Published in final edited form as:

Autism Res. 2017 February ; 10(2): 337–345. doi:10.1002/aur.1663.

Children with autism spectrum disorder have reduced otoacoustic emissions at 1 kHz mid-frequency region

Loisa Bennetto¹, Jessica M. Keith¹, Paul D. Allen², and Anne E. Luebke^{3,4}

¹Dept. of Clinical and Social Sciences in Psychology, University of Rochester, Rochester, NY 14627

²Dept. of Otolaryngology, University of Rochester Medical Center, Rochester NY 14642

³Dept. of Biomedical Engineering, University of Rochester Medical Center, Rochester NY 14642

⁴Dept. of Neuroscience, University of Rochester Medical Center, Rochester NY 14642

Abstract

Autism spectrum disorder (ASD) is a behaviorally diagnosed disorder of early onset characterized by impairment in social communication and restricted and repetitive behaviors. Some of the earliest signs of ASD involve auditory processing, and a recent study found that hearing thresholds in children with ASD in the mid-range frequencies were significantly related to receptive and expressive language measures. In addition, otoacoustic emissions have been used to detect reduced cochlear function in the presence of normal audiometric thresholds. We were interested then to know if otoacoustic emissions in children with normal audiometric thresholds would also reveal differences between children with ASD and typical developing (TD) controls in mid-frequency regions. Our objective was to specifically measure baseline afferent otoacoustic emissions (distortion-product otoacoustic emissions; DPOAEs), transient-evoked otoacoustic emissions (TrOAEs) and efferent suppression, in 35 children with high-functioning ASD compared with 42 aged-matched TD controls. All participants were males 6-17 years old, with normal audiometry, and rigorously characterized via ADI-R and ADOS. Children with ASD had greatly reduced DPOAE responses in the 1 kHz frequency range, yet had comparable DPOAE responses at 0.5 and 4-8 kHz regions. Furthermore, analysis of the spectral features of TrOAEs revealed significantly decreased emissions in ASD in similar frequencies. No significant differences were noted in DPOAE or TrOAE noise floors, middle ear muscle reflex activity, or efferent suppression between children with ASD and TD controls. In conclusion, attention to specific-frequency deficits using noninvasive measures of cochlear function may be important in auditory processing impairments found in ASD.

Lay Abstract

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by impairments in social-communication skills and restricted and repetitive behaviors and interests. Some of the earliest and consistent signs of ASD involve auditory communication. In fact, a recent study found

Corresponding author: Anne E. Luebke, University of Rochester Medical Center, 601 Elmwood Avenue, Box 603, Rochester NY 14642, Work: (585) 273-1635, Cell: (585) 260-4200, FAX: (585) 756-5334, anne_luebke@urmc.rochester.edu.

Conflict of Interest: The authors declare no competing financial interests.

that hearing thresholds in mid-range frequencies in children with ASD were significantly related to behavioral measures of language usage. We used two objective, noninvasive measures of cochlear function to investigate if differences in these measures existed between children with ASD (n=35, 6-17 yrs) and typically developing (TD) children (n=42) of the same age. We found that children with ASD had reduced cochlear responses at 1 kHz speech frequency range across both measures, yet had comparable responses at 4-8 kHz frequency ranges when compared to TD children of the same age. We conclude that non-invasive measures of cochlear function may be a window into auditory processing deficits of ASD.

Keywords

DPOAE; distortion-product otoacoustic emissions; TrOAE; transient-evoked otoacoustic emissions; autism; cochlea; efferent suppression; middle ear muscle reflex

Introduction

Autism Spectrum Disorder (ASD) is a behaviorally diagnosed disorder of early onset characterized by impairment in social communication and restricted and repetitive behaviors. Some of the earliest signs of ASD involve atypical processing and response to auditory input. For example, analyses of home-based videotapes and prospective studies have consistently shown that children who are later diagnosed are more likely than those who do not develop ASD to fail to respond to their name being called (e.g., Baranek et al., 2013; Dawson, Meltzoff, Osterling, Rinaldi, & Brown, 1998; Nadig et al., 2007). Studies of older children and adults with ASD have similarly documented atypical processing of auditory input across a range of measures, including atypical perception of basic acoustic properties of both speech and nonspeech stimuli (e.g., pitch, intensity) as well as more complex information (e.g., prosody, affect), difficulty perceiving speech in background noise, and both hypo- and hyper-responsiveness to sounds (for reviews, Haesen, Boets, & Wagemans, 2011; O'Connor, 2012). Abnormalities in auditory processing have been shown to be related to functional deficits in individuals with ASD. (e.g., Demopoulos et al., 2015; Edgar et al., 2015). Moreover, peripheral hearing deficits are common among children with ASD (for review, Hitoglou, Ververi, Antoniadis, & Zafeiriou, 2010). While hearing loss is not causative for ASD, there is evidence that hearing-impaired children show deficits common to ASD, such as impaired emotion or vocal affect recognition abilities (Dyck, Farrugia, Shochet, & Holmes-Brown, 2004; Most & Michaelis, 2012). In fact, Demopoulos and Lewine (2015) found that in children with ASD, there was a relationship between mid-frequency pure-tone auditory thresholds and expressive and receptive language measures.

In addition to auditory pure-tone threshold testing, the integrity of the peripheral auditory system can be evaluated reliably and objectively using otoacoustic emissions (OAEs). Sound causes basilar membrane motion that results in voltage changes across cochlea outer hair cells causing them to change their length (due to the cochlear amplifier) and these length changes generate acoustic signals that can be recorded in the external ear canal (i.e., sound-evoked otoacoustic emissions, see Kemp (2002); Fig 1A). We now understand that the traveling wave is boosted by a local electromechanical amplification process present only in

cochlear outer hair cells. Fully functioning outer hair cells are needed to enable humans to discriminate between two sounds whose frequencies differ by only 0.2-0.5%. Loss or lesser functioning outer hair cells cause reduced ability to discriminate between two sounds or impaired auditory tuning (Dallos, 1992). In fact, distortion-product otoacoustic emissions (DPOAEs) have been used to detect reduced cochlear function in the presence of normal audiometric thresholds (Arnold, Lonsbury-Martin, & Martin, 1999). We were interested then to determine if otoacoustic emissions could be used to detect reduced cochlear function in mid-frequency regions in children with ASD with clinically acceptable pure-tone thresholds (i.e., no hearing loss).

In addition, deficits in descending pathways [olivocochlear (OC) efferent system] from the midbrain to the cochlea have been shown to also cause impaired auditory sensitivity and impaired cochlear tuning in a frequency-specific fashion (Warr & Guinan, 1979). Outer hair cells are synapsed directly by efferent neurons originating in the vicinity of the nuclei of the superior olivary complex corresponding to the medial olivocochlear bundle (MOC), and the activity of the MOC bundle itself is regulated by information descending from the upper part of the brain. Interestingly, when autopsied or MRI imaged brains from adults with ASD have been investigated, this same brain region (superior olivary complex) was either absent, reduced in size, or misaligned compared to control brains, suggesting that the olivocochlear region is affected in ASD (Gaffney, Kuperman, Tsai, & Minchin, 1988; Hashimoto et al., 1995; Kulesza & Mangunay, 2008; Rodier, Ingram, Tisdale, Nelson, & Romano, 1996).

In this study, we examined two different types of otoacoustic emissions, evoked by different generation mechanisms, i) DPOAEs, where two primary tones, f_1 and f_2 , are introduced into the ear and a distortion-product of those two tones is generated in the cochlea and detected as an emission at $2f_1-f_2$ frequency and ii) TrOAEs, where a multi-frequency click stimulus is introduced into the ear and the otoacoustic emissions generated in the cochlea are monitored over a specific time domain (6-18 msec) (Shera & Guinan, 1999). The TrOAE responses survey many frequencies of the cochlea, and the DPOAE responses can be tailored to survey certain frequency regions by choice of the f_1 and f_2 primary tone frequencies. Measuring these otoacoustic emissions (OAEs) is noninvasive and reliable, does not require behavioral responses, and is a routine approach to testing cochlear function in children as young as infancy (Bergman et al., 1995).

Methods

Subjects

Males with ASD ($n=35$) and TD controls ($n=42$), ages 6 through 17, participated in this study. Diagnostic evaluations were conducted by experienced and trained staff, under the supervision of the first author. Autism diagnoses were rigorously confirmed in the ASD group with the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2012) and Autism Diagnostic Interview-Revised (ADI-R; Rutter, LeCouteur, & Lord, 2003), and ruled out in the TD group with the ADOS and Social Responsiveness Scale (SRS; Constantino, 2005). Groups were matched on chronological age (see Table 1 for demographic information). They were also matched on hand dominance (assessed with the Edinburg Handedness Inventory; Oldfield, 1971), as there is some evidence that this may influenced

effluent function (Khalfa, Veuillet, & Collet, 1998). IQ was measured with a 4-subtest version of the age-appropriate Wechsler scale (Wechsler, 2004, 2008). We enrolled subjects with ASD with Full Scale IQs ≥ 85 to ensure comprehension of the tasks, while also representing a spectrum of functioning. The TD group was significantly higher than the ASD group on FSIQ, $F(1,73)=10.55$, $p=0.002$. Pure tone audiometric screening (Maico Diagnostics; Eden Prairie, MN) was performed on both ears for all participants. All participants could detect tones ≥ 20 dB SPL for 500, 1000, 2000, and 4000 Hz, and ≥ 25 dB SPL for 8000 Hz. Additional exclusion criteria for all participants included history of neurological injury or disorders, persistent, frequent, or recurring ear infections, genetic disorders, and other conditions or illnesses that could affect auditory function. TD participants were excluded if they had a 1st or 2nd degree relative with an ASD. Parents of all participants provided written informed consent, and participants gave assent, as approved by the University's Research Subject Review Board.

All Audiometry, DPOAE, and TrOAE measurements were conducted in a double-walled soundbooth (Industrial Acoustics Co [IAC]; New York, NY).

Otoacoustic emissions

Distortion-product otoacoustic emissions (DPOAEs) and **Transient-evoked otoacoustic measurements (TrOAEs)** were acquired using Intelligent Hearing Systems (IHS; Miami, FL) Smart OAE hardware and software interfaces. **DPOAEs** were conducted for pure tones from 0.5-8 kHz. An Etymotic Research (Elk Grove Village, IL) ER 10C probe was inserted into the external ear canal and used with an ER2 speaker. Stimulus response signals were sampled at a rate of 128 kHz using a 16-bit D/A converter. L_1 and L_2 amplitudes were set to 70 dB SPL. Equilevel primary tones of moderate level were used in this study as equilevel primaries have been used successfully to detect reduced cochlear function in the presence of normal behavioral sensitivities (Arnold et al., 1999). Frequencies were acquired with an F_2 – F_1 ratio of 1.22. Stimuli were presented starting from the lowest frequencies increasing to the highest frequencies with 32 averages/per frequency and DPOAEs were only included if ≥ 6 dB above the noise floor.

TrOAEs were defined as having a stimulus stability exceeding 80% and a signal-to-noise amplitude in the frequency bands centered at 1000 and 2000 Hz exceeding 4 dB. TrOAEs were recorded with a commercial instrument (IHS) with the standard 80 dB peak sound pressure click default protocol with a commercially available OAE probe (Etymotic Research 10C) in the ear canal, with 512 sweeps were performed in each ear. In addition to overall TrOAE amplitude (click response), the responses were separated in the spectral domain across frequency bands (1, 1.5, 2, 3, and 4 kHz) using customized software (HIS, Miami, FL).

Binaural suppression was measured using ER 10C probe microphones/transducers in both ears with binaural noise bursts presented at 70 dB SPL through both speakers. This noise/click relationship was chosen because Hood and colleagues (1996) showed them to elicit emissions and a substantial suppression effect. Broadband noise (BBN) bursts, 400 ms duration, were presented binaurally at 70 dB peak SPL, in a forward masking paradigm with an interstimulus interval of 10 ms separating the noise from the click. Again, 512 sweeps

were averaged for each ear. To determine efferent suppression, the root mean square (RMS) amplitude difference between baseline and suppression was compared using custom software (IHS), with a value for the overall RMS suppression derived from the time window between 8-18 ms, as this is the time window within which the most suppression occurs (Berlin, Hood, Hurley, Wen, & Kemp, 1995; Veuillet, Collet, & Duclaux, 1991) (see Figs. 2A & 3A). All statistical analyses were performed using SPSS v.22 (IBM; Armonk, NY) computer software, using repeated-measures analysis of variance (ANOVA) to examine group differences across frequency, followed by post-hoc analyses.

Results

All included participants had clinically acceptable audiometric levels (≤ 20 dB SPL for frequencies 0.5-4 kHz; and ≤ 25 dB SPL for 8 kHz) and DPOAE responses were present in both ears, in both the ASD ($n=35$) and TD ($n=42$) groups. We excluded four of our consented participants with ASD, as they exhibited audiometric thresholds above the screening cutoffs in at least one ear, for at least one frequency. As shown in Fig. 1B-1D, we found a significant decrease in DPOAE signal to noise ratio (SNR) at 1 kHz in both ears for the children with ASD compared to TD controls (Left ear, $F(1,74)=5.4$, $P=0.02$; Right ear, $F(1,73)=5.9$, $P=0.02$). Averaged (right and left) group difference was also significant at 1 kHz ($F(1,73)=8.0$, $P=0.006$). In contrast, for the other frequencies tested from 500 Hz to 8 kHz, there were no significant differences in DPOAE SNR levels. These differences at 1 kHz were not due to noise floor differences, as there were no significant differences between the DPOAE noise floors between the two groups (ASD & TD) at any frequency or ear tested.

The DPOAE response can be influenced by the action of the middle ear muscle (MEM-R) acoustic reflex. The equilevel primaries used for DPOAE testing were 70 dB SPL, which should be below the threshold for MEM-R responses; however to ensure differences in MEM-R responses to DPOAE primary tones did not cause the differences in DPOAE SNR measures, we computed a MEM-R difference for each ear and frequency. To compute MEM-R differences, we determined the L_1-A_1 difference (see Fig 1A), which is the difference in dB between the amplitudes of the tone entering the ear canal minus the amplitude of that same tone exiting the ear canal. As shown in Fig. 1E-1G, all MEM-R differences were less than 1 dB SPL, and were less than 0.25 dB SPL when averaged. Furthermore, no significant differences were observed between children with ASD and TD controls at any level for either ear.

TrOAEs were also tested in the same groups of children in both ears. There were no significant differences in TrOAEs in the left ears between children with ASD or TD controls (Fig. 2B). However, as seen in Fig. 2C, there were significant differences between the groups in the right ears for both the overall click RMS values ($F(1,73)=7.8$, $P=0.007$) and at 1-2 kHz when the responses were spectrally separated (1 kHz, $F(1,73)=5.72$, $P=0.02$; 1.5 kHz, $F(1,73)=5.91$, $P=0.02$; 2 kHz, $F(1,73)=5.96$, $P=0.02$). The observed asymmetry in TrOAE responses, with right ear responses greater than left responses, is known (Keefe, Gorga, Jesteadt, & Smith, 2008). Fig. 2D shows this increased TrOAE responses with both ears averaged together in children with ASD as compared with TD children. Again, there is

a significant difference between children with ASD and TD controls for the overall click ($F(1,72)=5.9$, $P=0.02$) and 1 kHz response ($F(1,72)=4.33$, $P=0.04$).

To test cochlear efferent feedback suppression, binaural forward masking was used prior to testing the TrOAE emission. The difference in RMS values between baseline and BBN suppression (Fig 3A) testing was the TrOAE suppression SNR value. There were no significant differences in TrOAE suppression values between children with ASD and TD controls in either the right, left, or when both ears are averaged (Fig 3B). As can be observed in Figs 3B and 3C, the average TrOAE suppression in the left ear is ~1dB greater in the TD controls, yet this difference is not statistically significant.

Previous studies have reported relationships between auditory function and other skills (e.g., language, symptom severity). We examined the relationship between the Verbal Comprehension Index and Full Scale IQ to OAEs in the 1 kHz mid-frequency range. We used the averaged DPOAE at 1 kHz, and performed analyses separately by group. We found no significant relationships in either group between 1 kHz DPOAE and Verbal Comprehension (ASD: $r(33)=0.06$, $P=0.75$; TD: $r(40)=0.11$, $P=0.50$) or Full Scale IQ (ASD: $r(33)=0.07$, $P=0.70$; TD: $r(40)=-0.03$, $P=0.84$). In contrast, 1 kHz DPOAE was significantly related to symptom severity in the ASD group, as measured by the ADOS Calibrated Severity Score (Gotham, Pickles, & Lord, 2009; Hus & Lord, 2014), $r(33)=-0.48$, $P=0.004$, with more severe symptoms associated with lower DPOAE responses.

Discussion

In this study, we found that children and adolescents with ASD had reduced outer hair cell function at the 1 kHz mid-frequency region using two different measures of outer hair cell integrity –DPOAEs and TrOAEs. Specifically, we have discovered that high functioning participants with ASD have greatly reduced (~25%) DPOAE responses compared to TD controls in the 1 kHz mid-frequency range, yet have comparable DPOAE responses outside this critical range (at 0.5 and 4-8 kHz regions). We also examined multi-frequency click TrOAEs; an analysis of the spectral features of the TrOAE revealed similarly decreased emissions in the 1-2 kHz mid frequency regions in participants with ASD compared to TD controls. Importantly, all children had normal audiometric screening levels < 20 dB HL, so this DPOAE loss was not due to a general sensorineural or conductive hearing loss. Moreover, there were no significant differences in DPOAE noise floors, MEM-R reflexes to 70 dB tones, or efferent feedback strengths (TrOAE suppression) between children with ASD and TD controls. Additional correlational analyses showed that DPOAE responses in the 1 kHz mid-frequency range were unrelated to verbal or overall cognitive ability. In contrast, we found a significant relationship between 1 kHz DPOAE response and symptom severity in the ASD group.

The observed decreases in OAE amplitudes at 1 kHz mid-frequency region could cause reduced ability to discriminate between two sounds or impair auditory tuning (Dallos, 1992). In fact, Boets, Verhoeven, Wouters, and Steyaert (2015) noted that children with ASD had impaired auditory tuning when compared with TD children. In addition, mammalian cochlea development is a process with both a basal (high-frequency region) to apical (low frequency

region) developmental gradient over several prenatal days (i.e., tonotopic development), so deficits in the 1 kHz frequency regions could give insight into a developmental window of cochlear function deficits (Lavigne-Rebillard & Pujol, 1986, 1990).

Reduced OAE amplitudes around 1 kHz may also impair speech perception and comprehension in challenging environments, since this is in a sensitive region of the audiogram, and much of vowel discrimination (1st and 2nd formants) are in this mid-frequency region (Bell, Dirks, & Trine, 1992; Duggirala, Studebaker, Pavlovic, & Sherbecoe, 1988; French & Steinberg, 1947; Ling & Ling, 1978).

Our finding of reduced mid-frequency OAEs in children with clinically normal audiometric levels, parallels recent finding by Demopoulos and Lewine (2015) who found that in children with ASD, there was a relationship between mid-frequency pure-tone auditory thresholds and expressive and receptive language measures. In our study, screening pure tone audiometry was performed to rule out hearing loss (i.e., normal pure tone audiometry 20 dB SPL), so we do not know what percentage of children had even lower auditory thresholds (i.e., -5 dB SPL). In addition to auditory threshold and tuning differences between children with ASD and TD controls, other auditory abilities have been investigated in high-functioning children with ASD and have found differences in children with ASD, such as frequency selectivity (Plaisted, Saksida, Alcantara, & Weisblatt, 2003), pitch discrimination (Bonnell et al., 2003), pitch segmentation (Heaton, 2003), frequency modulation detection (Samson et al., 2011), hearing in background noise (Alcantara, Weisblatt, Moore, & Bolton, 2004; Groen et al., 2009), and auditory temporal envelope resolution (Alcantara, Cope, Cope, & Weisblatt, 2012). Moreover, we are also not the first group to study DPOAEs and TrOAEs in children with ASD, and there are conflicting findings with reports of decreased DPOAE SNRs at all frequencies (Collet et al., 1993; Danesh & Kaf, 2012; Kaf & Danesh, 2013; Khalifa et al., 2001; Tas et al., 2007) to no DPOAE changes (Gravel, Dunn, Lee, & Ellis, 2006; Tharpe et al., 2006). However, all previous DPOAE measurements used uneven primary levels ($L_2 > L_1$) whereas our study used equilevel primaries (L_1 and $L_2 = 70$ dB). We used mid-level equilevel primaries for DPOAE testing modeled after the study by Arnold et al. that showed that they were able to detect deficits in cochlear function (as assessed by DPOAEs) in the presence of normal audiometric thresholds. We had piloted DPOAE testing with uneven primaries ($L_1 = 75$ dB SPL, $L_2 = 65$ dB SPL) but noticed that at these higher L_1 levels there were differences in the noise floors between children with ASD and TD controls, whereas equilevel primaries at 70 dB SPL yielded robust DPOAE responses (6 dB above noise floor) with no differences in DPOAE noise floors across groups. Additionally, the overall difference in TrOAE measurements on the right between children with ASD and TD controls was explained by reduced TrOAE responses in the ASD group at similar mid-frequency regions (1-2 kHz) when the overall TrOAE responses were spectrally separated into frequency bands.

Other explanations for the loss of 1 kHz OAEs could be due to differences in either the middle ear muscle (MEM) reflex or the efferent suppression, as there is regulation by the brain onto cochlear activity via both of these descending auditory pathways (Warr & Guinan, 1979). Children with ASD can have asymmetrical and reduced MEM reflexes to high-level sounds (>110 dB SPL; Lukose, Brown, Barber, & Kulesza, 2013). However,

when the possible influence of MEM reflexes was assayed as to their contributions to mid-level sounds used in our DPOAE and TrOAE measures (i.e., at 70dB SPL), we found no difference between children with ASD and TD controls with very little MEM muscle involvement.

We also did not find any differences in binaural efferent suppression of TrOAE responses between high-functioning children with ASD and TD controls. Khalfa et al. (2001) had previously shown that young (10 years) low-functioning children with ASD have reduced olivocochlear efferent feedback using contralateral suppression of TrOAEs when compared with typically developing subjects. So perhaps differences between the current study and Khalfa et al. could be due to differences in age, severity of ASD, multiple subgroups in ASD with different pathophysiologies, or the fact that our study used binaural (vs. contralateral) broadband noise activation of efferent feedback. Finally, neither the current study nor Khalfa et al. assayed DPOAE-based efferent feedback; this may provide a more sensitive measure of frequency differences in olivocochlear feedback (Danesh & Kaf, 2012; Humes, 1983).

As many of the above mentioned assays of auditory abilities need behavioral responses, OAEs do not, and these non-invasive measures may be performed in children as young as infancy. This may be important as while an accurate ASD diagnosis can reliably be made by 24 months, signs of the ASD are oftentimes present even earlier, yet the majority of children with ASD are not diagnosed until after age 4 (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators, 2014). Delayed identification results in starting treatment later, which likely attenuates positive outcomes associated with early intervention (Bradshaw, Steiner, Gengoux, & Koegel, 2015; Koegel, Koegel, Ashbaugh, & Bradshaw, 2014).

Future experiments aimed at testing both younger and non-verbal children with confirmed ASD using both DPOAE- and TrOAE-based afferent baseline and efferent suppression measures will be required to fully elucidate the potential for such OAE measures to test auditory processing deficits and their role in the pathogenesis of ASD communication symptoms.

Acknowledgements

This research was supported by grants from NIH R21 DC011094, P30 DC05409, Clinical & Translational Science Institute Pilot Award (UL1 RR024160) and R01 DC009439. We thank Ranisha Nelson, Alyssa Lord, Ruth Davis, and Jiashu Li for help with data collection and processing, and we also thank the children and families who participated in these studies.

References

- Alcantara JI, Cope TE, Cope W, Weisblatt EJ. Auditory temporal-envelope processing in high-functioning children with autism spectrum disorder. *Neuropsychologia*. 2012; 50:1235–1251. [PubMed: 22349444]
- Alcantara JI, Weisblatt EJ, Moore BC, Bolton PF. Speech-in-noise perception in high-functioning individuals with autism or Asperger's syndrome. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2004; 45:1107–1114.

- Arnold DJ, Lonsbury-Martin BL, Martin GK. High-frequency hearing influences lower-frequency distortion-product otoacoustic emissions. *Archives of Otolaryngology - Head and Neck Surgery*. 1999; 125:215–222. [PubMed: 10037289]
- Autism and Developmental Disabilities Monitoring Network Surveillance Year 2010 Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR: Surveillance Summaries*. 2014; 63:1–21.
- Baranek GT, Watson LR, Boyd BA, Poe MD, David FJ, McGuire L. Hyporesponsiveness to social and nonsocial sensory stimuli in children with autism, children with developmental delays, and typically developing children. *Development and Psychopathology*. 2013; 25:307–320. [PubMed: 23627946]
- Bell TS, Dirks DD, Trine TD. Frequency-importance functions for words in high- and low-context sentences. *Journal of Speech and Hearing Research*. 1992; 35:950–959. [PubMed: 1405551]
- Bergman BM, Gorga MP, Neely ST, Kaminski JR, Beauchaine KL, Peters J. Preliminary descriptions of transient-evoked and distortion-product otoacoustic emissions from graduates of an intensive care nursery. *Journal of the American Academy of Audiology*. 1995; 6:150–162. [PubMed: 7772784]
- Berlin CI, Hood LJ, Hurley AE, Wen H, Kemp DT. Binaural noise suppresses linear click-evoked otoacoustic emissions more than ipsilateral or contralateral noise. *Hearing Research*. 1995; 87:96–103. [PubMed: 8567448]
- Boets B, Verhoeven J, Wouters J, Steyaert J. Fragile spectral and temporal auditory processing in adolescents with autism spectrum disorder and early language delay. *Journal of Autism and Developmental Disorders*. 2015; 45:1845–1857. [PubMed: 25503681]
- Bonnell A, Mottron L, Peretz I, Trudel M, Gallun E, Bonnell AM. Enhanced pitch sensitivity in individuals with autism: A signal detection analysis. *Journal of Cognitive Neuroscience*. 2003; 15:226–235. [PubMed: 12676060]
- Bradshaw J, Steiner AM, Gengoux G, Koegel LK. Feasibility and effectiveness of very early intervention for infants at-risk for autism spectrum disorder: A systematic review. *Journal of Autism and Developmental Disorders*. 2015; 45:778–794. [PubMed: 25218848]
- Collet L, Roge B, Descouens D, Moron P, Duverdy F, Urgell H. Objective auditory dysfunction in infantile autism. *Lancet*. 1993; 342:923–924.
- Constantino, JN. *Social Responsiveness Scale*. Western Psychological Services; Los Angeles: 2005.
- Dallos P. The active cochlea. *Journal of Neuroscience*. 1992; 12:4575–4585. [PubMed: 1464757]
- Danesh AA, Kaf WA. DPOAEs and contralateral acoustic stimulation and their link to sound hypersensitivity in children with autism. *International Journal of Audiology*. 2012; 51:345–352. [PubMed: 22299666]
- Dawson G, Meltzoff AN, Osterling J, Rinaldi J, Brown E. Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders*. 1998; 28:479–485. [PubMed: 9932234]
- Demopoulos C, Hopkins J, Kopald BE, Paulson K, Doyle L, Andrews WE, Lewine JD. Deficits in auditory processing contribute to impairments in vocal affect recognition in autism spectrum disorders: A MEG study. *Neuropsychology*. 2015; 29:895–908. [PubMed: 26011112]
- Demopoulos C, Lewine JD. Audiometric profiles in autism spectrum disorders: Does subclinical hearing loss impact communication? *Autism Research*. 2015
- Duggirala V, Studebaker GA, Pavlovic CV, Sherbecoe RL. Frequency importance functions for a feature recognition test material. *Journal of the Acoustical Society of America*. 1988; 83:2372–2382. [PubMed: 3411027]
- Dyck MJ, Farrugia C, Shochet IM, Holmes-Brown M. Emotion recognition/understanding ability in hearing or vision-impaired children: do sounds, sights, or words make the difference? *Journal of Child Psychology and Psychiatry*. 2004; 45:789–800. [PubMed: 15056310]
- Edgar JC, Khan SY, Blaskey L, Chow VY, Rey M, Gaetz W, Roberts TPL. Neuromagnetic oscillations predict evoked-response latency delays and core language deficits in autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2015; 45:395–405. [PubMed: 23963591]
- French NR, Steinberg JC. Factors governing the intelligibility of speech sounds. *Journal of the Acoustical Society of America*. 1947; 19:90–119.

- Gaffney GR, Kuperman S, Tsai LY, Minchin S. Morphological evidence for brainstem involvement in infantile autism. *Biological Psychiatry*. 1988; 24:578–586. [PubMed: 3167146]
- Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*. 2009; 39:693–705. [PubMed: 19082876]
- Gravel JS, Dunn M, Lee WW, Ellis MA. Peripheral audition of children on the autistic spectrum. *Ear and Hearing*. 2006; 27:299–312. [PubMed: 16672798]
- Groen WB, van Orsouw L, Huurne N, Swinkels S, van der Gaag RJ, Buitelaar JK, Zwiers MP. Intact spectral but abnormal temporal processing of auditory stimuli in autism. *Journal of Autism and Developmental Disorders*. 2009; 39:742–750. [PubMed: 19148738]
- Haesen B, Boets B, Wagemans J. A review of behavioural and electrophysiological studies on auditory processing and speech perception in autism spectrum disorders. *Research in Autism Spectrum Disorders*. 2011; 5:701–714.
- Hashimoto T, Tayama M, Murakawa K, Yoshimoto T, Miyazaki M, Harada M, Kuroda Y. Development of the brainstem and cerebellum in autistic patients. *Journal of Autism and Developmental Disorders*. 1995; 25:1–18. [PubMed: 7608030]
- Heaton P. Pitch memory, labelling and disembedding in autism. *Journal of Child Psychology and Psychiatry and Allied Disciplines*. 2003; 44:543–551.
- Hitoglou M, Ververi A, Antoniadis A, Zafeiriou DI. Childhood autism and auditory system abnormalities. *Pediatric Neurology*. 2010; 42:309–314. [PubMed: 20399382]
- Hood LJ, Berlin CI, Hurley A, Cecola RP, Bell B. Contralateral suppression of transient-evoked otoacoustic emissions in humans: Intensity effects. *Hearing Research*. 1996; 101:113–118. [PubMed: 8951438]
- Humes LE. Psychophysical measures of two-tone suppression and distortion products (2f1-f2) and (f2-f1). *Journal of the Acoustical Society of America*. 1983; 73:930–950. [PubMed: 6841819]
- Hus V, Lord C. The Autism Diagnostic Observation Schedule, Module 4: Revised algorithm and standardized severity scores. *Journal of Autism and Developmental Disorders*. 2014; 44:1996–2012. [PubMed: 24590409]
- Kaf WA, Danesh AA. Distortion-product otoacoustic emissions and contralateral suppression findings in children with Asperger's Syndrome. *International Journal of Pediatric Otorhinolaryngology*. 2013; 77:947–954. [PubMed: 23562236]
- Keefe DH, Gorga MP, Jesteadt W, Smith LM. Ear asymmetries in middle-ear, cochlear, and brainstem responses in human infants. *Journal of the Acoustical Society of America*. 2008; 123:1504–1512. [PubMed: 18345839]
- Kemp DT. Otoacoustic emissions, their origin in cochlear function, and use. *British Medical Bulletin*. 2002; 63:223–241. [PubMed: 12324396]
- Khalifa S, Bruneau N, Roge B, Georgieff N, Veuillet E, Adrien JL, Collet L. Peripheral auditory asymmetry in infantile autism. *European Journal of Neuroscience*. 2001; 13:628–632. [PubMed: 11168571]
- Khalifa S, Veuillet E, Collet L. Influence of handedness on peripheral auditory asymmetry. *European Journal of Neuroscience*. 1998; 10:2731–2737. [PubMed: 9767403]
- Koegel LK, Koegel RL, Ashbaugh K, Bradshaw J. The importance of early identification and intervention for children with or at risk for autism spectrum disorders. *International Journal of Speech-Language Pathology*. 2014; 16:50–56. [PubMed: 24328352]
- Kulesza RJ, Mangunay K. Morphological features of the medial superior olive in autism. *Brain Research*. 2008; 1200:132–137. [PubMed: 18291353]
- Lavigne-Rebillard M, Pujol R. Development of the auditory hair cell surface in human fetuses: A scanning electron microscopy study. *Anat Embryol*. 1986; 174:369–377. [PubMed: 3766993]
- Lavigne-Rebillard M, Pujol R. Auditory hair cells in human fetuses: synaptogenesis and ciliogenesis. *Journal of Electron Microscopy Technique*. 1990; 15:115–122. [PubMed: 2355265]
- Ling, D., Ling, AH. *Aural habilitation: The foundations of verbal learning in hearing-impaired children*. 1st ed.. Alexander Graham Bell Association for the Deaf; Washington: 1978.
- Lord, C., Rutter, M., DiLavore, P., Risi, S., Gotham, K., Bishop, S. *The Autism Diagnostic Observation Schedule*. 2nd ed.. Western Psychological Services; Torrance, CA: 2012.

- Lukose R, Brown K, Barber CM, Kulesza RJ Jr. Quantification of the stapedial reflex reveals delayed responses in autism. *Autism Research*. 2013; 6:344–353. [PubMed: 23825093]
- Most T, Michaelis H. Auditory, visual, and auditory-visual perceptions of emotions by young children with hearing loss versus children with normal hearing. *Journal of Speech Language and Hearing Research*. 2012; 55:1148–1162.
- Nadig AS, Ozonoff S, Young GS, Rozga A, Sigman M, Rogers SJ. A prospective study of response to name in infants at risk for autism. *Archives of Pediatrics and Adolescent Medicine*. 2007; 161:378–383. [PubMed: 17404135]
- O'Connor K. Auditory processing in autism spectrum disorder: A review. *Neuroscience and Biobehavioral Reviews*. 2012; 36:836–854. [PubMed: 22155284]
- Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. *Neuropsychologia*. 1971; 9:97–113. [PubMed: 5146491]
- Plaisted K, Saksida L, Alcantara J, Weisblatt E. Towards an understanding of the mechanisms of weak central coherence effects: Experiments in visual configural learning and auditory perception. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*. 2003; 358:375–386. [PubMed: 12639334]
- Rodier PM, Ingram JL, Tisdale B, Nelson S, Romano J. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *Journal of Comparative Neurology*. 1996; 370:247–261. [PubMed: 8808733]
- Rutter, M., LeCouteur, A., Lord, C. *Autism Diagnostic Interview, Revised*. Western Psychological Services; Los Angeles: 2003.
- Samson F, Hyde KL, Bertone A, Soulieres I, Mendrek A, Ahad P, Zeffiro TA. Atypical processing of auditory temporal complexity in autistics. *Neuropsychologia*. 2011; 49:546–555. [PubMed: 21192958]
- Shera CA, Guinan JJ. Evoked otoacoustic emissions arise by two fundamentally different mechanisms: a taxonomy for mammalian OAEs. *Journal of the Acoustical Society of America*. 1999; 105:782–798. [PubMed: 9972564]
- Tas A, Yagiz R, Tas M, Esme M, Uzun C, Karasalioglu AR. Evaluation of hearing in children with autism by using TEOAE and ABR. *Autism*. 2007; 11:73–79. [PubMed: 17175575]
- Tharpe AM, Bess FH, Sladen DP, Schissel H, Couch S, Schery T. Auditory characteristics of children with autism. *Ear and Hearing*. 2006; 27:430–441. [PubMed: 16825892]
- Veuille E, Collet L, Duclaux R. Effect of contralateral acoustic stimulation on active cochlear micromechanical properties in human subjects: dependence on stimulus variables. *Journal of Neurophysiology*. 1991; 65:724–735. [PubMed: 2051201]
- Warr WB, Guinan JJ. Efferent innervation of the organ of corti: two separate systems. *Brain Research*. 1979; 173:152–155. [PubMed: 487078]
- Wechsler, D. *Wechsler Intelligence Scale for Children*. 4th Ed.. Pearson; San Antonio, TX: 2004.
- Wechsler, D. *Wechsler Adult Intelligence Scale*. 4th Ed.. Pearson; San Antonio, TX: 2008.

Figure 2. Children with ASD have reduced TrOAEs in the 1-2 kHz frequencies

A. Schematic of TrOAE baseline. Baseline TrOAEs are elicited with a unilateral click stimulus (black trace) with the RMS value averaged over the 8-18 ms window. **B & C.** There is a difference in the click TrOAE baseline values for the right ear (RE) between children with ASD and TD controls, and when the click response is separated into spectral bands, the 1-2 kHz region is significantly different between children with ASD and TD children in the right ear. **D.** Average (across ear) differences between TD TrOAE values and ASD TrOAE values (click and spectrally separated by frequency bands), showing that children with ASD had reduced TrOAE values in the click response and the 1 kHz region, with a trend at 1.5 and 2 kHz.

Figure 3. Children with ASD have no differences in TrOAE suppression to binaural BBN stimulus

A. Schematic of TrOAE suppression testing. Baseline TrOAES are elicited with a unilateral click stimulus (black trace), and binaural suppression testing used binaural forward masking of broadband noise (BBN) 400 ms prior to click stimulus presentation (gray trace), with difference between traces showing the suppressed response. **B.** There are no differences in TrOAE binaural suppression values in either ear or averaged ears (combined ears) between children with ASD and TD children. **C.** Average differences between TD TrOAE suppression values and ASD TrOAE suppression values show no differences in TrOAE binaural suppression values in either ear or averaged ears (combined ears) between children with ASD and TD children.

Table 1

Demographic information for the ASD and TD groups

	ASD (<i>n</i> =35)		TD (<i>n</i> =42)		<i>F</i> or <i>X</i> ²	<i>P</i>
	Mean	(SD)	Mean	(SD)		
Age (years)	11.98	(2.82)	12.49	(3.25)	0.53	0.47
Full Scale IQ ^{<i>a</i>}	104.89	(13.01)	114.69	(13.34)	10.55	0.002
Verbal Comprehension ^{<i>a</i>}	105.09	(11.95)	116.14	(15.28)	12.13	0.001
Perceptual Reasoning ^{<i>a</i>}	103.49	(16.36)	110.17	(14.43)	3.63	0.06
Full Scale IQ ^{<i>a</i>}	104.89	(13.01)	114.69	(13.34)	10.55	0.002
SRS Total T-Score	76.77	(12.04)	41.46	(6.68)	259.43	<0.001
ADOS Calibrated Severity ^{<i>b</i>}	6.60	(1.97)	1.12	(0.33)	306.53	<0.001
Handedness (R:L)	30:5		32:10		1.10	0.29

ASD, autism spectrum disorder; ADOS, Autism Diagnostic Observation Schedule; SRS, Social Responsiveness Scale; TD, typically developing

^{*a*} Full Scale IQ and Index scores based on a four-item short form of the Wechsler Intelligence Scale for Children, 4th ed. or the Wechsler Adult Intelligence Scale, 4th ed.

^{*b*} ADOS Severity Scores calculated based on module (Gotham et al., 2009; Hus & Lord, 2014)