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# Neonatal brainstem auditory function associates with early receptive language development in preterm children

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## Abstract

**Aim:** To study whether auditory function measured with brainstem auditory evoked potential and brainstem audiometry recordings in the neonatal period associates with language development 1 year later in preterm infants.

**Methods:** This retrospective study included 155 preterm infants (birthweight ≤1500 g and/or birth ≤32 gestational weeks) born between 2007 and 2012 at the Turku University Hospital. Auditory function was recorded in neonatal period. Information of language development was gathered at the mean corrected age of 1 year by using the Finnish version of the MacArthur Communicative Development Inventory.

**Results:** Slower auditory processing (longer interpeak interval, IPI I-V) in the right ear in the neonatal brainstem auditory evoked potential recording associated with smaller receptive lexicon size at 1 year ($P = .043$). Infants with longer IPI I-V were more likely to have a deviant (≤17 words) receptive lexicon size ($P = .033$). The absence of a contralateral response with right ear stimulation increased the risk for deviant lexicon size ($P = .049$).

**Conclusion:** The results suggest that impaired auditory function in the neonatal period in preterm infants may lead to a poorer receptive language outcome 1 year later. Auditory pathway function assessment provides information for the identification of preterm children at risk for weak language development.

KEYWORDS
brainstem auditory evoked potentials, language development, preterm, receptive lexicon

## 1 | INTRODUCTION

The maturation of the auditory pathway can be disrupted by premature birth as many critical periods of brain development, including myelination and synaptogenesis, occur during the 27th gestational weeks onwards. For preterm children, this maturation occurs during the period when they are in a hospital environment.[1,2] Neonatal intensive care unit (NICU) treatment is considered to be a risk factor

**Abbreviations:** BA, Brainstem audiometry; BAEP, Brainstem auditory evoked potentials; CDI, The MacArthur Communicative Development Inventory; IPI, Interpeak interval; NICU, Neonatal intensive care unit.

for abnormal auditory maturation.[3] Auditory function can also be influenced by gestational age and gender.[3-5]

Premature birth increases the risk of an adverse neurodevelopmental outcome[6] including delayed language development.[7] At the corrected age of 1 year, language abilities can be studied by gathering information on the receptive and expressive lexicon which represent the number of words that the child understands and says. Normally child begins to understand words at the age of 9 months, and the first spoken words appear at the age of 12-13 months.[8] In the Finnish normative study including healthy full-term infants, at the age of 12 months children understood a mean of 89 and produced a mean of seven words.[9] At this age, prematurely born very low birthweight (birthweight ≤1500 g) infants understood a mean of 56 and produced a mean of five words,[10] which is a poorer result compared to full-term infants. It has also been discovered that the receptive lexicon size grows more slowly in very low birthweight children compared to full-term children.[10,11] The early weak receptive lexicon has been shown to predict a weak expressive lexicon and weak language abilities in preterm infants at the corrected age of 2 years.[10-12]

Children's very early language development can be measured in different ways.[8,13] The most typical method types are standardised testing, direct observation and the use of validated, normed parental report instruments. Each assessment type has its pros and cons. In Finland, there is no standardised test which could be used to measure early receptive lexical development at 1 year of age, and direct observation is not suitable to measure this ability. One well-known parental report instrument is the words and gestures form of the Communicative Development Inventory (CDI)[8,13] which has been normed and validated for the Finnish population.[9] Validated and normed parental report instruments are especially useful when children are very young. Parents are able to observe their children for long periods of time in different situations. This is important since in clinical situations, young children may be shy or tired, and due to this, information derived on children's language skills may not always be representative.[8,13] The possible parental bias (over or underestimation) can be minimised by using structured questionnaires. It is also important that the instruments focus on current development, not on memory.[8,13] Different parent report instruments exist. In addition to the CDI method, the LittlEARS Auditory Questionnaire is available. This method has been shown to correlate well with the CDI method.[14,15]

Previous studies have concluded that especially a timely maturation of the auditory pathway is a prerequisite for normal language development.[16] The maturation and function of the auditory pathway in neonates can be examined reliably and objectively with brainstem auditory evoked potentials (BAEP) and brainstem audiometry (BA) recordings. BAEP waveforms arise along the auditory pathway from the cochlear nerve to the brainstem, from the lower pontine nuclei to the inferior colliculus. In a normally hearing child, BAEP response usually consists of five peaks.[17] The latencies and interpeak intervals (IPIs) can be measured, and their normality assessed against reference values.[4] Latencies and IPIs represent the auditory processing in the auditory pathway and they decrease with increasing age of the child up to 2 years of age, due to myelination and synaptogenesis.[5,18] In addition, normally hearing preterm born infants present with delayed conduction in the auditory pathway at term age compared with full-term infants.[3]

Slow conduction in auditory pathway has been shown to predict later language development.[19] To our knowledge, only two studies so far have analysed the association between early BAEP and BA recordings and later language development.[19,20] The language abilities in both these studies were evaluated at the age of over 2 years, which is later in childhood than in the present study; thus, there is need for further study in this area. The aim of the present study was to investigate the association between neonatal brainstem auditory function in neurophysiological recordings and receptive lexicon at the corrected age of 1 year in infants born preterm.

**Key Notes**

- The aim was to investigate whether neonatal auditory pathway function could predict weak receptive language development already at the corrected age of 1 year in preterm infants.
- The present study found that slow auditory processing associates with smaller receptive lexicon size and increases the risk for a deviant receptive lexicon.
- The results suggest that preterm infants at risk for delayed language development could be recognised during the neonatal period.

## 2 | METHODS

### 2.1 | Participants

The formation of the study population is presented in the Figure 1. This retrospective register study included preterm infants whose birthweight was ≤1500 g and/or who were born ≤32 gestational weeks in Turku University Hospital between 2007 and 2012. We chose to use both birthweight and/or gestational age as inclusion criteria in order to study all children at risk for delayed language development.[10,11] From this group of preterm infants, we excluded infants who did not attend the routine follow-up in our preterm follow-up clinic of the Turku University Hospital for example due to death of the child or if the child was living outside the catchment area of Turku University Hospital. A total of 214 children were followed in our clinic where preterm infants are routinely referred to BAEP/BA examination and CDI forms are used. Afterwards, we included only children who were from monolingual Finnish speaking families. In addition, the following information had to be available for all the children: BAEP recordings in the neonatal period at the corrected age of ≤2.5 months and information on the lexical development gathered using the validated Finnish form of the MacArthur Communicative

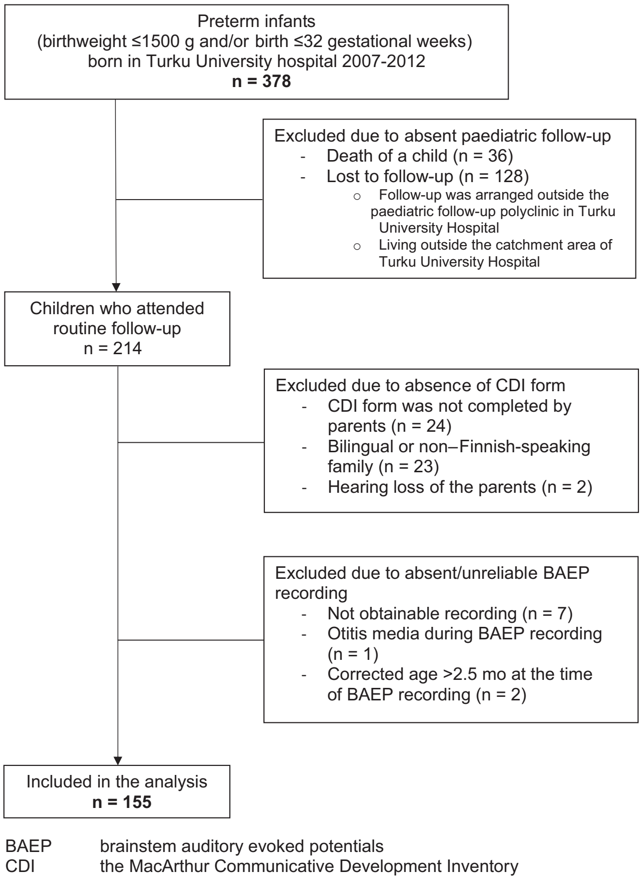


**FIGURE 1** The formation of the study group. BAEP, brainstem auditory evoked potentials; CDI, the MacArthur Communicative Development Inventory.

Development Inventory (CDI) at the corrected age of 1 year. Due to absent or unreliable BAEP recordings or absent CDI forms, 59 children were excluded from the final study group.

Information on the gestational age, birthweight, small for gestational age status, gender, hearing loss, age at the time of BAEP and BA recordings was gathered from patient files. Hearing loss diagnosis was gathered from patient files in 2016 at which time the youngest children of the study group were 4 years old. The hearing was considered impaired if a hearing loss was diagnosed in the Department of Audiology, which is the only unit providing hearing rehabilitation for children in the catchment area of Turku University Hospital.

The procedure for this retrospective study was approved by the Hospital District of Southwest Finland Ethics Review Committee in 2016.

## 2.2 | Measurements

### 2.2.1 | Brainstem audiometry recordings

Brainstem auditory evoked potentials and BA were recorded at the Department of Clinical Neurophysiology of Turku University Hospital in a quiet room by experienced event-related potential technologists. The ear canals of the children were checked and cleaned before the recordings. All infants were naturally asleep or peacefully awake. An eight-channel Nicolet Viking IV (Nicolet Biomedical Instruments) was used to record the BAEP and BA of 25 infants (recorded mostly in 2007), and a Viking Select (VIASYS Neurocare, Nicolet Biomedical Inc) was used for 130 infants. The recording electrodes were placed on both mastoids and the reference electrode at the vertex anterior to the fontanelle, and the ground on the forehead. The stimulus was delivered to the ear canal with tubal insert earphones (Nicolet model TIP 300 Ω).

In a BAEP recording, broadband rarefaction click stimuli were administered to the infant´s ear at an intensity of 85 dB nHL (stimulation rate 10.3 Hz) while the non-stimulated ear received masking white noise at 45 dB nHL. The high-pass filter was set to 150 Hz and the low-pass filter to 3 kHz. The sensitivity of the amplifier was 10 µV. The sample of 2000 responses was measured and averaged at least twice. If clear BAEP waveforms were not identified, the stimulus level was raised to 95 dB nHL. Each ear was stimulated separately, and ipsilateral and contralateral responses were recorded. An experienced technologist designated the peaks I, II, III, IV and V, and the troughs following the peaks I and V. A specialist in clinical neurophysiology (SKJ) checked the recordings and the reports. Later, the first writer (JA) evaluated all the recordings and identified BAEP components III and V on the contralateral recording. The contralateral response was considered present if the BAEP wave III and/or V were detectable and absent if neither of these waves were identified.

After a successful BAEP recording, a BA was recorded to determine the click threshold for both ears separately. Initially, the stimulus intensity was 35 dB nHL (33.3 Hz) with a masking white noise of 15 dB nHL in the non-stimulated ear. If no clear waveforms III-V were found, the intensity level was increased in increments of 10 dB nHL up to 65 dB nHL (and masking white noise up to 40 dB nHL) if necessary, until waves III and V were identified. BA was considered normal if the BA threshold was 35 dB in both ears and abnormal if the level was 45 dB or more in at least one ear.[4]

### 2.2.2 | Receptive lexicon data

To gather the data of the lexical development at the corrected age of 1 year, the standardised Finnish version of the MacArthur CDI: words and gestures were used.[9] The Finnish CDI has been found to be a reliable and valid method for studying early language development and it has been found to correlate well with formal language tests.[9,21] CDI is a structured parental rating instrument including 380 words presented in 19 semantic categories. Parents are advised to mark the words their child understands but does not say—comprising their receptive lexicon, and the words their child understand and says —comprising their expressive lexicon. In this study, only the receptive lexicon was utilised. This was done since expressive lexicon is very small at 1 year of age whereas the mean receptive lexicon size for full-term children is already roughly 80-90 words at this age.[9,10,13] The word was acknowledged to be understood if the child repeatedly and clearly responded correctly to the word. These instructions were given in writing to the parents. The parents also marked the day when they completed the form. This date was used to calculate the corrected age of the child at the time of CDI completion. After the parents had completed the CDI, words and gestures form it was returned to Turku University Hospital during a routine clinical follow-up of preterm infants.

The data were also divided into two groups according to the total receptive lexicon size. In the deviant CDI group, the children understood ≤17 words and in the normal CDI group >17 words. According to the normative data of the Finnish CDI, 17 receptive words are the weakest 10th percentile cut-off value at the age of 12 months[9] (personal communication by Eklund, 2017). The cut-off of 10% was chosen because it is used by most researchers using CDI and comparable methods.[22] If a child's value is below this cut-off, it means that 90% of their age companions have a better value in a skill in question. The weakest 10th percentile corresponds roughly with a −1.25 standard deviation from the mean.

### 2.3 | Statistical analysis

Initially, univariate associations were analysed between BAEP parameters (latency of BAEP component I, III, V, IPI I-V, I-III, III-V (ms), amplitude I and V (μV), amplitude ratio I/V), contralateral BAEP responses and BA variables, and the receptive lexicon. A Pearson's correlation was used to study the associations between continuous, normally distributed explanatory variables (BAEP/BA variables, gestational age, birthweight, age at the time of CDI completion, age at the time of BAEP/BA recording) and the size of receptive lexicon (number of words the child understands at the age of 1 year). A *t* test for independent samples was used to study the associations between continuous explanatory variables and CDI normality as well as associations between dichotomous explanatory variables (presence of contralateral responses, BA normality, small for gestational age, gender, presence of hearing loss) and the size of the receptive lexicon. The associations between dichotomous explanatory variables and CDI normality were studied using a chi-square test, or, in the case of too few observations, with Fisher´s exact test. Both ears were analysed separately.

In the regression analyses, the latency of the BAEP component V, the IPI I-V and the contralateral response were grouped one at a time together with gestational age and gender. In addition, latency of the BAEP component V, IPI I-V and the contralateral BAEP response were analysed in one group and gestational age and gender in one group. Linear regression analysis was used with the continuous receptive lexicon variable (the size of receptive lexicon) and a binary logistic regression analysis with odds ratios (OR) and 95% confidence intervals (95% CI) were calculated to quantify the significant associations with the dichotomous lexicon variable (CDI normality).

**TABLE 1** Clinical characteristics of the study sample (n = 155)

| Clinical characteristic | N (%)/ mean (SD), range |
|---|---|
| Male | 93 (60) |
| At birth | |
| Weight, grams | 1245 (366), 535-2180 |
| ≤1500 g | 115 (74) |
| Gestational age, weeks | 29 (2.4), 24-35 |
| ≤32 wk | 137 (88) |
| ≤1500 g and/or ≤32 wk | 155 (100) |
| Small for gestational age | 49 (32) |
| Corrected age (months) at the time of BAEP recordings | 1.1 (0.3), 0.3-2.2 |
| Corrected age (months) at the time of CDI completion[a] | 12.1 (0.6), 10.0-15.5 |
| Hearing loss diagnosis[b] | 2 (1.3) |
| Receptive lexicon (number of words) at the age of 1 y | 71 (67), 0-311 |

Abbreviations: BAEP, brainstem auditory evoked potentials; CDI, the MacArthur Communicative Development Inventory; SD, standard deviation.

[a]n = 133 (22 missing values).

[b]Hearing loss was diagnosed until the age of 2 y by an audiologist in the Department of Otorhinolaryngology in Turku University Hospital.

## 3 | RESULTS

Clinical characteristics are presented in Table 1. A total of 155 preterm infants completed the study (60% boys). Based on the CDI method, 33 children (21%) had a deviant score of <17 understood words at the corrected age of 12 months.

In univariate analysis, the latency of the BAEP component V and the IPI I-V of the right ear ipsilateral response and left contralateral response with right ear stimulation showed significant associations with receptive lexicon size and thus, they were chosen for the regression analysis. Only the right ear BAEP variables were included as in the univariate analysis the left ear BAEP variables did not show any significant associations with the receptive lexicon. In addition, the right ear has been found to be the dominant ear in new-borns.[23,24] In the univariate analysis, the confounding factors did not show any significant associations. For example, the receptive lexicon size did not differ between boys and girls. In addition, gestational age did not influence the receptive lexicon size. However, gender and gestational age were included in the regression analysis as they can influence auditory function according to the literature.[3,4]

In the regression analyses, infants with longer IPI I-V in the right ear in neonatal BAEP recording had smaller receptive lexicon at 1 year (*P* = .043) after controlling for gestational age and gender. When BAEP variables were analysed separately, infants with longer IPI I-V were more likely to have deviant receptive lexicon size (OR 29.9; 95% CI: 1.3-683.7; *P* = .033). With right ear stimulation, the absence of contralateral response increased the risk for deviant lexicon size (OR 0.2; 95% CI: 0.02-0.99; *P* = .049). In summary, long IPI I-V increased the risk for a deviant receptive lexicon at 1 year by up to 29-fold and a visible contralateral response reduced the risk for a poor receptive lexicon by 80%.

Brainstem audiometry results did not have any significant associations with the receptive lexicon in the univariate analyses. Whether the BA threshold was normal or abnormal it did not affect receptive lexicon size or CDI normality. In addition, higher BA threshold did not associate with weaker receptive lexicon size.

## 4 | DISCUSSION

The results of the present study suggest that abnormalities in the neonatal BAEP recording at the corrected age of 1 month were associated with weak receptive lexicon size at the corrected age of 1 year in preterm infants. Thus, BAEP recordings can provide important information about auditory processing in the neonatal period. It is known that especially congenital permanent childhood hearing loss increases the risk for language development problems.[25] In our data, there were only two children who were diagnosed with hearing loss later in childhood. Most of the children in our study had normal hearing until the age of 4 years. This could indicate that milder defects in auditory processing could also have an adverse impact on language development. Preterm children have been shown to have a higher risk for weak language development than full-term children at the corrected age of 2 years[10] and up to the age of 12 years.[7]

Impaired auditory processing was identified in our study in the form of prolongation of BAEP latencies in the right ear and absent contralateral responses with right ear stimulation in BAEP recordings. Prolongation of latencies can be explained by delayed myelination and poorer synaptic efficacy in the auditory pathways. The absence of a contralateral response in the present study especially supports the conclusion that poorer synaptic efficacy interferes with the auditory processing.

Our finding that neonatal BAEP associates with later lexical development, is in line with two previous studies.[19,20] Amin et al[19] found that when BAEP was performed at 35 weeks postmenstrual age IPI I-V associated with auditory comprehension and expressive communication at the age of 3 years in premature infants (birth ≤33 gestational weeks). In addition, another study found that early BAEP (done before hospital discharge) of very low birthweight children may predict intelligence quotient, language development and academic achievement at the age of 8 years.[20] In these previous studies, however, the study groups were smaller compared to the present study and children at very different stages of language development were included. In the present study, the information on language development was gathered already at the corrected age of 1 year compared to previous studies where language development was evaluated at the ages of 3 and 8 years.[19,20] In addition, in the study by Amin et al,[19] the BAEP was performed at the postmenstrual age of 35 weeks when the BAEP may be more unreliable due to very small ear canals and fluid in the ears. In the present study, BAEP was conducted at the corrected age of 1 month, when the children were clinically stable and there were no acute conditions.

The MacArthur Communicative Development Inventory was used to collect information on language performance at the corrected age of 1 year. The CDI method is widely used and it has been shown to be a valid method to assess early language and communicative development.[9,13] Studies have shown that a small early receptive lexicon size is an early sign of weak lexical and language development in preterm children.[10-12] The present findings provide information on the possible background factors for the weak receptive lexicon growth in preterm infants. The results imply that accurate hearing testing with BAEP recording in the neonatal period could be used to reliably detect infants who require a closer follow-up of language development.

The early detection of infants at risk for delayed language development opens an opportunity for even earlier intervention. Preterm infants have been found to benefit from postnatal auditory experience[26] and they have also shown better cognitive and language outcomes at the corrected age of 7 and 18 months in relation to the amount of parental talk exposure in the NICU period.[27] Evidence exists that the quality of the early language environment provided by caregivers is considered an important factor in language development.[28] Early intervention could include information to parents on how to enrich the language environment of the child. In addition, augmentative and alternative communication methods such as pictures and speech-supporting signs can be utilised in order to improve language development and communication between the child and the parents.[29]

In the present study, the evaluated confounding factors did not associate with the receptive lexicon in the univariate analyses. The lack of association between gestational age and the receptive lexicon in the present univariate analyses might be due to the fact that all the children in our study were preterm and thus, the gestational age range was quite small.

### 4.1 | Strengths and limitations of the study

In the present study, we utilised BAEP and BA recordings which are considered to be sensitive and reliable methods for assessing hearing and function of the auditory pathways in high-risk neonates.[30] In addition, in our department we have our own large reference value database for neonates.[4] To obtain good quality BAEP and BA recordings can be challenging. However, in our department due to standardised methods the quality of recordings is good and in the present study none of the infants had to be excluded due to disturbances in BAEP/BA recording. Due to ongoing maturation of auditory pathway, latencies in BAEP recording decrease with increasing age.[18] Thus, it is possible that the presence of prolonged BAEP latencies and IPIs could have been transitory.

Because this was a retrospective study all the tests (BAEP, BA and CDI) were part of the routine clinical follow-up in Turku University Hospital. Consequently, some information is lacking. For example, we did not have information about maternal educational status or socioeconomic status. In addition, 59 infants had to be excluded from the study due to absent BAEP or CDI data. In this group of infants, the most common exclusion criterion was parents not returning the CDI form (n = 24). However, gestational ages and birthweights did not differ significantly between children whose parents did not return the CDI form and children who were included in the study.

## 5 | CONCLUSIONS

In the present study, right ear auditory pathway abnormalities in the neonatal period of premature infants associated with weak receptive lexicon 1 year later. An early weak receptive lexicon size has been shown to be an early sign of weak expressive lexical development[11] and weak general language development at 2 years of corrected age in preterm children.[10,12] This finding suggests that at the corrected age of 1 month preterm infants, who are at increased risk for language development, could already be identified. Neonatal BAEP recording is thus a useful method for diagnosing not only brainstem abnormalities and hearing loss but also delayed auditory maturation that can impair early language development. The use of BAEP can help with the early identification of children at risk for language problems, thus enabling prompt intervention in the neonatal period by giving information to the parents and providing alternative communication methods. By improving communication between a parent and a child language development can also be influenced positively.

### CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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