Research paper

Auditory brainstem responses in adults with autism spectrum disorder

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ABSTRACT

Objective: To investigate possible differences in the auditory peripheral and brainstem functions between adults with autism spectrum disorder (ASD) and neurotypical (NT) adults.
Methods: Click-evoked auditory brainstem responses (ABRs) were obtained from 17 high-functioning ASD adults (aged 21–38 years) and 20 NT adults (aged 22–36 years). A relatively large number of stimulus presentations (6000) were adopted, and ABRs by horizontal and vertical electrode montages were evaluated, in order to allow precise evaluations of early ABR components.
Results: Waves I, II, III, and V were identified in the vertical electrode montage, and wave I and the summating potential (SP) in electrocochleograms were identified in the horizontal electrode montage. There were no significant group differences in the wave I, II, III, and V latencies or the interpeak latencies (IPLs) in the vertical electrode montage. In the horizontal montage, the ASD adults exhibited significantly shortened SP latencies compared with the NT adults, whereas there was no significant group difference in the wave I latency.
Conclusion: The ASD adults may have the abnormalities of processing more in the peripheral auditory system than in the brainstem.
Significance: The current study suggests that the peripheral abnormality is associated with ASD.
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1. Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social interaction and communication and by restricted, repetitive behavioural patterns (American Psychiatric Association, 2013). In addition to these symptoms, many individuals with ASD have sensory dysfunction, particularly in the auditory domain, such as auditory hypersensitivity (Danesh et al., 2015; Khalfa et al., 2004; Rosenhall et al., 1999), difficulty in speech understanding in noise (Alcantara et al., 2004; O'Connor, 2012), and impaired sound localization (Visser et al., 2013). The sensory dysfunction can make ASD symptoms worse. For example, the ability to understand speech in noise is necessary in daily conversation, and the deficits in this ability negatively affect social interaction and communication. Therefore, understanding the characteristics and mechanisms of sensory dysfunction and providing an adequate environment or treatment could improve the quality of life of individuals with ASD (Hitoglou, 2010).

Recent studies have suggested that the brainstem is involved in ASD (Dadalko and Travers, 2018; Inui et al., 2017). The subcortical auditory system plays a key role in processing temporal and spatial information about sounds, such as periodicity, temporal fine structures, amplitude/spectral envelopes, amplitude/frequency modulation, and interaural time/level differences, as bases for pitch, timbre, sound localization, and so on (Burser and Imbert, 1992; Pickles, 1988). Therefore, brainstem abnormalities have been considered to cause auditory dysfunction in ASD (Pillion et al., 2018), and there is some evidence to support this. Anatomical studies have shown a decreased number of neurons and neural dysmorphology in the brainstem nuclei of individuals with ASD relative to control individuals, especially in the superior olivary complex (SOC) (Kulesza and Mangunay, 2008; Kulesza et al., 2011; Lukose et al., 2015). In an adult with ASD, the structures at the junction of the pons and the medulla were closer to the structures of the lower medulla (Rodier et al., 1996; Rodier, 2000). Magnetic resonance imaging (MRI) studies have shown a reduction in the pons in individuals with ASD compared with control individuals (Ciesielski et al., 1997; Hashimoto et al., 1992, 1995).

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A number of studies have used auditory brainstem responses (ABRs) to assess functional abnormalities of the auditory nerve and brainstem in ASD. The ABR to click sounds consists of seven positive peaks within 10 ms after the stimulus onset, denoted as waves I–VII. Waves I and II are generated by the auditory nerve. Waves with numbers from III up to and including wave V are generated in the auditory brainstem. Wave III is believed to originate from the cochlear nucleus; wave IV from the SOC; and wave V from the lateral lemniscus and the inferior colliculus (Eggermont., 2019; Møller and Jannetta, 1983; Møller et al., 1988; Parkkonen et al., 2009).

A large number of studies have focused on the latencies of waves I, III, and V in infants and children with ASD, and have reported prolonged absolute wave III and V latencies and interpeak latencies (IPLs) I–V, I–III, and III–V (Azouz et al., 2014; Cohen et al., 2013; Kwon et al., 2007; Magliaro et al., 2010; Maziade et al., 2000; Miron et al., 2016; Rosenblum et al., 1980; Rosenhall et al., 2003; Roth et al., 2012; Skoff et al., 1980; Taylor et al., 1982; Ververi et al., 2015). Meanwhile, the relatively few studies that have investigated the ABRs in adults with ASD have shown that absolute wave III and V latencies were normal (Courchesne et al., 1985; Grillon et al., 1989). According to a recent meta-analysis, prolonged wave V latencies in infants and young children with ASD change into normal or short latencies with aging (Miron et al., 2018; Talge et al., 2018). Taken together, the findings suggest an unusually fast developmental trajectory of the brainstem function in ASD (Miron et al., 2018).

In contrast to the consistent findings of waves III and V in individuals with ASD, the evidence of abnormalities in wave I latency remains equivocal (Pillion et al., 2018). Some studies reported normal absolute wave I latencies (Courchesne et al., 1985; Demopoulos and Lewine, 2016; Garreau et al., 1984; Grillon et al., 1989; Known et al., 2006; Magliaro et al., 2010; Miron et al., 2016; Rosenblum et al., 1980; Santos et al., 2017; Sersen et al., 1990; Skoff et al., 1980; Tharpe et al., 2006), and others reported abnormal latencies that were prolonged (Azouz et al., 2014; Rosenhall et al., 2003; Roth et al., 2012; Tanguay et al., 1982) or shortened (Dabbous, 2012). The reason for these diverse results may be that ASD participants with a wide age range were tested (e.g., range 3–24 years; 4–21 years). Taking into account that wave V latency in ASD changes with aging, it is likely that wave I latency also does. Accordingly, wave I latencies should be investigated in individuals with ASD in each age group from infant to adulthood; however, the data are scarce, especially for adults with ASD. Meanwhile, wave I is often smaller compared with wave V, and a poor signal-to-noise ratio (SNR) of electroencephalography (EEG) activity makes identification of wave I difficult. Therefore, this difficulty of identification may contribute to the inconsistent wave-I results.

In the present study, we examined adults with ASD and focused on their ABRs, especially the responses of the peripheral auditory system. In addition, we took two approaches to clearly identify each wave when measuring the ABRs. First, we used many stimulus presentations (6000) in the ABR measurement to enhance the SNR. The averaging method for obtaining the ABR is based on the assumption that the noisy EEG signal is uncorrelated with the ABR waveform, and in theory it enhances the signal on the order of $\sqrt{N}$ relative to noise, where N is the number of averaged epochs. The large number of stimulus presentations in present study enable us to obtain ABRs whose SNRs are about 1.7 times higher compared with those obtainable with the generally used number of stimulus presentations (about 2000). Second, we utilized a horizontal (earlobe to earlobe) electrode montage in addition to the vertical (vertex to earlobe) electrode montage commonly used ABR studies. The vertical montage reflects more rostral brainstem activity, while the horizontal montage reflects the activity of more caudal brainstem structures (Chandrasekaran and Kraus, 2010). In addition, electrocochleograms (ECochGs) were measured by placing an electrode on or near the tympanic membrane as opposed to in the ear canal or on the ear lobe. This placement increases the amplitude of the action potential (AP) whose first and largest wave is identical to wave I of the ABR (Ferraro and Durrant, 2006; Liberman et al., 2016; Minaya and Atcherson, 2015). Accordingly, the horizontal electrode montage could better reflect activities of the peripheral auditory system compared with the vertical electrode montage. Taking these approaches, we obtained the ABRs from adults with ASD and neurotypical (NT) adults and compared them between the two groups.

2. Methods

2.1. Participants

Of the 18 high-functioning adults with ASD and 23 NT adults originally recruited for this study, one ASD adult and three NT adults were excluded: because of hearing loss ≥ 30 dB HL at one or more frequencies ($n = 1$ for ASD; $n = 2$ for NT) or a full IQ score ≤ 70 (NT: $n = 1$). Final participants included 17 high-functioning adults with ASD (aged 21–38 years, two females) and 20 NT adults (aged 22–36 years, three females). Eight of the 17 participants with ASD were using one or more of the following medications: anti-depressants (two participants), hypnotic drugs (three participants), anti-anxiety drugs (one participant), anti-psychotic drugs (two participants), mood stabilizers (two participants), and central nervous system stimulant drugs (two participants). The ASD participants were recruited from outpatient units of Karasuyama Hospital, Tokyo, Japan. The diagnosis of ASD was based on a consensus reached by two or three experienced psychiatrists according to the criteria of the Diagnosis and Statistical Manual of Mental Disorders (DSM-5).

All participants had normal hearing, defined as pure-tone hearing thresholds equal to or less than 25 dB HL from 125 to 8000 Hz. The two groups were matched on age, the average of pure tone thresholds (PTA) at 500, 1000, 2000 and 4000 Hz at left and right ears, full IQ, performance IQ, and verbal IQ. We also assessed Autism Spectrum Quotient (AQ) scores (Wakabayashi et al., 2006). The AQ scores in the ASD group were higher than those in the NT group (see Table 1).

The experiment was approved by the Ethical Committees at NTT Communication Science Laboratories and was conducted in accordance with the Declaration of Helsinki. All participants signed written informed consent.

2.2. Click-evoked ABR measurement

All recordings were performed using a Biosemi Active-Two system (BioSemi, Amsterdam, Netherlands). The active ABR electrodes were placed on the high forehead (Fz), the ipsilateral (right) earlobe (A2), the contralateral (left) earlobe (A1), and the forehead as ground. The sampling frequency was 16,384 Hz. The offsets of the active electrodes were kept below 20 mV at the start of the measurement. We created a 100-µs click sound using Matlab R2017b (The MathWorks, Inc., Mass., USA). Click sounds with alternating polarity were presented to their right ear using Audacity software (http://audacity.sourceforge.net/) through Fireface UCX (RME, Haimhausen, Germany) and a magnetically-shielded inserted earphone (E-A-RTONE Insert Earphone 3A ABR, 3M Company, Indianapolis, IN, USA), at 100 dB peSPL (67.9 dB nHL), with a presentation rate of 10.2/s. Two separate recordings included 6,000 individual sweeps. During the recording, participants were instructed to lie in a supine position on a comfortable flat chair in an acoustically- and electrically shielded booth and refrain from

Table 1
Participant demographics and questionnaire scores.

	ASD ($n = 17$)	NT ($n = 20$)	Independent t-test		
	Mean (SD)	Mean (SD)	t	df	p
Age (years)	30.5 (4.7)	29.3 (3.9)	−0.84	35	0.41
PTA right (dB HL)	5.4 (3.5)	4.3 (4.1)	−0.89	35	0.38
PTA left (dB HL)	4.6 (2.6)	4.1 (4.1)	−0.48	35	0.63
Full IQ	101.8 (11.6)	100.3 (11.6)	−0.40	35	0.69
Performance IQ	89.9 (13.7)	95.6 (13.3)	1.29	35	0.21
Verbal IQ	109.8 (13.5)	104.3 (12.7)	−1.27	35	0.21
AQ score	32.5 (6.4)	19.0 (5.0)	−7.09	35	**<0.001**

moving their body as much as possible. We allowed them to sleep during ABR measurements. The ABR collection lasted approximately 10 min. The continuous recordings were converted to EDF files using Convert 86 software (BioSemi, Amsterdam, Netherlands), and the data were converted to microvolts. Responses of the vertical (Cz to A2) and horizontal (A1 to A2) electrode montages were filtered between 70 and 2000 Hz with Matlab. Trials with activity greater than ±35 µV were considered artifacts and were excluded from the following averaging. The responses were averaged with a time window from −5 to 15 ms relative to the stimulus onset at 0 ms, with baseline correction from −5 to 0 ms.

2.3. Statistical analyses

All statistical analyses were conducted with SPSS software version 23 (SPSS Inc., Chicago, IL, USA). To compare the two groups, we used the Mann-Whitney U test for each ABR component. Unidentifiable data were excluded from the corresponding analyses. A parallel gatekeeping strategy was adopted to control the Type I error and sensitivity to the primary interests of the present study (i.e., more periphery related components) for multiple tests of the ABR components (Dmitrienko et al., 2003; Food and Drug Administration, 2017). Because the evidence of abnormalities in wave I latency remains equivocal as mentioned in introduction, we focused on the auditory peripheral function associated with wave I. In the parallel gatekeeping strategy, the items associated with the auditory peripheral function were grouped into a primary family, and the items associated with the brainstem functions and the IPLs were grouped into a secondary family. p-values were adjusted by Bonferroni correction in each stage.

3. Results

Grand average ABR waveforms of the ASD and NT groups in the vertical and horizontal electrode montages are shown in Fig. 1. Clear peaks of waves I, II, and III and the IV–V complex were observed at latencies around 1.8 ms, 2.9 ms, 3.9 ms, and 5.8 ms, respectively, in the ABR waveforms of the vertical electrode montage. In the horizontal electrode montages, clear peaks of wave I were observed at a latency of around 1.8 ms. Wave I amplitudes for the horizontal electrode montage were larger than those for the vertical electrode montage.

In addition to these peaks, we observed a ledge preceding wave I in the ABR of the horizontal electrode montage in all the participants except for two ASD adults and four NT adults (as shown in Fig. 2). We consider that this ledge corresponds to summating potential (SP) in the ECochGs, sustained potential during stimulus presentation (Harvey and Steel, 1992). Since the stimulus in this study was a short-duration (100 µs) click, the SPs were observed as a ledge with a short duration. Then, we obtained the SP latencies in addition to the ABR latencies and compared them between the ASD and NT groups.

For the purpose of subsequent statistical analyses, we visually identified waves I, II, III, IV, and V for vertical electrode montage. Three ASD adults showed unidentifiable wave II. Eight ASD adults and 11 NT adults had unidentifiable waves IV ($n = 7$ for ASD, $n = 11$ for NT) or V (ASD: $n = 1$) due to the IV–V complex. Thus, wave IV was not included in the statistical analyses. Then, we derived the IPLs (I-III, III-V, and I-V). Similarly to the vertical montage, SP and wave I latencies were obtained for the horizontal montage.

The absolute peak latencies and the IPLs were compared between the ASD and NT adults using the Mann-Whitney U test (see Table 2). The parallel gatekeeping strategy was used to control the Type I error for multiple tests. The primary and secondary families consisted of the four items associated with the auditory peripheral function (wave I and II latencies in the vertical electrode montage and wave I and SP latencies in the horizontal electrode montage) and the five items associated with the brainstem functions and the IPLs (wave III and V latencies and the IPLs of I-III, III-V, and I-V), respectively. A significant group difference was found in the SP latency (adjusted $p = 0.044$). There were, however, no significant group differences in wave I, II, III, and V latencies and the IPLs in the vertical electrode montage and the wave I latency in the horizontal electrode montage.

The quartile deviations (QDs) of wave I in the horizontal electrode montage were half the values of those in the vertical electrode montage. This indicates that the identification of wave I in the horizontal electrode montage was more stable than in the vertical electrode montage.

4. Discussion

The main aim of the current study was to investigate possible differences in the ABRs between adults with ASD and NT adults. In the vertical montage, there were no significant group differences in the wave I, II, III, and V latencies or the IPLs. There was also no significant group difference in the wave I latency in the horizontal montage. However, the adults with ASD showed shorter SP latencies in ECochGs compared with the NT adults. The SP is believed to be generated from the hair cells, mainly the inner hair cells, of the organ of Corti (Russell and Sellick, 1978; Zheng et al., 1997). Accordingly, these results suggest that adults with ASD have abnormalities of processing more in the peripheral auditory system than in the brainstem.

In this study, we focused on the responses of the peripheral auditory system. To allow precise evaluations of early ABR components, we measured the ABR using a method that is somewhat different from that is used in common clinical practice namely a relatively large number of stimulus presentations (6000) were adopted, and ABRs obtained with horizontal and vertical electrode montages were evaluated. This approach indeed appeared to contribute to improving the sensitivity of the electrophysiological technique to peripheral activities. Particularly, with the horizontal electrode montage, the amplitude of wave I was greater (Fig. 1) and
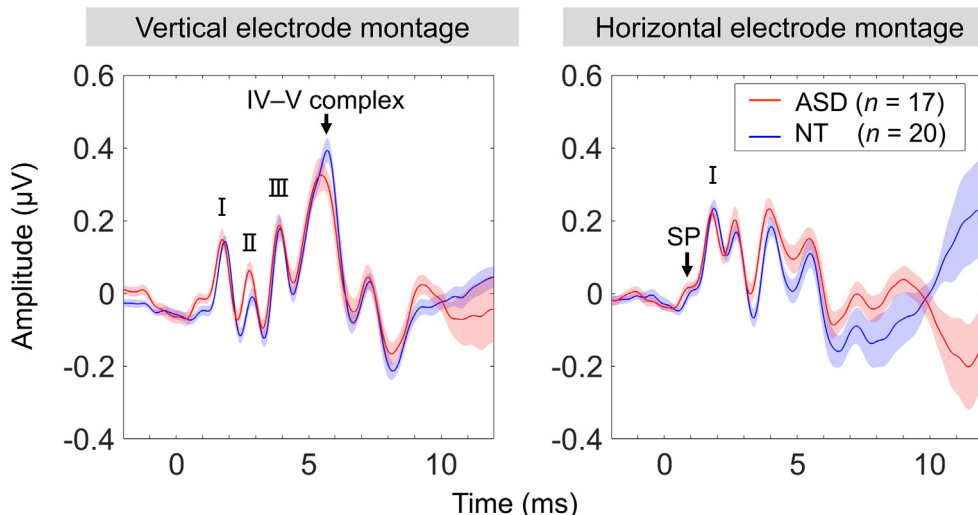
Fig. 1. Grand average ABR waveforms in the vertical (left) and horizontal (right) electrode montages. Red lines and blue lines represent the ASD group and NT group, respectively. The shaded areas indicate the standard error of each response. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
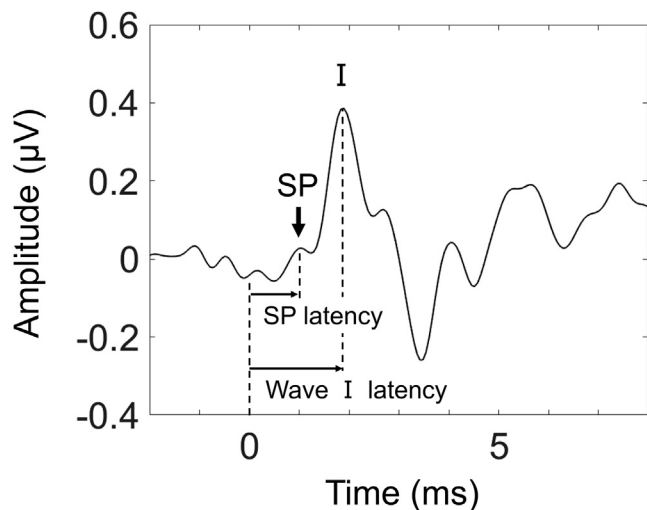

Fig. 2. ABR waveform with the peak of the SP in the horizontal electrode montage, from a representative participant.

the QDs were smaller (Table 2) than those observed with the standard vertical montage. In addition, a significant group difference in the SP latency was detected with the horizontal montage. The

improved sensitivity of our method could lead to future modifications of the 'standard' ABR examination for evaluating auditory peripheral functions in ASD and other individuals.

The lack of evidence for the abnormality of wave I latency in the ASD group is consistent with some earlier studies (Courchesne et al., 1985; Demopoulos and Lewine, 2016; Garreau et al., 1984; Grillon et al., 1989; Known et al., 2006; Magliaro et al., 2010; Miron et al., 2016; Rosenblum et al., 1980; Santos et al., 2017; Sersen et al., 1990; Skoff et al., 1980; Tharpe et al., 2006). The negative results were also found in the horizontal montages (see above) and thus cannot be explained simply by the sensitivity of the recording technique. There are, on the other hand, studies that showed abnormal latencies in individuals with ASD (Azouz et al., 2014; Dabbous, 2012; Rosenhall et al., 2003; Roth et al., 2012; Tanguay et al., 1982). The positive evidence in those studies may reflect the fact that their ASD participants were much more severely affected than those in this study.

Our data demonstrated significantly shorter SP latencies in adults with ASD. The shortened SP latencies could be interpreted to indicate early changes in potentials at the hair cells, which would shorten the firing of the auditory nerves. However, the group differences in the latencies in wave I and II did not reach the criterion of statistical significance. It is possible that the slight group difference observed at the level of the hair cells was smeared at the level of auditory nerves due to neuronal jitter.

Table 2

Comparison of the median latencies in the vertical and horizontal electrode montages across the ASD and NT adults. To control the Type I error for multiple tests, p-values were adjusted using the parallel gatekeeping strategy. Asterisks indicate significant group difference (p < 0.05).

Wave	ASD			NT			Mann-Whitney U test	
	n	Median	QD	n	Median	QD	z-score	Adj. p
Vertical electrode montage								
I	17	1.77	0.12	20	1.84	0.06	−1.631	0.440
II	14	2.81	0.08	20	2.90	0.06	−2.184	0.120
III	17	3.91	0.12	20	3.91	0.08	−0.354	1
V	16	5.80	0.20	20	5.80	0.17	−1.009	1
I-III	17	2.14	0.06	20	2.08	0.09	−0.887	1
III-V	16	1.86	0.14	20	1.86	0.13	−0.655	1
I-V	16	3.94	0.15	20	3.97	0.16	−0.941	1
Horizontal electrode montage								
I	17	1.77	0.06	20	1.90	0.03	−2.092	0.156
SP	15	0.86	0.09	16	1.01	0.06	−2.542	***0.044*** *

What is the mechanism underlying the shortened SP latencies? We consider two plausible explanations. One is that the abnormalities of the inner ear affect the shortened latencies. It has been reported that individuals with ASD exhibited reductions in the transient-evoked otoacoustic emission (TEOAE) responses and distortion product otoacoustic emission (DPOAE) responses, both of which are believed to have a cochlear origin (Bennetto et al., 2017; Boger et al., 2018; Danesh et al., 2012). Moreover, animals lacking the Hoxa1 function, which is one of the genes associated with ASD, exhibited malformations of the inner ears (Carpenter et al., 1993; Lufkin et al., 1991). These findings imply that individuals with ASD may have functional and/or structural abnormalities of the inner ear, although the ears in the autopsy case were not examined. Since all participants in this study showed normal hearing, they would not have severe abnormalities of the inner ears. However, it is possible that minor inner ear abnormalities (e.g., higher stiffness of the basilar membrane) shorten the SP latencies. Moreover, the inner ear supports the exquisite sensitivity, fine frequency tuning, and large operating dynamic range of the ear (Burser and Imbert, 1992; Pickles, 1988), and plays an important role in speech understanding in noise, and the perception of loudness, and so on. Specially, the auditory filter characteristic, which is related to speech understanding in noise, could change in spite of normal hearing (Badri et al., 2011). Taken together, it is possible that the inner ear abnormalities contribute to not only the shortened latencies but also to the auditory dysfunction in ASD, such as auditory hypersensitivity and difficulty in speech understanding in noise.

The other explanation is that the shortened latencies are due to abnormalities in the olivocochlear efferent feedback. As mentioned, anatomical and MRI studies have found structural abnormalities of the SOC of the brainstem in ASD (Ciesielski et al., 1997; Hashimoto et al., 1992, 1995; Kulesza and Mangunay, 2008; Kulesza et al., 2011; Lukose et al., 2015; Rodier et al., 1996; Rodier, 2000). The inner ear receives two types of efferent feedback from the SOC: one pathway provides gain control on the outer hair cells' contribution to cochlear amplification, and the other modulates the excitability of the cochlear nerve. Each efferent feedback works to protect the inner ear from acoustic trauma at moderate and high sound levels (Darrow et al., 2007; Zheng et al., 1999). The sound level of stimuli used in this study was high enough (100 dB peSPL) to activate the olivocochlear efferent feedback. Taking into account the structural abnormalities of the SOC in ASD, it is likely that the olivocochlear efferent feedback in ASD does not work well and could not reduce the sound-induced cochlear motion and/or the excitability of the cochlear nerve. There are few studies of the effects of stimulus intensity on the SP because identification of the SP is less reliable at low or intermediate stimulus levels (Burkard et al., 2007). However, it is likely that suppression deficiency of sound-induced cochlear motion at high sound levels leads to the shortened SP latencies.

There were no significant group differences in the absolute wave III and V latencies or the IPLs (I-III, III-V, and I-V). It is possible that the slight group difference observed in the SP latency was smeared due to neuronal jitter as auditory processing progressed. Meanwhile, a meta-analysis study reported that the prolonged wave V latencies in young children change into shortened wave V latencies in adults (Miron et al., 2018; Talge et al., 2018). Our data support those findings and suggest that adults with ASD have, at least partially, normal auditory processing in the brainstem.

The current study suggests that peripheral abnormality is associated with ASD. This implies that researchers should shed light on potential dysfunctions of the peripheral auditory system to understand the mechanisms underlying ASDs and resulting difficulties in daily life. Further studies are needed to identify exact sources of the present observations and to clarify their implications in clinical settings. Such studies might include detailed comparisons of SPs measured with various electrode montages (horizontal, vertical, or others) or placements (e.g., on or near the tympanic membrane) in a sufficiently larger population of participants than in the present study adopting a relatively small number of participants (17 adults with ASD and 20 NT adults).

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Conflict of interest statement

None of the authors have potential conflicts of interest to be disclosed.

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References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorder. 5th ed. Text Revision (DSM-5). Washington DC: American Psychiatric Association; 2013.

Alcantara, J.I., Weisblatt, E.J.L., Moore, B.C.J., Bolton, P.F., 2004. Speech-in-noise perception in high-functioning individuals with autism or Asperger's syndrome. J. Child Psychol. Psychiatry 45 (6), 1107–1114.

Azouz, H.G., kozou, H., Khalil, M., Abdou, R.M., Sakr, M., 2014. The correlation between central auditory processing in autistic children and their language processing abilities. Int. J. Pediatr. Otorhinolaryngol. 78 (12), 2297–2300.

Badri, R., Siegel, J.H., Wright, B.A., 2011. Auditory filter shapes and high-frequency hearing in adults who have impaired speech in noise performance despite clinically normal audiograms. J. Acoust. Soc. Am. 129 (2), 852–863.

Bennetto, L., Keith, J.M., Allen, P.D., Luebke, A.E., 2017. Children with autism spectrum disorder have reduced otoacoustic emissions at 1 kHz mid-frequency region. Autism Res. 10, 337–345.

Boger, M.E., Siqueira, J., Araujo, C., Maciel, A., Torquato, D., 2018. Distortion product otoacoustic emissions in children with autism spectrum disorder. Glob. J. Med. Res. K Interdiscip. 18, 3–7.

Burkard, R.F., Don, M., Eggermont, J.J., 2007. Auditory Evoked Potentials. Basic Principles and Clinical Application. Lippincott Williams & Wilkins, Philadelphia.

Burser P, Imbert M. Audition. Cambridge, MA: MIT Press; 1992.

Carpenter, E.M., Goddard, J.M., Chisaka, O., Manley, N.R., Capecchi, M.R., 1993. Loss of Hoxa-1 (Hox-1.6) function results in the reorganization of the murine hindbrain. Development 118, 1063–1075.

Chandrasekaran, B., Kraus, N. The scalp-recorded brainstem response to speech: neural origins and plasticity. Psychophysiol 2010; 47: 236–46.

Ciesielski, K.T., Harris, R.J., Hart, B.L., Pabst, H.F., 1997. Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. Neuropsychologia 35 (5), 643–655.

Courchesne, E., Courchesne, R.Y., Hicks, G., Lincoln, A.J., 1985. Functioning of the brain-stem auditory pathway in non-retarded autistic individuals. Electroencephalogr. Clin. Neurophysiol. 61 (6), 491–501.

Cohen, I.L., Garner, J.M., Karmel, B.Z., Phan, H.T.T., Kittler, P., Gomez, T.R., et al., 2013. Neonatal brainstem function and four-month arousal modulated attention are jointly associated with autism. Autism Res. 6, 11–22.

Dabbous, A.O., 2012. Characteristics of auditory brainstem response latencies in children with autism spectrum disorders. Audiol. Med. 10 (3), 122–131.

Dadalko, O.I., Travers, B.G., 2018. Evidence for Brainstem contributions to autism spectrum disorders. Front. Integr. Neurosci. 12, 1–17.

Danesh, A.A., Kaf, W.A., 2012. DPOAEs and contralateral acoustic stimulation and their link to sound hypersensitivity in children with autism. Int. J. Audiol. 51 (4), 345–352.

Danesh, A.A., Lang, D., Kaf, W., Andreassen, W.D., Scott, J., Eshraghi, A.A., 2015. Tinnitus and hyperacusis in autism spectrum disorders with emphasis on high functioning individuals diagnosed with Asperger's Syndrome. Int. J. Pediatr. Otorhinolaryngol. 79 (10), 1683–1688.

Darrow, K.N., Maison, S.F., Liberman, M.C., 2007. Selective removal of lateral olivocochlear efferents increases vulnerability to acute acoustic injury. J. Neurophysiol. 97 (2), 1775–1785.

Demopoulos, C., Lewine, J.D., 2016. Audiometric profiles in autism spectrum disorders: does subclinical hearing loss impact communication? Autism Res. 9 (1), 107–120.

Dmitrienko, A., Offen, W.W., Westfall, P.H., 2003. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. Stat. Med. 22 (15), 2387–2400.

Eggermont, J.J., 2019. Auditory brainstem response. Handb. Clin. Neurol. 160, 451–464.

Ferraro, J.A., Durrant, J.D., 2006. Electrocochleography in the evaluation of patients with Meniere's disease/endolymphatic hydrops. J. Am. Acad. Audiol. 17 (1), 45–68.

Food and Drug Administration. Draft guidance for multiple endpoints in clinical trials. Food and drug administration. 2017.

Garreau, B., Tanguay, P., Roux, S., Lelord, G., 1984. Brain stem auditory evoked potentials in the normal and autistic child (in French). Rev. Electroencephalogr. Neurophysiol. Clin. 14, 25–31.

Grillon, C., Courchesne, E., Akshoomoff, N., 1989. Brainstem and middle latency auditory evoked potentials in autism and developmental language disorder. J. Autism Dev. Disord. 19 (2), 255–269.

Harvey, D., Steel, K.P., 1992. The development and interpretation of the summating potential response. Hear. Res. 61 (1-2), 137–146.

Hashimoto, T., Tayama, M., Miyazaki, M., Sakurama, N., Yoshimoto, T., Murakawa, K., Kuroda, Y., 1992. Reduced brainstem size in children with autism. Brain Dev. 14 (2), 94–97.

Hashimoto, T., Tayama, M., Murakawa, K., Yoshimoto, T., Miyazaki, M., Harada, M., Kuroda, Y., 1995. Development of the brainstem and cerebellum in autistic patients. J. Aut. Dev. Disord. 25 (1), 1–18.

Hitoglou, M., Ververi, A., Antoniadis, A., Zafeiriou, D.I., 2010. Childhood autism and auditory system abnormalities. Pediatr. Neurol. 42 (5), 309–314.

Inui, T., Kumagaya, S., Myowa-Yamakoshi, M., 2017. Neurodevelopmental hypothesis about the etiology of autism spectrum disorders. Front. Hum. Neurosci. 11, 1–19.

Khalfa, S., Bruneau, N., Rogé, B., Georgieff, N., Veuillet, E., Adrien, J.L., Barthélémy, C., Collet, L., 2004. Increased perception of loudness in autism. Hear. Res. 198 (1-2), 87–92.

Kwon, S., Kim, J., Choe, B.H., Ko, C., Park, S., 2007. Electrophysiologic assessment of central auditory processing by auditory brainstem responses in children with autism spectrum disorders. J. Korean Med. Sci. 22 (4), 656.

Kulesza, R.J., Lukose, R., Stevens, L.V., 2011. Malformation of the human superior olive in autistic spectrum disorders. Brain Res. 1367, 360–371.

Kulesza, R.J., Mangunay, K., 2008. Morphological features of the medial superior olive in autism. Brain Res. 1200, 132–137.

Liberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. PLoS One 2016; 11(9): e0162726.

Lufkin, T., Dierich, A., LeMeur, M., Mark, M., Chambon, P., 1991. Disruption of the Hox-1.6 homeobox gene results in defects in a region corresponding to its rostral domain of expression. Cell 66 (6), 1105–1119.

Lukose, R., Beebe, K., Kulesza, R.J., 2015. Organization of the human superior olivary complex in 15q duplication syndromes and autism spectrum disorders. Neuroscience 286, 216–230.

Magliaro, F.C.L., Scheuer, C.I., Júnior, F.B.A., Matas, C.G., 2010. Study of auditory evoked potentials in autism. Pró-Fono R Atual Cient 22, 31–37.

Maziade, M., Mérette, C., Cayer, M., Roy, M.A., Szatmari, P., Côté, R., Thivierge, J., 2000. Prolongation of brainstem auditory-evoked responses in autistic probands and their unaffected relatives. Arch. Gen. Psychiatry 57 (11), 1077. https://doi.org/10.1001/archpsyc.57.11.1077.

Minaya, C., Atcherson, S.R., 2015. Simultaneous extratympanic electrocochleography and auditory brainstem responses revisited. Audiol. Res. 5 (1), 105–110.

Miron, O., Beam, A.L., Kohane, I.S., 2018. Auditory brainstem response in infants and children with autism spectrum disorder: a meta-analysis of wave V. Autism Res. 11 (2), 355–363.

Miron, O., Ari-Even Roth, D., Gabis, L.V., Henkin, Y., Shefer, S., Dinstein, I., Geva, R., 2016. Prolonged auditory brainstem responses in infants with autism. Autism Res. 9 (6), 689–695.

Møller, A.R., Jannetta, P.J., 1983. Monitoring auditory functions during cranial nerve microvascular decompression operations by direct recording from the eighth nerve. J. Neurosurg. 59, 493–499.

Møller, A.R., Jannetta, P.J., Sekhar, L.N., 1988. Contributions from the auditory nerve to the brain-stem auditory evoked potentials (BAEPs): results of intracranial recording in man. Electroencephalogr. Clin. Neurophysiol. 71 (3), 198–211.

O'Connor, K., 2012. Auditory processing in autism spectrum disorder: a review. Neurosci. Biobehav. Rev. 36 (2), 836–854.

Parkkonen, L., Fujiki, N., Mäkelä, J.P., 2009. Sources of auditory brainstem responses revisited: Contribution by magnetoencephalography. Hum. Brain Map. 30, 1772–1782.

Pickles, J.O., 1988. An introduction to the physiology of hearing. Academic Press, Cambridge, Massachusetts.

Pillion, J.P., Boatman-Reich, D., Gordon, B., 2018. Auditory brainstem pathology in autism spectrum disorder: a review. Cogn. Behav. Neural 31, 53–78.

Rodier, P.M., 2000. The early origins of autism. Sci. Am. 282 (2), 56–63.

Rodier, P.M., Ingram, J.L., Tisdale, B., Nelson, S., Romano, J., 1996. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. J. Comp. Neur. 370 (2), 247–261.

Rosenblum, S.M., Arick, J.R., Krug, D.A., Stubbs, E.G., Young, N.B., Pelson, R.O., 1980. Auditory brainstem evoked responses in autistic children. J. Autism Dev. Disord. 10 (2), 215–225.

Rosenhall, U., Nordin, V., Brantberg, K., Gillberg, C., 2003. Autism and auditory brain stem responses. Ear Hear. 24 (3), 206–214.

Rosenhall, U., Nordin, V., Sandstrom, M., Ahlsen, G., Gillberg, C., 1999. Autism and hearing loss. J. Autism Dev. Disord. 29 (5), 349–357.

Roth DA. Muchnik C, Shabtai E, Hildesheimer M, Henkin Y. Evidence for atypical auditory brainstem responses in young children with suspected autism spectrum disorders. Dev Med Child Neurol 2012; 54: 23–29.

Russell, I.J., Sellick, P.M., 1978. Intracellular studies of hair cells in the mammalian cochlea. J. Physiol. 284 (1), 261–290.

Santos, M., Marques, C., Nóbrega Pinto, A., Fernandes, R., Coutinho, M.B., Almeida e Sousa, C., 2017. Autism spectrum disorders and the amplitude of auditory brainstem response wave I. Autism Res. 10 (7), 1300–1305.

Sersen, E.A., Heaney, G., Clausen, J., Belser, R., Rainbow, S., 1990. Brainstem auditory-evoked responses with and without sedation in autism and Down's syndrome. Biol. Psychiatry 27 (8), 834–840.

Skoff, B.F., Mirsky, A.F., Turner, D., 1980. Prolonged brainstem transmission time in autism. Psychiatry Res. 2 (2), 157–166.

Talge, N.M., Tudor, B.M., Kileny, P.R., 2018. Click-evoked auditory brainstem responses and autism spectrum disorder: a meta-analytic review. Autism Res. 11 (6), 916–927.

Tanguay, P.E., Edwards, R.M., Buchwald, J., Schwofel, J., Allen, V., 1982. Auditory brainstem evoked responses in autistic children. Arch. Gen. Psychiatry 38, 174–180.

Taylor, M.J., Rosenblatt, B., Linschoten, L., 1982. Auditory brainstem response abnormalities in autistic children. J. Can. Sci. Neurol 9 (4), 429–433.

Tharpe, A.M., Bess, F.H., Sladen, D.P., Schissel, H., Couch, S., Schery, T., 2006. Auditory characteristics of children with autism. Ear Hear. 27, 430–441.

Ververi, A., Vargiami, E., Papadopoulou, V., Tryfonas, D., Zafeiriou, D.I., 2015. Brainstem auditory evoked potentials in boys with autism: Still searching for the hidden truth. Iran J. Child Neurol 9 (2), 21–28.

Visser, E., Zwiers, M., Kan, C., Hoekstra, L., van Opstal, J., Buitelaar, J., 2013. Atypical vertical sound localization and sound-onset sensitivity in people with autism spectrum disorders. J. Psychiatry Neurosci. 38 (6), 398–406.

Wakabayashi, A., Baron-Cohen, S., Wheelwright, S., Tojo, Y., 2006. The autism-spectrum quotient (AQ) in Japan: a cross-cultural comparison. J. Autism Dev. Disord. 36 (2), 263–270.

Zheng, X.Y., Henderson, D., Hu, B.H., Ding, D.L., McFadden, S.L., 1997. The influence of the cochlear efferent system on chronic acoustic trauma. Hear. Res. 107 (1-2), 147–159.

Zheng, X.Y., Henderson, D., McFadden, S.L., Ding, D.L., Salvi, R.J., 1999. Auditory nerve fiber responses following chronic cochlear de-efferentation. J. Comp. Neurol. 406 (1), 72–86.