J Am Acad Audiol 26:30–35 (2015)

Continued Maturation of the Click-Evoked Auditory Brainstem Response in Preschoolers

DOI: 10.3766/jaaa.26.1.4

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Abstract

Background: Click-evoked auditory brainstem responses (ABRs) are a valuable tool for probing auditory system function and development. Although it has long been thought that the human auditory brainstem is fully mature by age 2 yr, recent evidence indicates a prolonged developmental trajectory.

Purpose: The purpose of this study was to determine the time course of ABR maturation in a preschool population and fill a gap in the knowledge of development.

Research Design: Using a cross-sectional design, we investigated the effect of age on absolute latencies, interwave latencies, and amplitudes (waves I, III, V) of the click-evoked ABR.

Study Sample: A total of 71 preschoolers (ages 3.12–4.99 yr) participated in the study. All had normal peripheral auditory function and IQ.

Data Collection and Analysis: ABRs to a rarefaction click stimulus presented at 31/sec and 80 dB SPL (73 dB nHL) were recorded monaurally using clinically-standard recording and filtering procedures while the participant sat watching a movie. Absolute latencies, interwave latencies, and amplitudes were then correlated to age.

Results: Developmental changes were restricted to absolute latencies. Wave V latency decreased significantly with age, whereas wave I and III latencies remained stable, even in this restricted age range.

Conclusions: The ABR does not remain static after age 2 yr, as seen by a systematic decrease in wave V latency between ages 3 and 5 yr. This finding suggests that the human brainstem has a continued developmental time course during the preschool years. Latency changes in the age 3–5 yr range should be considered when using ABRs as a metric of hearing health.

Key Words: Auditory brainstem response, child, preschool, development

Abbreviations: AEP = auditory-evoked potential; ABR = auditory brainstem response; cABR = auditory brainstem response to complex sounds; DPOAE = distortion product otoacoustic emissions; nHL = normal hearing level; SPL = sound pressure level

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This work was presented at Illinois Academy of Audiology Convention, January 29, 2014, Chicago, IL.

This work was supported by the National Institutes of Health (grant R01HD069414) and the Knowles Hearing Center.

INTRODUCTION

Since Jewett and Williston first described the auditory brainstem response (ABR) (Jewett and Williston, 1971), it has become a valuable tool for probing auditory system function and development. The ABR is used in clinical practice to assess hearing thresholds and the integrity of the auditory pathway across the lifetime. The response is reliable, easy to obtain, and objective (Hood, 1998). Furthermore, the ABR can be used in cross-sectional and longitudinal studies to assess development of the auditory pathway.

ABRs may be elicited in response to many kinds of sounds, including clicks, tone bursts, chirps, speech, etc.; however, the click-evoked ABR is most commonly used in the clinic for broadly assessing hearing thresholds as well as neurodiagnostic testing (Stapells and Oates, 1997; Bauch and Olsen, 1986; Starr and Achor, 1975). Synchronous firing of neurons along the auditory pathway in response to a stimulating sound generates the ABR. There are five primary waves in the click-evoked ABR, three of which (waves I, III, and V) are extremely reliable in humans. Wave I is generated by summed activity up to the distal portion of the auditory nerve (Møller and Jannetta, 1983). Wave III originates predominately from the cochlear nucleus as well as the superior olivary complex (Moore, 1987). Lastly, wave V arises largely from neurons spanning the lateral lemniscus and the inferior colliculus contralateral to the stimulated ear (Møller et al, 1995) and is the convergence of neuronal activity in the preceding structures. Thus, the interwave latency of waves I–V can be thought of as a measure of central conduction time between the auditory nerve and midbrain (Hood, 1998).

Auditory structures generally mature in a caudal to rostral direction. Consequently, ABRs, measuring comparatively caudal stages of sound processing, are one of the first auditory evoked potentials (AEPs) to reach adult latency values (Hall, 2007). Within the ABR itself, wave latencies decrease and approach adult values in a peripheral to central direction as well. Wave I is mature by 45–50 wk conceptional age (Eggermont and Salamy, 1988). Historically, it has been reported that click-evoked waves III and V reach adult-like latencies by 2 yr (Hall, 2007; Gorga et al, 1989; Fria and Doyle, 1984; Moore et al, 1996). However, newer research suggests a prolonged developmental time course (Khatoon et al, 2012; Coenraad et al, 2010; Skoe et al, 2013).

Although recent investigations have begun to look more closely at the developmental trajectory of click-evoked ABRs in young children, they lack the sample size to be precise within such a narrow age range as ages 3 and 4 yr, a critical time of language development (Chaney, 1992). We conducted the present study to delineate the maturational time course of click-evoked ABRs within this age range, a maturational course that remains poorly understood in the extant literature.

MATERIALS AND METHODS

Participants

A total of 71 English-monolingual preschoolers between ages 3.12–4.99 yr ($M = 4.22$ yr, $SD = 0.54$ yr) participated in the study. All participants passed a screening of peripheral auditory function as determined by normal (Type A) results on tympanograms and distortion product otoacoustic emissions (DPOAEs) (>6 dB above the noise floor for 1000, 2000, 4000, and 8000 Hz), and had a replicable wave V click-evoked ABR. Inclusionary criteria included a normal IQ as measured by the WPPSI–IV (Pearson, Inc.) and no diagnosis of autism or history of neurologic disorders. There was a balanced number of boys (n = 34) and girls (n = 37) in the study ($\chi^2 = 0.127, p = 0.722$), and there was no age difference between the genders [$t_{(69)} = 0.014$, $p = 0.989$].

The Northwestern Institutional Review Board approved all study measures. Written informed consent and verbal assent were obtained from all parents or guardians and children, respectively. Participants were monetarily compensated for their time.

Stimulus and Recording

A 100-μs square wave click stimulus was used. Stimuli were presented monaurally via insert earphones (ER-3A, Etymotic Research, Inc.) to the right ear at 80.0 dB SPL (73 dB nHL). Clicks were presented in the rarefaction polarity at a rate of 31/sec. Rarefaction clicks were used because they have been known to produce shorter latencies and larger amplitudes, and disambiguate waves IV and V better than condensation clicks (Schwartz et al, 1990).

The click-ABR collection lasted approximately 10 min. During the recording, participants sat either alone or on a parent's lap in a comfortable chair while watching a movie. ABRs were collected in a soundproof booth using the Bio-logic Navigator Pro AEP System (Natus Medical, Inc.) with three Ag/Cl-plated electrodes. A vertical montage was used with the noninverting electrode placed at the vertex and the inverting electrode on the ipsilateral ear. Recordings were grounded to the forehead. Electrode impedance was kept at less than 5 kΩ and interelectrode impedance was kept at less than 3 kΩ. Responses were filtered online using a 100–1500 Hz bandpass filter and were digitized at 24,015 Hz. The recording window was 0 to 10.65 msec. Trials with activity greater than ±23.8 μV were considered artifact and were not included in the final average. Recording continued until 6,000 artifact-free trials were recorded, collected in three subaverages of 2,000 trials.

Data Analysis

Waves I, III, and V were manually identified using the AEP system by an experienced peak picker and were confirmed by a second rater blind to participant age. Waves were picked at the point with the highest amplitude (relative to the baseline) within the expected time window (Wave I: 1.2 to 2 msec; Wave III: 3.4 to 4.1 msec; Wave V: 5.2 to 6.2 msec); that is, the last data point before a change in slope. In cases where peak amplitude was equivalent at two adjacent data points, the earlier point was chosen. If the peak was broad (multiple adjacent data points at the peak amplitude), those points were bisected and the middle point was chosen. Peak identification on the 6,000-trial average waveform was confirmed using the subaverages as a reference for determining peak reliability. If any individual wave was not identifiable, it was excluded from the analyses. One participant had an unidentifiable wave I, which was excluded from the analyses. I–III and I–V interwave latencies were calculated by subtracting wave I latency from the wave III and V latencies, respectively; III–V interwave latency was calculated by subtracting wave III latency from wave V latency.

Statistical Analysis

All statistical analyses were performed using SPSS (version 21, IBM). Bivariate correlations between age and wave I, III, and V latencies, and I–V, I–III, and III–V interwave latencies were performed. A repeated-measures analysis of variance comparing the latencies and amplitudes between a group of the 20 oldest and 20 youngest participants was also performed. This analysis was also used to determine the effect of sex on latencies and amplitudes.

RESULTS

Absolute Latency

There were no effects of age on waves I [$r_{(70)} = –0.059$, $p = 0.627$] or III [$r_{(71)} = –0.178$, $p = 0.136$]. However, the latency of wave V decreased with increasing age [$r_{(71)} = –0.356$, $p = .002$] (Fig. 1).

To further quantify this effect, we performed a repeated-measures analysis of variance with click wave (I, III, V) as the within-participant factor and age group as the between-participants factor on the 20 youngest (ages 3.12–3.84 yr) and 20 oldest (ages 4.67–4.99 yr) participants (Table 1). There was a wave-specific effect of age (wave by age interaction), $F_{(4,136)} = 2.721$, $p = 0.032$. Post hoc *t*-tests revealed an age group difference for wave V [$t_{(38)} = 3.018$, $p = .005$] but not for waves I [$t_{(38)} = 0.028$, $p = 0.978$] or III [$t_{(38)} = 1.202$, $p = 0.237$], again suggesting a maturational effect specific to wave V.

Interwave Latency

After determining that wave I latencies remained constant through this age range, whereas wave III decreased minimally and wave V decreased significantly, we calculated the interwave latencies and correlated them with the age for the entire participant cohort. As expected, I–V interwave latency showed the greatest decrease due to development [$r_{(70)} = –0.317$, $p = 0.007$], whereas the III–V interval showed a more moderate correlation [$r_{(71)} = –0.265$, $p = 0.026$]. The I–III interwave latency was not affected by age [$r_{(71)} = –0.141$, $p = 0.231$].

Amplitude

We analyzed peak amplitude for all three waves of the click-ABR and, unlike latency, found no relationship with age [wave I: $r_{(70)} = 0.118$, $p = 0.329$; wave III: $r_{(71)} = –0.015$, $p = 0.903$; wave V: $r_{(71)} = 0.048$, $p = 0.690$].

Sex

The effect of sex on wave V latency was also analyzed. Both sexes separately show a correlation between age and wave V latency [females: $r_{(37)} = –0.343$, $p = 0.037$; males: $r_{(34)} = -0.429$, $p = 0.011$]. Neither sex

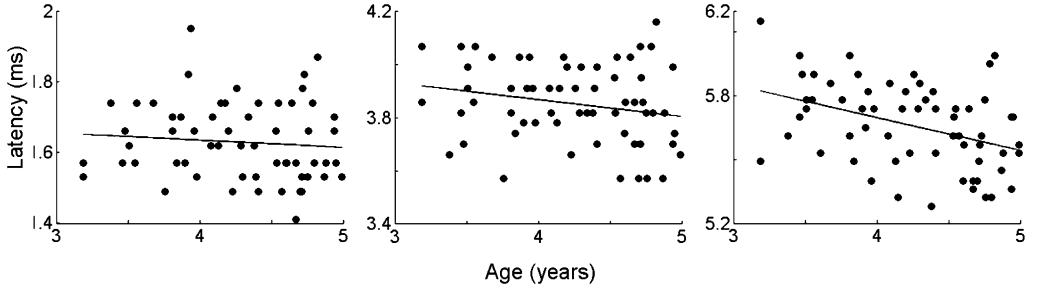

Figure 1. Wave V decreases with age. Scatterplots are shown comparing increasing age with latency for each wave. Although waves I (*left,* $r = -0.059, p = 0.627$) and III (*center,* $r = -0.178, p = 0.136$) latencies do not show any correlation with age, wave V latency (*right,* $r = -0.356$, $p = 0.002$) shows a negative relationship with increasing age.

Table 1. Click-ABR Mean Latencies (and SDs) for Waves I, III, and V for the 20 Oldest and 20 Youngest Participants

Group	Click I Latency	Click III Latency	Click V Latency
Youngest	1.63 (0.111)	3.87 (0.143)	5.76 (0.181)
Oldest	1.63 (0.115)	3.81 (0.174)	5.57 (0.206)

shows a correlation between age and amplitude for any of the click-ABR waves, nor is there an interaction between amplitude and sex for any click-ABR wave.

DISCUSSION

Summary of Results

Our results indicate that wave V latency of the click-evoked ABR continues to shorten throughout the preschool years. Specifically, older children (closer to age 5 yr) had earlier wave V latencies than the younger children in our sample (age 3 yr). This developmental trend was not observed for wave I. Wave III, although not significant, did show a small trend of development, consistent with the view that AEPs develop in a caudal-to-rostral direction (Hall, 2007; Kaga and Tanaka, 1980; Ponton et al, 2000). However, this finding diverges from the conventional wisdom that click ABR latencies mature by ages 2 or 3 yr (Eggermont and Moore, 2012; Moore et al, 1996). For example, classic studies found that wave V was adult-like by ages 12–18 mo (Hecox and Galambos, 1974) and age 2 (Salamy, 1984). Thus, it was presumed that latencies between age 2 yr and adulthood were stable because of a dearth of maturational studies of intervening ages. Here, we show evidence for a prolonged developmental time course of the click ABR (and, by extension, of the auditory brainstem) at least up until age 5 yr. The correlations between interwave latencies and age suggest that central conduction time, as measured by the I–V interwave latency, continues to develop throughout preschool.

For all three peaks, the amplitude did not relate to age; this may suggest that amplitudes have stabilized by age 3, or are too variable among individuals to discern an effect of age within this restricted range (Chiappa et al, 1979). When looking at the role of sex, we find both males and females show earlier wave V latencies with increasing age.

Although we have found developmental differences between ages 3–5 yr, these findings are not a complete divergence from the traditional view of AEP maturation because mean latencies are within the range of expected values for adults (Hood, 1998), suggesting that although latencies continue to decrease throughout preschool, they do increase again during later childhood to eventually converge with adult values (Skoe et al, 2013). Given that our sample size was much larger than previous studies of this age group, we have identified latency differences that were potentially previously obscured by inter-participant variability in smaller datasets and by collapsing across this preschool age range. Because the present study is one of the first to focus solely on the preschool age range, it fills a gap in previous developmental studies of the ABR.

What mechanisms drive these developmental changes? One possibility is that children in this age range undergo variable rates of auditory system maturation, suggesting that the ABR reaches adult-like values for some, but not all, children by age 2 yr. We believe that this explanation is unlikely, however, because we observed a correlation between chronological age and wave V latency in addition to the absence of a correlation between age and waves I or III (see Fig. 2).

Instead, we believe that there is a prolonged period of maturation that extends throughout preschool years. Some structures, such as the cochlea, appear to be fully developed by birth (Pujol and Lavigne-Rebillard, 1992). However, our findings suggest that postnatal maturation of central structures in the brainstem may continue at least through the preschool years, potentially not reaching a developmental stabilization point until school age. We speculate that there may be a prolonged period of developmental plasticity in the lateral lemniscus and/or inferior colliculus that bears on ABR wave V latency. This mechanism could reflect a developmental increase in synchronous firing in the rostral brainstem with age. Additionally, increases in myelination of the auditory pathway may speed neural conduction, in addition to developmental changes of the top-down corticofugal network, which could also influence auditory processing in subcortical auditory centers.

Although our findings differ from conventional wisdom about the development of the ABR, they are, in fact, consistent with recent evidence suggesting continued brainstem development past age 2 yr (Mochizuki et al, 1983; Mochizuki et al, 1982; Skoe et al, 2013). For example, Coenraad et al (2010) fit a mathematical model to click-evoked ABRs from a wide age range (birth to age 4 yr) and found that waves III and V did not reach adult latency values until at least age 3 yr, and that population variability in wave V latency continued to decrease. Khatoon et al (2012) suggested that wave I is fully mature by age 3 yr, whereas wave V latency may not be mature until age 5 yr. Here, we document a similar developmental trajectory with a larger sample size.

These findings also support those of Skoe et al (2013), who looked at ABR development from age 3 mo through 72 yr. They found that ABR wave V latencies decrease in childhood to earlier latencies than seen in adults, and then increase after age 8 yr to the adult range. However, because of the large number of participants in that study, 3- and 4-yr-olds were grouped together, and small incremental changes within this age range were not considered. Our results confirm the overall trend demonstrated in Skoe et al (2013) by showing that latencies are still decreasing during preschool. By zeroing in on the preschool age

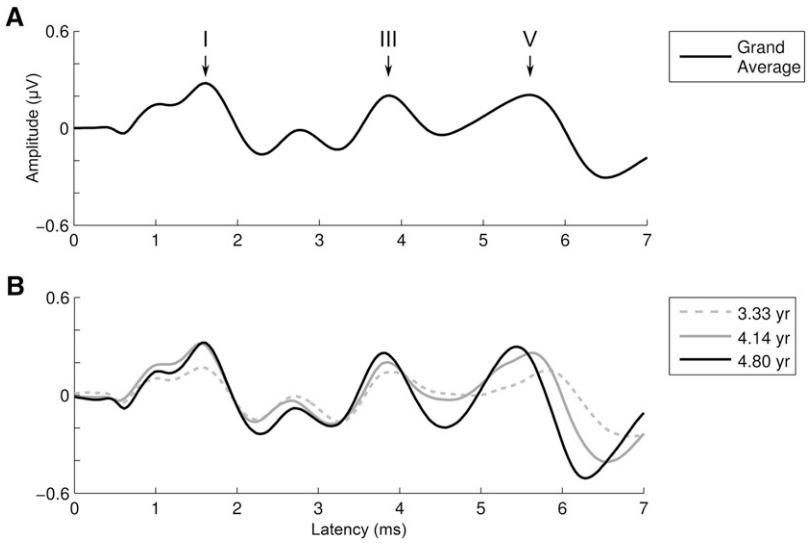

Figure 2. Auditory brainstem response to a click. (A) Grand average waveform shown for all participants with waves I, III, and V identified. (B) Representative participants are plotted to show latency changes in wave V due to aging. Latency differences were insignificant for waves I and III.

range, we are able to increase our resolution and offer further insights into auditory brainstem development.

To more fully understand ABR development during preschool, it is important to also consider ABRs to other stimuli. One such evaluation is the ABR in response to complex sounds (cABR), which is a reliable measure across the lifespan that is meaningful on an individual basis (Skoe and Kraus, 2010) and can provide valuable insight into language skills, auditory processing, and past auditory experience (for review, see Kraus and Nicol, 2014). cABR also has a prolonged developmental time course, with subcomponents of the response exhibiting distinct maturational trajectories (Skoe and Kraus, 2013; Skoe et al, 2013). cABR is a tool that may be a useful adjunct in audiological assessment of central auditory processing. Taken together, it would appear that auditory brainstem function holds rich developmental information with clinical and theoretical implications that have only recently been recognized (White-Schwoch and Kraus, 2013; Woodruff Carr et al, 2014). Given our findings of changes between ages 3–5 yr, future work might examine age-related changes in the cABR, in addition to other AEPs, in preschoolers.

Future Directions and Recommendations

Although the current study delineates timing changes in the ABR occurring in the preschool time range, more information is needed to determine the developmental characteristics beyond 5 yr. Moreover, our results represent a cross-section of the preschool population. Longitudinal research tracking the same children across time, which is already underway in our laboratory, will help to explain the maturational changes happening on an individual basis. ABRs to lower intensity clicks—which are more commonly used to determine hearing thresholds—as well as stimuli such as chirps or tone bursts, should be studied as well to determine if they follow a similar developmental trajectory to click-evoked ABRs.

One methodological limitation is our use of a relatively narrow low-pass filter (1500 Hz), which produces broader peaks. A higher low-pass filter might have allowed for more precise latency calculations that would be useful in a longitudinal assessment. However, despite this limitation, we found a reliable effect of age and thus do not believe that the effects we report are an artifact of the filtering parameters.

These results have important implications for auditory scientists interested in development. By demonstrating continued maturation of ABR latencies during preschool, we elucidate a developmental trajectory of the auditory system that is more prolonged than previously thought. The results presented may be useful in the development of clinical evaluations as well. While our population was not a clinical population, we present a trend of development during an age range where ABR latencies are thought to be static. Researchers and clinicians alike should consider that the auditory brainstem and its cortical inputs are still under development at this age when developing and interpreting audiological assessments.

REFERENCES

Bauch CD, Olsen WO. (1986) The effect of 2000–4000 Hz hearing sensitivity on ABR results. *Ear Hear* 7:314–317.

Chaney C. (1992) Language development, metalinguistic skills, and print awareness in 3-year-old children. *Appl Psycholinguist* 13:485–514.

Chiappa KH, Gladstone KJ, Young RR. (1979) Brain stem auditory evoked responses: studies of waveform variations in 50 normal human subjects. *Arch Neurol* 36:81–87.

Coenraad S, van Immerzeel T, Hoeve LJ, Goedegebure A. (2010) Fitting model of ABR age dependency in a clinical population of normal hearing children. *Eur Arch Otorhinolaryngol* 267(10): 1531–1537.

Eggermont JJ, Moore JK. (2012) Morphological and functional development of the auditory nervous system. In: Werner L, Fay RR, Popper AN, eds. *Human Auditory Development*. New York, NY: Springer, 61–105.

Eggermont JJ, Salamy A. (1988) Maturational time course for the ABR in preterm and full term infants. *Hear Res* 33(1):35–47.

Fria TJ, Doyle WJ. (1984) Maturation of the auditory brain stem response (ABR): additional perspectives. *Ear Hear* 5(6):361–365.

Gorga MP, Kaminski JR, Beauchaine KL, Jesteadt W, Neely ST. (1989) Auditory brainstem responses from children three months to three years of age: normal patterns of response. II. *J Speech Hear Res* 32(2):281–288.

Hall JW. (2007) *New Handbook of Auditory Evoked Responses*. Boston, MA: Pearson.

Hecox K, Galambos R. (1974) Brain stem auditory evoked responses in human infants and adults. *Arch Otolaryngol* 99(1): 30–33.

Hood LJ. (1998) *Clinical Applications of the Auditory Brainstem Response*. San Diego, CA: Singular Pub. Group.

Jewett DL, Williston JS. (1971) Auditory-evoked far fields averaged from the scalp of humans. *Brain* 94(4):681–696.

Kaga K, Tanaka Y. (1980) Auditory brainstem response and behavioral audiometry: Developmental correlates. *Arch Otolaryngol* 106(9): 564–566.

Khatoon M, Nighute S, Singh R, Awari A, Ishaque M. (2012) Maturation of brainstem auditory evoked potential from full term infants & children to young adult. *Int J Biomed Res* 3(12):439–443.

Kraus N, Nicol T. (2014) The cognitive auditory system: the role of learning in shaping the biology of the auditory system. In: Fay RR, Popper AN, eds. *Perspectives on Auditory Research,* Springer Handbook of Auditory Research 50. Heidelberg, Germany: Springer-Verlag, 219–319.

Mochizuki Y, Go T, Ohkubo H, Motomura T. (1983) Development of human brainstem auditory evoked potentials and gender differences from infants to young adults. *Prog Neurobiol* 20(3-4): 273–285.

Mochizuki Y, Go T, Ohkubo H, Tatara T, Motomura T. (1982) Developmental changes of brainstem auditory evoked potentials (BAEPs) in normal human subjects from infants to young adults. *Brain Dev* 4(2):127–136.

Møller AR, Jannetta PJ. (1983) Auditory evoked potentials recorded from the cochlear nucleus and its vicinity in man. *J Neurosurg* 59(6): 1013–1018.

Møller AR, Jho HD, Yokota M, Jannetta PJ. (1995) Contribution from crossed and uncrossed brainstem structures to the brainstem auditory evoked potentials: a study in humans. *Laryngoscope* 105(6):596–605.

Moore JK. (1987) The human auditory brain stem as a generator of auditory evoked potentials. *Hear Res* 29(1):33–43.

Moore JK, Ponton CW, Eggermont JJ, Wu BJ, Huang JQ. (1996) Perinatal maturation of the auditory brain stem response: changes in path length and conduction velocity. *Ear Hear* 17(5): 411–418.

Ponton CW, Eggermont JJ, Kwong B, Don M. (2000) Maturation of human central auditory system activity: evidence from multichannel evoked potentials. *Clin Neurophysiol* 111(2):220–236.

Pujol R, Lavigne-Rebillard M. (1992) Development of neurosensory structures in the human cochlea. *Acta Otolaryngol* 112(2): 259–264.

Salamy A. (1984) Maturation of the auditory brainstem response from birth through early childhood. *J Clin Neurophysiol* 1(3): 293–329.

Schwartz DM, Morris MD, Spydell JD, Ten Brink C, Grim MA, Schwartz JA. (1990) Influence of click polarity on the brain-stem auditory evoked response (BAER) revisited. *Electroencephalogr Clin Neurophysiol* 77(6):445–457.

Skoe E, Kraus N. (2010) Auditory brain stem response to complex sounds: a tutorial. *Ear Hear* 31(3):302–324.

Skoe E, Kraus N. (2013) Musical training heightens auditory brainstem function during sensitive periods in development. *Front Psychol* 4:622.

Skoe E, Krizman J, Anderson S, Kraus N. (2013) Stability and plasticity of auditory brainstem function across the lifespan. *Cereb Cortex* 10.1093/cercor/bht311.

Stapells DR, Oates P. (1997) Estimation of the pure-tone audiogram by the auditory brainstem response: a review. *Audiol Neurotol* 2:257–280.

Starr A, Achor LJ. (1975) Auditory brainstem responses in neurological disease. *Arch Neurol* 32:761–768.

White-Schwoch T, Kraus N. (2013) Physiologic discrimination of stop consonants relates to phonological ability in pre-readers: A biomarker for subsequent reading ability? *Front Hum Neurosci* 7:899.

Woodruff Carr K, White-Schwoch T, Tierney A, Strait DL, Kraus N. (2014) Beat synchronization predicts neural speech encoding and reading readiness in preschoolers. *Proc Natl Acad Sci* 111(40):14559–14564.