of brainstem mediated auditory hypo-responsiveness and hyper-reactivity. Participants completed a passive paradigm of auditory tasking which included ABR as a measure of neural responsivity and ASR as a measure of behavioral reactivity. We hypothesized that the Autistic children would present altered neural responsivity while Autistic adults will have normalized auditory brainstem responsivity and increased behavioral reactivity. This auditory profile could be due to compensatory adaptive auditory gain formed during critical windows of experience induced plasticity in Autistic children that impacts their reactivity to sound long term. The auditory system expresses increased experience-induced plasticity in younger age. For example, in congenitally deaf children, the maturation of the auditory evoked potentials depended on the age of cochlear implantation with optimal development occurring in implantation before the age of

3.5 years[75]. Therefore, the hypo-responsivity experienced in early-life of Autistic children could have cascading effects on their auditory system long-term.

Indeed, Autistic children showed reduced neural responsivity and slower neurotransmission in their ascending auditory pathway, evidenced by increased latencies and reduced amplitudes of ABR waves. Autistic children presented with increased ABR absolute latencies in the ascending brainstem auditory pathway starting at the auditory nerve, lateral lemniscus, and the inferior colliculus. In contrast, Autistic adults did not show increased latency, meaning the ascending auditory pathway could be experiencing a perturbation in development that eventually normalizes, a finding consistent with multiple studies (for review, see[59,76]).

In addition, one of the possible cascading effects of hypo-responsivity in the ascending auditory pathway could be the hyper-reactivity to sounds. In this study, we investigated acoustic reactivity to sounds using the acoustic startle response. The Autistic participants had an increased reactivity to sound in combination with the reduced responsivity in the brainstem auditory pathway, a contradiction posed previously. This was even more pronounced in the Autistic adults as indicated by the age by reactivity interaction. An explanation for this observation is the presence of a compensatory gain that is mediating the startle response. The primary startle pathway includes the cochlear nerve and the cochlear nucleus in the brainstem that relays the signal to the caudal pontine reticular nucleus (PnC), which coordinates motor responses via projections to spinal and cranial motor neurons. It is modulated by midbrain circuits such as the inferior colliculus, amygdala, and periaqueductal gray to adjust the reflex based on sensory or emotional context.

The ABR and ASR pathways directly intersect at the cochlear nerve and the cochlear nucleus. They also indirectly intersect through the midbrain ASR modulatory pathways (inferior colliculus - superior colliculus - Pedunculopontine Tegmental Nucleus) that adjust the response intensity based on the sensory context. The increased magnitude of the startle response associated with Autism is regulated by the excitability, size and number of recruited PnC giant neurons, as recently shown in an *Cntnap2* knock-out Autism rat model[83]. A similar modulation in the sensorimotor interface of those pathways is most likely causing the increased reactivity to sound in Autistic individuals.

Autistic participants with more severe disruptions in the ascending auditory pathway also experience higher hyper-reactivity. There is an intuitive understanding of an increase in responsivity inducing hyper-reactivity. However, the negative relationship observed in the Autistic participants is an indication that disruptions in the ascending auditory pathway highlight systematic differences in the auditory brainstem. The change in the auditory responses across development hint toward compensatory changes in the auditory gain.

The idea of maladaptive sensory gain stems from reports of reduced neurotransmission of the ascending auditory pathway of newborn babies later diagnosed with Autism[51,84]. During early postnatal development neural circuits, both structural and functional, are shaped by exposure to sensory input. These periods of heightened plasticity play a crucial role in the maturation of sensory representations in both subcortical and cortical regions, influencing the development of

behavior and cognition. In the auditory system, this period of rapid refinement supports the acquisition of specialized skills such as phoneme recognition, language learning, absolute pitch, and musical ability, but it also marks a time of heightened vulnerability to sensory deprivation. The early reduced responsivity and slowed neurotransmission regardless of the molecular reason could induce adaptive excitatory gain or reduced inhibitory gain within the auditory system. As evidenced in our results, the ABR pathway partially recovers its output and therefore what was considered adaptive would induce maladaptive gain, leading to behavioral hyper-reactivity.

Mechanistically, the ABR differences could be linked to possible molecular and cellular changes. Slower neural transmission could be due to dysfunction in myelination, pathway length, axonal diameter, the (a)synchronization of neuronal firing, or synaptic efficacy[77]. Those factors cannot be directly linked or consistently linked to Autism as there is evidence of opposing findings within the central nervous system. For example, diffusion tensor imaging mean diffusivity of white matter microstructure findings has shown both increased[78] and decreased[79] in Autism. While ABRs do not directly measure white matter microstructure, ABRs are sensitive to changes in axonal morphology and myelination, axon bundle density and fiber orientation distribution, and other intra- and extra-cellular processes.

In addition, Autistic children had reduced amplitude of waves I, III and V, which implies reduced neural responsivity across the ascending auditory pathway starting at the dorsal end of the auditory nerve through the cochlear nucleus and the superior olivary complex to the lateral lemniscus and inferior colliculus. The ABR wave amplitudes are related to synchronized neural activity [54], and a reduced amplitude could be due to numerous reasons such as desynchrony in the neural firing, reduced number of firing neurons, or synaptic dysfunction. Amplitudes are not commonly examined clinically and in research, and results are limited and contradicting. For example, Wave III has been previously reported to have reduced [71] or increased amplitude [80] in Autism. Moreover, typically ABR wave amplitudes reduce with age, and this association is observed in our sample.

Unlike the children, there were no latency differences between Autistic and non-Autistic adult groups, therefore it seems like the speed of conduction recovers with age. For the non-Autistic group, latency of ABR wave I was positively associated with age as aging increase ABR peak latencies, with significant shifts limited to early waves[81]. The Autistic participants do not have the same developmental trajectory which results in Autistic adults having a normalized ABR waveform. Although neuronal responsivity and conduction may partially recover by adulthood, the cascading and lasting effects of these initial reductions could extend well beyond this period.

The atypical development of the ascending auditory pathway is also supported by differences in the brainstem being more often reported in Autistic children than Autistic adults[59]. Longitudinal ABR studies also report a decline in the group differences between Autistic and non-Autistic children across age[60,61].

There is no consensus on the structural or synaptic condition within the ascending brainstem pathways in Autism therefore it is difficult to disentangle the specific reasons for the reduction in action potential velocity and responsivity. One interpretation of our findings is that the ascending

auditory pathway has a combination of abnormalities such as reduced number of cellular nuclei, reduced axonal diameter, asynchronization of neuronal firing and changes in myelination that results in this unique ABR profile in Autism. Those kinds of changes are observed in post-mortem analysis of the superior olivary complex in which the nuclei have altered volumes[44,82], shapes[45], and number[45] (for a review[59]). Some of those features undergo tuning based on sensory experiences and this experience-based tuning may lead to cascading sensory and hyper-reactivity differences in Autistic children and adults.

Addressing ABR methodology heterogeneity

While the atypical ABR finding is not unique to our study, results in the field have been highly heterogeneous. Three factors have been previously suggested to contribute to the heterogeneity of the literature which our current design addresses. The first factor of variation is age[66,76] in which some studies have age-specific ranges, while others examine ABR across less-defined age ranges. In this study, we age-matched and included an age analysis. Another factor is the inclusion of participants with possible peripheral hearing loss - we controlled for this using a battery of periphery hearing evaluation (tables 3 and 4). Finally, another common confounding factor is the ABR click-rate, since it could be used to exert varying levels of challenge to the auditory nerve, with faster click rates eliciting longer wave latencies[66,85,86].This study employed a slow click-rate and a fast click-rate to eliminate the click-rate related variation. While there was a main effect of click-rate on ABR wave features, there was no group by rate interactions. All in, we present robust evidence for altered ABR waves of Autistic children and adults.

Limitations

This study has several limitations that warrant consideration when interpreting the findings. First, the exclusion of Autistic participants with the most severe auditory and sensory sensitivities introduces a potential selection bias. Some participants, particularly those with significant tactile sensitivities, were unable to complete the study due to discomfort caused by the conductive gel, despite the study being focused on auditory processing. This limits the generalizability of the results, as the participants who completed the study may represent a subset of the Autistic population with milder sensory challenges. Second, the underrepresentation of Autistic females in the study, combined with the fact that many Autistic women included were diagnosed in adulthood, introduces additional biases. Late-diagnosed women often present with less pronounced sensory differences due to either a milder symptom profile or the development of coping strategies over time. These factors may have skewed the findings, as the sample may not accurately reflect the broader variability of sensory experiences in Autistic individuals, particularly among females. Future studies should strive for greater inclusion of individuals with severe sensory sensitivities and ensure more representative sex diversity to better capture the full spectrum of sensory processing differences in Autism.

Conclusion

In conclusion, this study provides robust evidence for altered auditory brainstem responses in Autistic children and adults, highlighting unique patterns of neural responsivity and behavioral reactivity. Our findings suggest that disrupted auditory processing in childhood may have long-term effects on sensory integration and reactivity, potentially due to maladaptive neural plasticity during critical developmental periods. These disruptions likely involve a combination of factors, including changes in synaptic efficiency, neural synchronization, axonal properties, and brainstem nuclei structure, as supported by both our findings and the broader literature. While the normalization of ABR latency in Autistic adults suggest recovery in conduction speed, the persistence of hyper-reactivity underscores the lasting impact of early auditory pathway disruptions. These results not only deepen our understanding of auditory processing differences in Autism but also highlight the importance of investigating the interplay between brainstem-mediated sensory responsivity and higher-order cognitive and sensory functions. Overall, these findings underscore the atypical auditory brainstem profile of hypo-responsivity and hyper-reactivity in Autistic individuals and the partial recovery of the ascending auditory pathway across development.

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CRediT Statement. AS – Conceptualization, Methodology, Formal analysis, Investigation, writing – original draft, writing – review and editing, Visualization. RG – Investigation, MR – Investigation, CM – Investigation, KS – Investigation, RAS – Conceptualization, resources, writing – review and editing, supervision, project administration, funding acquisition. SS Conceptualization, review and editing

Table 1: Demographic information for the children sample.

Children Sample	*Autistic*	*Non-Autistic*
N	40	57
Age (years)	10 ± 2.9	9 ± 2.9
Sex (% male)	85 (% male)	51 (% male)
FSIQ-2 composite score	93.6 ± 20.8	109.7 ± 13.6

Table 2: Demographic information for the adult sample. A subset of the adult non-Autistic sample were undergraduate university students, and they did not complete a cognitive assessment as it was assumed to be IQ >70.

Adult Sample	*Autistic*	*Non-*

		Autistic
N	20	21
Age (years)	28 ± 6.5	23 ± 5.1
Sex (% male)	47%	31
FSIQ-2 composite score	112.4 ± 14.3	113.6 ± 15.9

Table 3: The values (mean ± standard deviation) of the periphery hearing evaluation for the children sample. The quietest loudness tested for all frequencies (250 – 8000 Hz) was 15 dB. It is much quieter than our stimuli and reduced the study time by forgoing thresholding at every frequency. All variables were not statistically significant different between groups.

Children Sample	*Autistic*		*Non-Autistic*	
Audiogram	Right	Left	Right	Left
250 Hz	15.9 ± 3.0	15.4 ± 2.0	16.2 ± 3.1	16.6 ± 3.7
500 Hz	15.5 ± 2.7	15.5 ± 2.0	15.4 ± 1.7	15.8 ± 2.7
1000 Hz	15.9 ± 3.9	15.5 ± 2.0	15.3 ± 1.7	15.4 ± 1.7
2000 Hz	15.3 ± 1.7	15.2 ± 0.9	15.2 ± 1.4	15.1 ± 0.7
4000 Hz	15.1 ± 0.7	15.0 ± 0.0	15.1 ± 0.7	15.2 ± 1.4
8000 Hz	15.2 ± 0.9	15.6 ± 2.1	15.5 ± 2.1	15.8 ± 2.7
Tympanogram				
Peak pressure (daPa)	-43.6 ± 57.6	-34.7 ± 51.5	-35.6 ± 42.0	-32.7 ± 47.4
Compliance (ml)	0.68 ± 0.2	0.74 ± 0.3	0.65 ± 0.5	0.64 ± 0.3
Ear canal volume (cc)	0.98 ± 0.3	0.95 ± 0.3	0.85 ± 0.3	0.89 ± 0.3

Table 4: The values (mean ± standard deviation) of the periphery hearing evaluation for the adult sample. The quietest loudness tested for all frequencies (250 – 8000 Hz) was 15 dB. It is much quieter than our stimuli and reduced the study time by forgoing thresholding at every frequency. All variables were not statistically significant different between groups.

Adult Sample	*Autistic*		*Non-Autistic*	
Audiogram	Right	Left	Right	Left
250 Hz	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
500 Hz	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
1000 Hz	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
2000 Hz	15.5 ± 2.2	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
4000 Hz	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0	15.0 ± 0.0
8000 Hz	15.8 ± 2.4	15.3 ± 1.1	15.5 ± 2.2	15.5 ± 2.2
Tympanogram				
Peak pressure (daPa)	-16 ± 44.8	-19.1 ± 15.1	-15 ± 6.7	-18.9 ± 21.4
Compliance (ml)	0.82 ± 0.3	0.83 ± 0.4	0.63 ± 0.3	0.66 ± 0.3

Ear canal volume (cc)	1.07 ± 0.3	1.12 ± 0.3	1.16 ± 0.4	1.19 ± 0.3

Table 5: List of variables with a main effect of sex.

Variable	*Main effect*
Absolute wave II	$F_{(1,244)} = 9.55$, $p = 0.0022$
Absolute wave III	$F_{(1,254)} = 13.60$, $p = 0.00028$
Absolute wave V	$F_{(1,234)} = 48.18$, $p < 0.0001$
Absolute negative wave V	$F_{(1,252)} = 8.02$, $p = 0.005$
IPL waves I-V	$F_{(1,240)} = 17.62$, $p<0.0001$
Amplitude wave V	$F_{(1,256)} = 16.72$, $p <0.0001$

Table 6: List of variables with a main effect of age.

Variable	
Absolute wave II	$F_{(1,244)} = 13.79$, $p = 0.00025$
Absolute negative wave V	$F_{(1,252)} = 4.91$, $p = 0.028$
IPL waves I-III	$F_{(1,258)} = 7.91$, $p = 0.0053$
IPL waves III-V	$F_{(1,244)} = 5.02$, $p = 0.026$
Amplitude wave III	$F_{(1,240)} = 9.71$, $p <0.002$
Amplitude wave V	$F_{(1,256)} = 33.48$, $p < 0.0001$

Table 7: List of variables with a main effect of ABR click-rate.

Variable	
Absolute wave III	$F_{(1,254)} = 22.42$, $p < 0.0001$
Absolute wave V	$F_{(1,234)} = 132.75$, $p < 0.0001$
Absolute negative wave V	$F_{(1,252)} = 58.57$, $p < 0.0001$
IPL waves I-III	$F_{(1,258)} = 11.71$, $p = 0.00072$
IPL waves III-V	$F_{(1,244)} = 29.92$, $p <0.0001$
IPL waves I-V	$F_{(1,240)} = 68.48$, $p <0.0001$
Amplitude wave I	$F_{(1,256)} = 13.24$, $p = 0.0003$
Amplitude wave III	$F_{(1,240)} = 19.9$, $p <0.0001$

Amplitude wave V	$F_{(1,256)} = 13.24$, $p = 0.0003$

Table 8: Spearman's rank correlation of ABR features and reactivity with age, and difference in correlations between groups.

	Spearman ρ	*P-value*	*CI*	*Difference in Correlation*	*CI*
ABR Wave I latency					
Autistic	-0.02	0.903	[-0.30 0.25]		
Non-Autistic	0.33	0.006	[0.07 0.54]		
Autistic – non-Autistic				-0.35	[-0.72 -0.01]
ABR Wave I Negative latency					
Autistic	0.15	0.27	[-0.14 0.45]		
Non-Autistic	0.36	0.003	[0.13 0.57]	-0.22	[-0.56 0.15]
Autistic – non-Autistic					
ABR Wave II latency					
Autistic	0.31	0.022	[0.01 0.58]		
Non-Autistic	0.42	0.0004	[0.23 0.60]		
Autistic – non-Autistic				-0.11	[-0.48 0.23]
ABR Wave I amplitude					
Autistic	-0.28	0.03	[-0.51 0.01]		
Non-Autistic	-0.30	0.01	[-0.53 -0.06]		
Autistic – non-Autistic				-0.03	[-0.35 0.38]
ABR Wave V amplitude					
Autistic	-0.27	0.04	[-0.51 -0.01]		
Non-Autistic	-0.23	0.06	[-0.49 0.05]		
Autistic – non-Autistic				-0.04	[-0.40 -0.34]
ASR reactivity					
Autistic	-0.08	0.26	[-0.21 0.07]		
Non-Autistic	-0.12	0.04	[-0.24 -0.004]		
Autistic – non-Autistic				0.04	[-0.15 0.23]

Table 9: Spearman's rank correlation of ABR and ASR reactivity features, and difference in correlations between groups.

	Spearman ρ	*P-value*	*CI*	*Difference in Correlation*	*CI*	*P-value*
ABR Wave I and ASR magnitudes						
Autistic	-0.09	0.17	[-0.23 0.04]			
Non-Autistic	0.15	0.018	[0.03 0.27]			
Autistic – non-Autistic				-0.24	[-0.42 -0.07]	0.004
ABR Wave III and ASR magnitudes						
Autistic	-0.01	0.90	[-0.16 0.14]			
Non-Autistic	-0.01	0.93	[-0.13 0.11]	-0.003	[-0.21 -0.18]	0.98
Autistic – non-Autistic						
ABR Wave V and ASR magnitudes						
Autistic	-0.003	0.96	[-0.14 0.13]			
Non-Autistic	0.22	0.0004	[0.11 0.34]			
Autistic – non-Autistic				-0.23	[-0.41 -0.05]	0.016

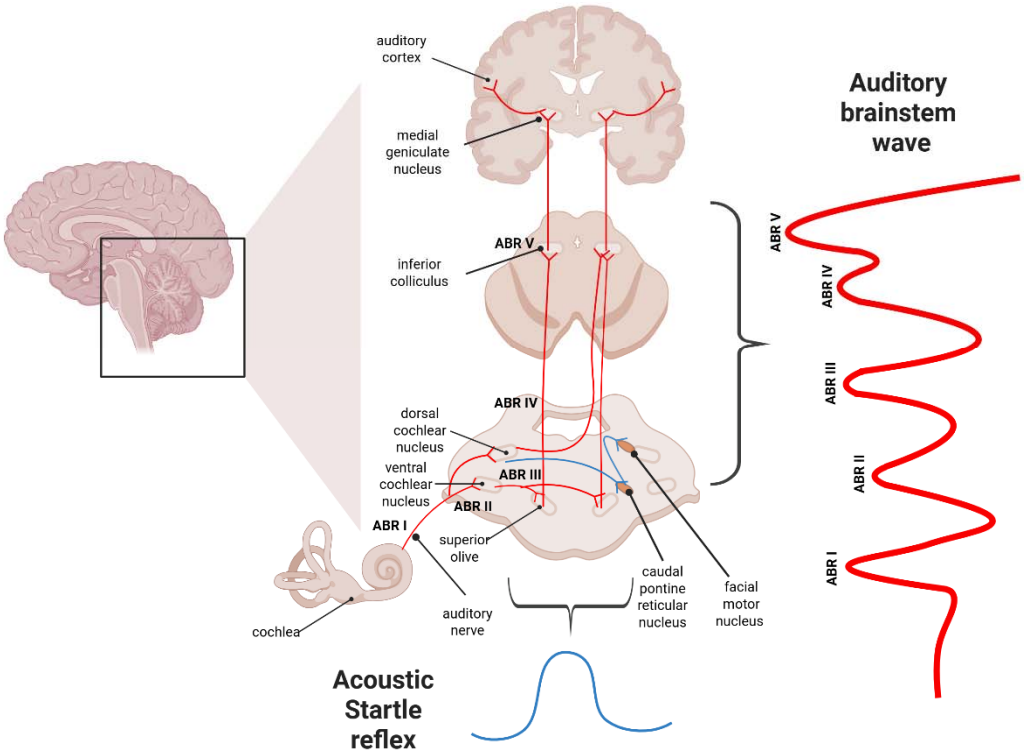

Figure 1: The pathways involved with the acoustic startle reflex and the auditory brainstem response.

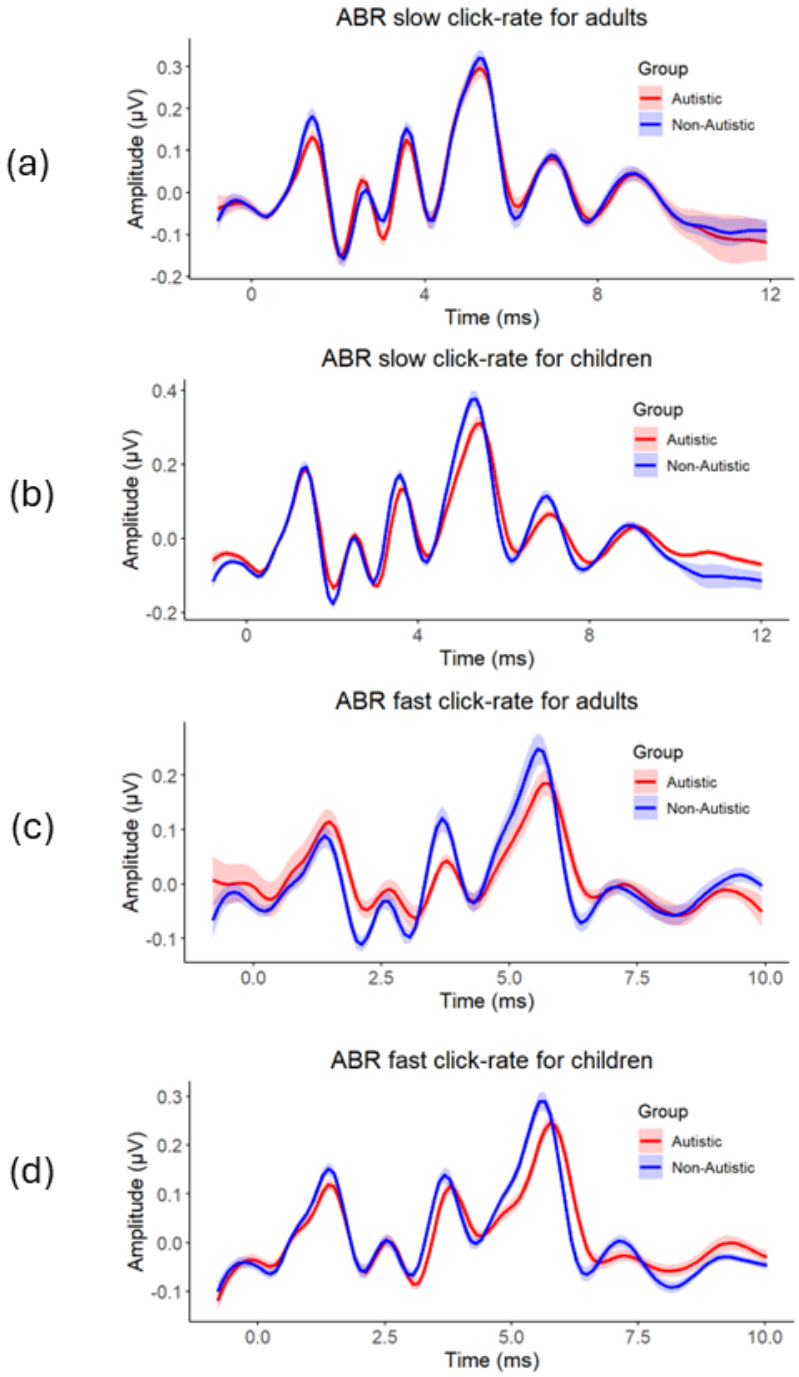

Figure 2: The averaged ABR waveforms. (a) The averaged ABR waveform of the fast click-rate for the children sample. (b) The averaged ABR waveform of the slow click-rate for the children sample. (c) The averaged ABR waveform of the fast click-rate for the adult sample. (d) The averaged ABR waveform of the slow click-rate for the adult sample.

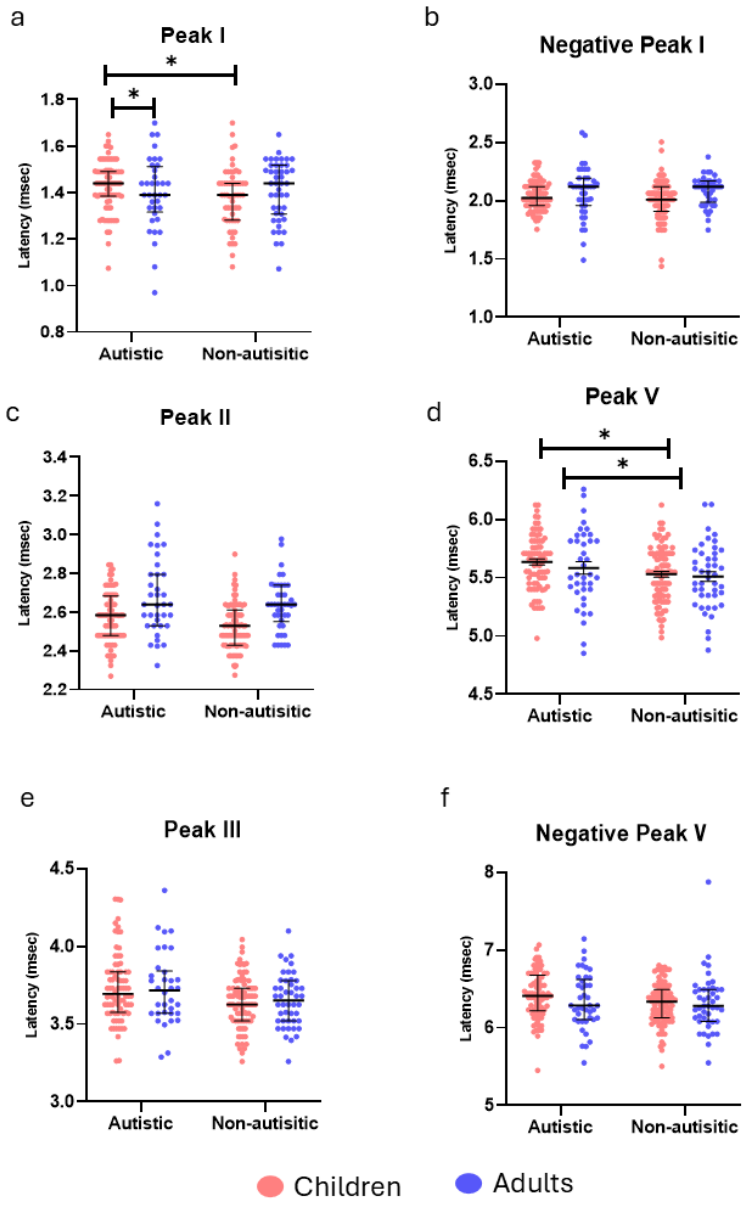

Figure 3: Absolute latency of ABR wave peaks. (a) There was a group by age interaction ($F_{(1,250)} = 6.28$, $p = 0.01$) on wave I absolute latency with a simple main effect of group for the children ($F_{(1,228)} = 4.26$, $p = 0.04$) with Autistic children having increased absolute latency. (b) Absolute negative wave 1 has no main effect of diagnostic group. (c) Absolute wave II has no main effect of diagnostic group. (d) Absolute wave III has no main effect of diagnostic group. (e) The absolute wave V latency had a main effect of diagnostic group ($F_{(1,234)} = 9.90$, $p = 0.0019$) and two thee-way interactions of diagnostic group by sex by age ($F_{(1,234)} = 4.47$, $p = 0.036$) and diagnostic group by rate by age ($F_{(1,234)} = 4.93$, $p = 0.027$). The simple main effects revealed a main effect of diagnostic group on the absolute wave V of Autistic children ($F_{(1,234)} = 13.7$, $p = 0.0005$ adjusted). (f) There was no main effect of diagnostic group on the absolute latency of negative wave V.

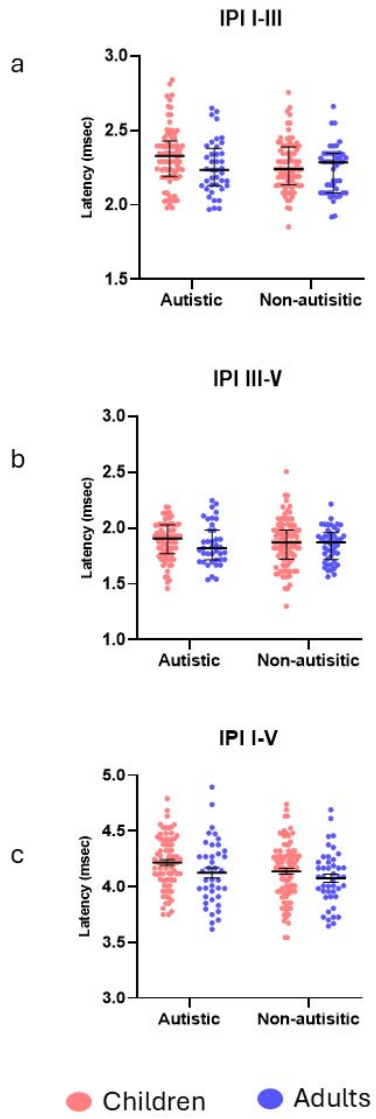

Figure 4: Interpeak latencies of ABR wave peaks. (a) There was no main effect of diagnostic group on interpeak latencies I-III. (b) There was no main effect of diagnostic group on interpeak latencies III-V. (c) There was no main effect of diagnostic group on interpeak latencies I-V. There was a group by rate by age interaction for IPL I-V approaching significance ($F_{(1,240)} = 3.61$, $p = 0.059$). Probing this interaction revealed a simple main effect of group for kids ($F_{(1,240)} = 5.94$, $p = 0.032$ adjusted).

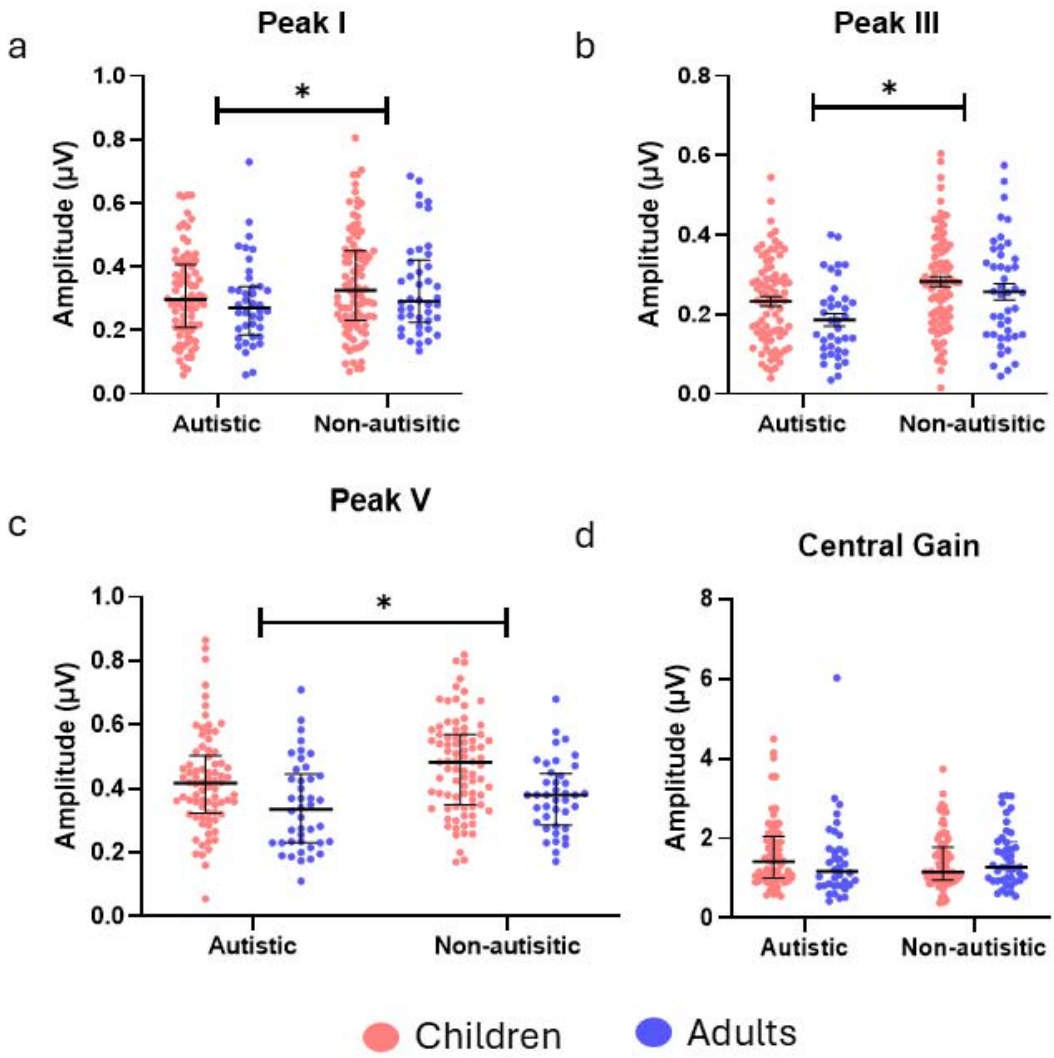

Figure 5: The amplitude of ABR wave peaks. (a) There was a main effect of diagnostic group on amplitudes of waves I ($F_{(1,244)} = 4.16$, $p = 0.043$). (b) There was a main effect of diagnostic group on amplitudes of waves III ($F_{(1,240)} = 4.44$, $p = 0.036$). (c) There was a main effect of diagnostic group on amplitudes of waves V ($F_{(1,256)} = 5.27$, $p = 0.023$). (d) There was no main effect of diagnostic group on central gain which is the ratio of wave V to wave I.

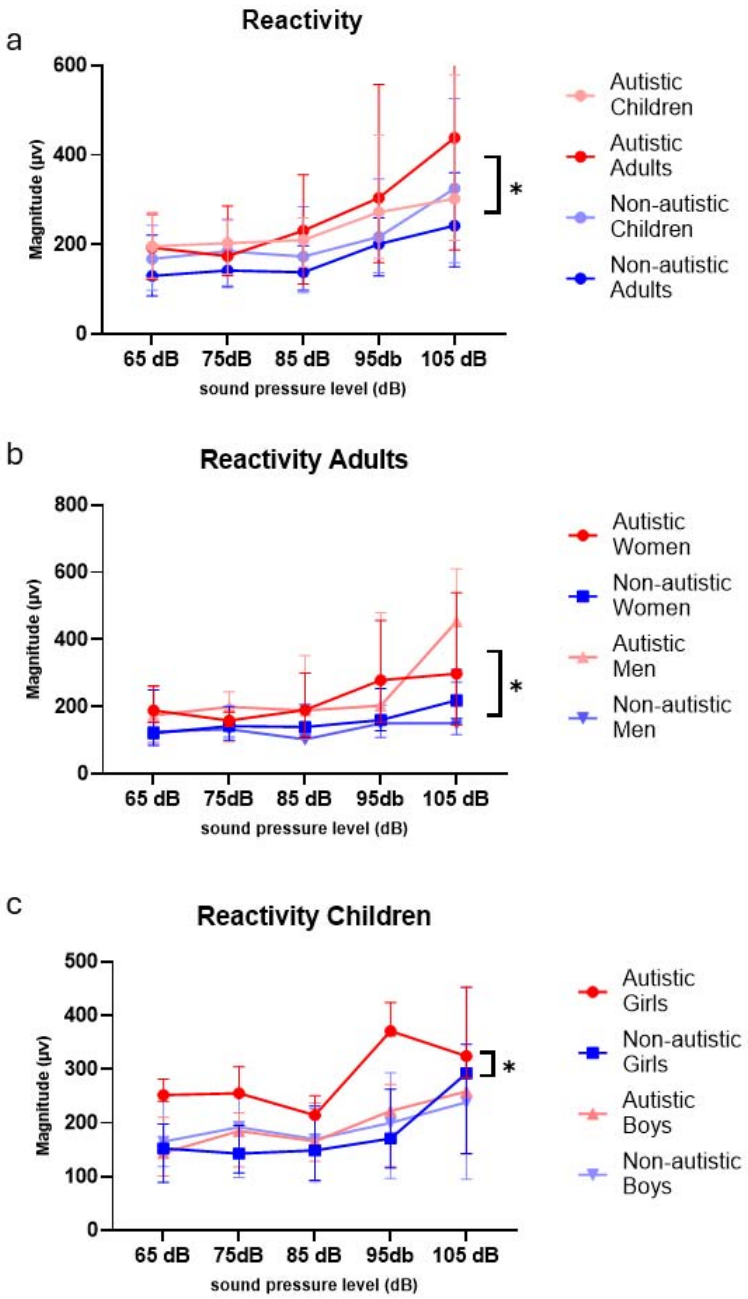

Figure 6: The acoustic startle reactivity magnitude. (a) There was a main effect of diagnostic group on startle magnitude ($F_{(1,285)} = 16.74$, $p < 0.0001$) and a 3-way interaction of diagnostic group by age by sex ($F_{(1,285)} = 16.84$, $p < 0.0001$). (b) There was a simple main effect of diagnostic group ($F_{(1,190)} = 7.13$, $p = 0.0166$ adjusted) on reactivity for Autistic adults. (c) There was a simple simple main effect of diagnostic group ($F_{(1,150)} = 8.11$, $p = 0.02$ adjusted) on Autistic female children.

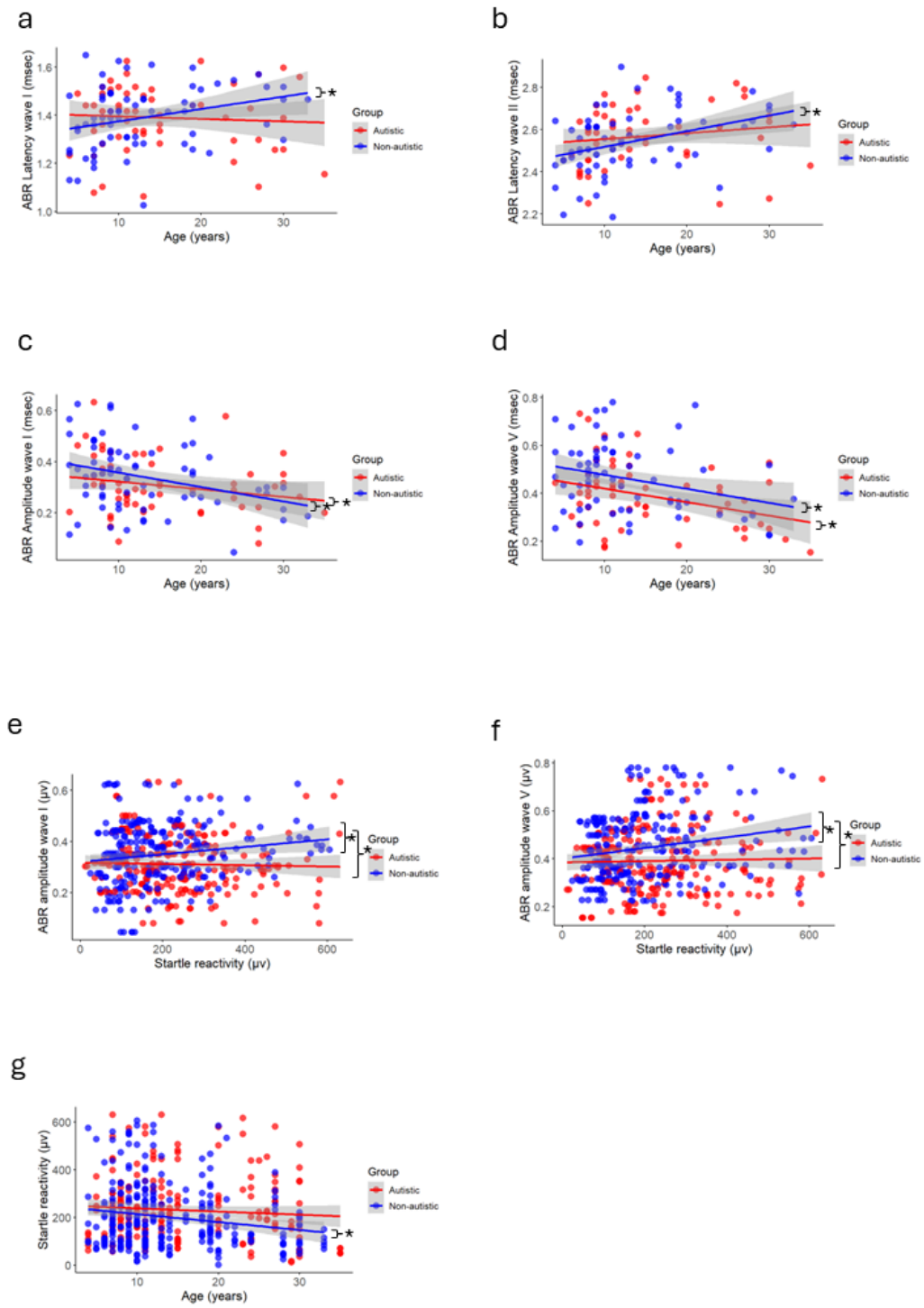

Figure 7: The ABR wave latencies was positively correlated with age for waves I (ρ= .18, p = .0498), negative wave I (ρ = .27, p < 0.0001), and wave II (ρ = .36, p <0.0001) across groups. Regarding amplitude, the age was negatively correlated with wave I (ρ = - .32, p = .0002) and wave V (ρ = - .30, p < 0.0001) amplitudes across diagnostic groups.

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