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# Abnormal auditory brainstem response in the pons region in youth with autism

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ABSTRACT

*Purpose of the article:* Autism spectrum disorder (ASD) is an impairing neurodevelopmental disorder with an unknown etiology. The present study aims to investigate if the auditory brainstem response (ABR) to complex stimuli in children and adolescents diagnosed with ASD can be a possible objective biomarker in autism.
*Materials and methods:* The ABR of 39 youth with ASD (7–18 years) were compared to the ABR of 34 typically developed youth (TD). The ABR consists of seven positive peaks (waves I–VII) that occur during 10 Ms following a sound stimulus.
*Results:* The amplitude of wave III (region 2.5–4.0 Ms) was higher in the ASD group compared to the TD group. The TD males showed a significant lower degree of correlation, between left and right ear compared to the ASD groups and the TD females.
*Conclusions:* Altered auditory processing was evident in the pons region of the brainstem for the ASD group when compared to the TD group. Implications of the findings are discussed in relation to the neurobiology and assessment of autism spectrum disorder in youth.

## 1. Background

Autism spectrum disorder (ASD) is an impairing and heterogeneous neurodevelopmental disorder with an early onset (Volkmar, Reichow, & Mcpartland, 2014). ASD is characterized by social impairments, communication difficulties, altered sensory processing, and repetitive and restricted behaviours (American Psychiatric Association, 2013) and affects 1%–3% of the population (Baron-Cohen, Scott, & Allison, 2009; Kim, Leventhal, & Koh, 2011; Baxter, Brugha, & Erskine, 2014).

Individuals with ASD show abnormal cortex activation when processing acoustic stimuli (Blasi, Lloyd-Fox, & Sethna, 2015; Hames, Murphy, & Rajmohan, 2016) and it is proposed that subcortical structures might be involved in this process (Orekhova, Tsetlin, & Butorin, 2012). In line with this, abnormal brainstem processing responses to auditory stimuli has been found in adults with ASD (Källstrand, Olsson, & Nehlstedt, 2010). Further, it has been suggested that brainstem abnormalities may be partly responsible for the difficulties with language, cognitive and social development in children with ASD (Baranek, David, & Poe, 2006). One study showed that the brainstem in children with ASD is smaller and has a slower growth rate than in TD children (Jou, Frazier, & Keshavan, 2013). Brainstem functioning is also strongly related to the development of behaviour and emotion regulation in infants. Hence, further exploration of possible alterations in subcortical and brainstem systems in individuals with ASD is warranted (Geva & Feldman, 2008).

Auditory brainstem response (ABR) was first described by Jewett and Williston in 1971 (Jewett & Williston, 1971). The ABR method measures the subcortical neuronal electrical activity in the auditory pathways 10 ms (Ms) after sound stimuli. The seven positive waves (wave I–VII) of a ABR each represent a different part of the auditory pathway (Fig. 1). The ABR wave-pattern provides information in terms of the latency (speed of transmission), amplitudes of the peaks (number of neurons firing), inter-peak latency (the time between peaks) and interaural correlation (correlation between left and right ear) (Musiek & Lee, 1995). During the 1980s and early 1990s several studies were published with a focus on ABR in populations with ASD (Gillberg, Rosenhall, & Johansson, 1983; Klin, 1993; Rosenblum, Arick, & Krug, 1980; Tanguay, 1982). Subsequent studies have confirmed that ABR is often affected in children with ASD (Cohen, Gardner, & Karmel, 2013; Dabbous, 2012; Miron, Ari-Eve, & Gabis, 2016; Rosenhall, Nordin, &

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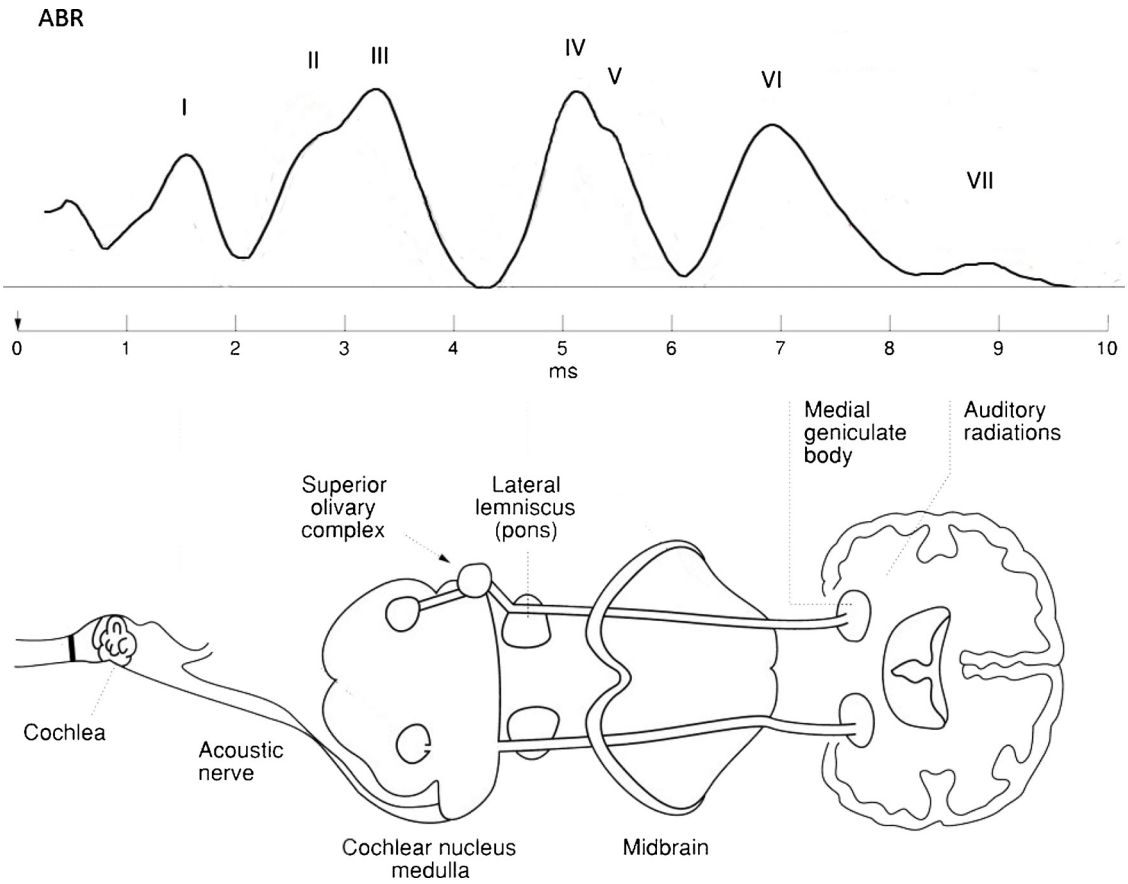


**Fig. 1.** Illustration of wave pattern of the standard ABR and corresponding anatomical structures within the first 10 ms after stimulation.

Brantberg, 2004). ABR has also been studied in other diagnostic groups such as ADHD (Baghdassarian, Markhed, & Lindström, 2017; Johnston, Mwangi, & Matthews, 2014), schizophrenia (Källstrand, Nehlstedt, & Sköld, 2012; Nielzén, Olsson, & Källstrand, 2008) and bipolar disorders (Sköld, Källstrand, & Nehlstedt, 2014) with evidence for both intact and altered auditory processing in populations with mental disorders (Baghdassarian et al., 2017; Manouilenko, Humble, & Georgieva, 2017).

The aim of the present study is to investigate brainstem response to complex stimuli in children with ASD. We will explore possible deviations in amplitude and interaural correlation.

## 2. Method

### 2.1. Subjects

The study included 39 children with ASD and 34 TD children. Twenty-one females with ASD (mean age 12.71 years, SD 3.36) and 18 males with ASD (mean age 11.50 years, SD 3.09). The TD group consisted of 24 females (mean age 13.12 years, SD 3.47) and 23 males (mean age 13.18 years, SD 3.22). The children with ASD were assessed in clinical settings by a senior psychologist using the ADOS (Lord, Rutter, DiLavore, & Rishi, 2001) and ADI-R (Rutter, Le Couteur, & Lord, 2003) (mean females 27.83, SD 16.34; mean males 33.00, SD 14.77) (Table 1). ADOS and ADI are diagnostic tools considered the "gold standard" in ASD diagnostics (Falkmer et al., 2013). To participate in the study, the ASD children were not allowed to have had any previous contact with the ear, nose and throat clinic to exclude hearing impairment. All ASD patients had an IQ of 70 or above, as measured by either the Wechsler Intelligence Scale for Children–Fourth edition (WISC-IV) (Lord et al., 2001) or the Wechsler Adult Intelligence Scale–Fourth edition (WAIS-IV) (Rutter et al., 2003). The ASD diagnoses were confirmed by a senior psychiatrist. To exclude TD participants with mental diagnoses or hearing impairment, the control group were not allowed to have any previous contact with mental health or ENT services. No participant in the TD group had a known intellectual disability or other NDD. Written informed consent was obtained from all participants and their parents/guardians. The study was approved by the regional ethics committee at the Lund University (Dnr: 2010/210, Dnr: 2015/11).

**Table 1**
Age distribution among the ASD patients and the TD. Age in years.

| Sex | N | Age(Mean) | SD |
|---|---|---|---|
| Female (ASD) | 21 | 12.71 | 3.36 |
| Female (TD) | 17 | 13.12 | 3.47 |
| Male(ASD) | 18 | 11.50 | 3.09 |
| Male(TD) | 17 | 13.18 | 3.22 |

### 2.2. Apparatus and stimuli

The ABR was measured with SensoDetect BERA (Brainstem Evoked Response Audiometry) A1000. The sound stimuli were presented via TDH-50 P headphones with Model 51 cushions (Telephonics, Farmingdale, New York, USA). Presentations were made binaurally with the stimuli in phase over headphones. The click pulses were repeated until a total of 1024 accepted evoked potentials had been collected for each sound stimulus. Transistor-transistor logic (TTL) trigger pulses coordinated the sweeps with the auditory stimuli. With a correctly timed TTL pulse, all ABR representations will be synchronized. Sound levels were calibrated using a Bruel & Kjaer 2203 sound level meter and Type 4152 artificial ear (Bruel & Kjaer S&VMeasurement,

**Table 2**
Deviation (DV) 1 and 2.ABR results for young patients with ASD compared to TD.

| Sex | DV | Diagnos/TD | N | Mean | Median | SD | P-value |
|---|---|---|---|---|---|---|---|
| Female | DV 1 | ASD | 21 | 0.56 | 0.57 | 0.09 | 0.0002 |
| Female | DV 1 | TD | 17 | 0.42 | 0.43 | 0.12 | |
| Male | DV 1 | ASD | 18 | 0.52 | 0.53 | 0.08 | 0.02 |
| Male | DV 1 | TD | 17 | 0.45 | 0.47 | 0.09 | |
| Female | DV 2 | ASD | 21 | 0.67 | 0.63 | 0.17 | 0.15 |
| Female | DV 2 | TD | 17 | 0.75 | 0.8 | 0.17 | |
| Male | DV 2 | ASD | 18 | 0.73 | 0.77 | 0.19 | 0.006 |
| Male | DV 2 | TD | 17 | 0.52 | 0.61 | 0.26 | |

DV 1 showing wave amplitude. DV 2 showing interaural correlation. Mann-Whitney U test was used.

Naerum, Denmark). The acoustic output from the earphones corresponded to SPL: 80 dB HL or 109 peSPL (peak equivalence). The collected evoked potentials for each sound stimulus from each ear of each individual was imported to Microsoft Excel (Microsoft Corp, Redmond, WA, USA) and analyzed using SensoDetect® BAS. Theparticipants were presented either a forward masked sound (FM) or a standard sound (Table 2) during a 30 min period of time. The sound stimuli were square-shaped click pulses (0.136 Ms duration, including 0.023 MS rise and fall; 192 Ms interstimulus interval. The forward masked sound had a 12.3 Ms gap from masker to click pulse. A 1500-Hz Butterworth low-pass filtered white noise, with 15 Ms duration (including 0.4 Ms rise and fall times) was used as masker for both forward and backward masking stimuli. All stimuli were constructed using MATLAB Signal Processing Toolbox (The MathWorks, Inc., Natick, Massachusetts, USA) and stored in a flash memory in the SensoDetect® BERA system.

### 2.3. Procedure

All ABR tests were performed and administered by trained staff. Participants were seated with a neck brace to make sure the neck was fixed and relaxed during testing. Two reference electrodes were placed on the mastoid bone behind the left and right ear, respectively, with two active electrodes and one ground electrode placed on the forehead. To ensure good transmission the sites were washed with disinfectant. Abrasive paste was used to fasten the electrodes. Absolute impedances and inter-electrode impedances were measured before and after the experiments to verify that electrode contact was maintained (below 5000 Ω). Earphones were fitted to cover both ears and the subjects were instructed to turn off their mobile phones and relax with their eyes closed. The test required no active participation.

### 2.4. Data analysis

Prior to further analysis, the audiogram was correlated to a norm ABR. A low correlation of $r \leq 0.35$ resulted in exclusion of the recording since there is a high risk the measurement is based on erroneous measurements du to coughing or tension (Källstrand et al., 2010, 2012). Due to poor audiogram quality 9 ASD males, 10 ASD females, 6 TD males and 7 TD females were excluded from the study resulting in the remaining subjects, 18 ASD males, 21 ASD females, 17 TD males and 17 TD females.

We analyzed the ABR in two predefined windows: amplitude in time window 2.5 Ms-4.0; 2; Ms interaural correlation in time window 3.3 Ms.- 4.4 Ms. Correlations between the data collected from the left and right ear were calculated using Pearson rho in order to discriminate differences between ABR wave sections. Pearson rho results in r-values

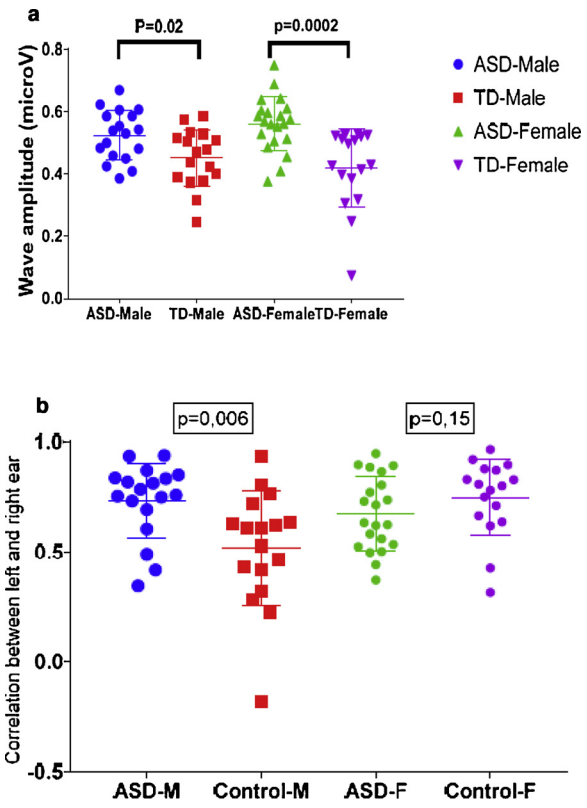


**Fig. 2.** (a) DV 1 and its p-value. Mean and Standard Deviation are indicated in the figure. (b) DV 2 and its p-value. Mean and Standard Deviation are indicated in the figure.

between -1 to +1 where a positive value indicates similarities and a negative value indicates an inverse relationship whereas values around zero indicate no relation at all. To identify specific alterations along the auditory pathway, correlations with a normative ABR curve were made. An aberrancy was denoted as a deviation (DV). Since the data was not normally distributed, the nonparametric test Mann–Whitney U was used.

## 3. Results

The amplitude of wave III (region 2.5–4.0 Ms) was higher in the ASD group compared to the TD group (denoted deviation 1 (DV 1)) (Table 2) (Fig. 2a).

The TD males showed a significant lower degree of correlation, between left and right ear compared to the ASD groups and the TD females (denoted deviation 2 (DV 2) (Table 2) (Fig. 2b).

## 4. Discussion

The aim of this study was to explore possible altered auditory processing in the brainstem in youth with ASD. The ABR in 39 youth with ASD were compared with the ABR for 34 TD youth.

We found that the amplitude of wave III was higher in the ASD group compared to the TD (DV 1) in the FM sound. From a neuroanatomical point of view, the DV 1 corresponds to the pons region. Hence the ASD group had more neurons firing in the pons region than the TD group as a response to acoustic stimuli (Falkmer et al., 2013). The pons region is involved in the processing of sensory information from hearing, taste, facial sensation, touch and pain as well as facial expression, chewing, swallowing, and secretion. Depending on the severity of ASD, autistic children can show difficulties within all of these areas (American Psychiatric Association, 2013). Difficulties with hyper- or hypo-sensitivity to touch and pain and limited facial expression are

also common in children with ASD. More severely autistic children often report difficulties with salivation, choking and chewing (Baranek et al., 2006). The simplest interpretation of more neurons firing in this specific area would be that we measured a hyper sensitivity to sound. Still it could be argued that the deviation of sound could represent a larger dysfunction of the pons area. Our finding is well in line with research showing increased pontine activity in children with ASD (Di martino, Kelly, & Grzadzinski, 2011; Sajdel-Sulkowska, Xu, & McGinnis, 2011; Suzuki, Sugihara, & Ouchi, 2013).

The TD males differed significantly from all the other groups by having a lower correlation between the left and right ear in the ABR in a neuroanatomical region corresponding to the midbrain. Interaural differences have for a long time been considered to represent brainstem pathology (Hall, 1984), although later studies show that healthy humans use *small* interaural differences to locate sound (Undurraga, Haywood, & Marquardt, 2016). However, the TD females did not exhibit this pattern of correlation. The high correlation between the auditory processing of the left and right ear in the ASD group could be related to difficulties in the processing of everyday sounds, an impairment often reported by children with ASD (Alcantara, Weisblatt, & Moore, 2004). This theory is supported by (Lepistö, Kultunen, and Sussman (2009) who concluded that children with ASD have difficulties segregating concurrent sound streams. However, this deviation (DV2) has to be confirmed in a future study.

The results in this study are based on group differences. Other obvious limitations are the small number of participants and the fact that no clinical comparisons group were included. Further, around 30% of the total number of children participating (ASD and TD) were excluded due to low quality ABR. Several of the ASD youth had complaints during testing about the sound level and having sensors attached to their foreheads. Hence the ASD youth with the most sensory processing difficulties have been excluded due to tensions and movement during testing, which might have impacted our results.

In sum, the results of this study support the notion of altered auditory brainstem processing in youth with ASD. However, the results need to be replicated and extended to further explore the potential of ABR as a possible biomarker in ASD.

## Conflict of interest

None of the authors declare any conflict of interest.

## Ethical statement

The study was approved by the regional ethics committee at the Lund University (Dnr: 2010/210, Dnr: 2015/11).

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