

# Stability and Plasticity of Auditory Brainstem Function Across the Lifespan

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**The human auditory brainstem is thought to undergo rapid developmental changes early in life until age ~2 followed by prolonged stability until aging-related changes emerge. However, earlier work on brainstem development was limited by sparse sampling across the lifespan and/or averaging across children and adults. Using a larger dataset than past investigations, we aimed to trace more subtle variations in auditory brainstem function that occur normally from infancy into the eighth decade of life. To do so, we recorded auditory brainstem responses (ABRs) to a click stimulus and a speech syllable (da) in 586 normal-hearing healthy individuals. Although each set of ABR measures (latency, frequency encoding, response consistency, nonstimulus activity) has a distinct developmental profile, across all measures developmental changes were found to continue well past age 2. In addition to an elongated developmental trajectory and evidence for multiple auditory developmental processes, we revealed a period of overshoot during childhood (5–11 years old) for latency and amplitude measures, when the latencies are earlier and the amplitudes are greater than the adult value. Our data also provide insight into the capacity for experience-dependent auditory plasticity at different stages in life and underscore the importance of using age-specific norms in clinical and experimental applications.**

**Keywords:** auditory, auditory brainstem response, development

## Introduction

The central nervous system (CNS) engages in a delicate balancing act of preserving stability while at the same time retaining flexibility to adapt to new environments and auditory challenges. Maintaining constant physiology, or homeostasis, requires active processes that are present throughout the lifespan (Davis and Bezprozvanny 2001; Hua and Smith 2004). During the extensive changes associated with development, these active processes stabilize young labile connections by removing inefficient connections and increasing information processing (Rubel et al. 1990; Johnson 2001).

The development of the auditory system involves an elaborate series of events that begins early in gestation and continues into adolescence (reviewed in Eggermont and Moore 2012). This process is assumed to proceed from peripheral to central structures, with the auditory brainstem maturing before thalamic and cortical areas. The auditory brainstem response (ABR)—a far-field electrical potential measured from the scalp reflecting the electrophysiological activity of large populations of neurons in the auditory brainstem—can be first observed around the 25th–32nd week postconception (Krumholz et al. 1985). The ABR has a nonlinear developmental timeline,

marked by extensive changes within the first few years of life (Salamy et al. 1975; Salamy and McKean 1976; Gorga et al. 1989). Because of the repeated demonstration that ABRs do not differ between 2 year olds and adults, the trajectory of the ABR was presumed to be stable from late infancy until senescence (Stockard et al. 1979; Jerger and Hall 1980; Otto and McCandless 1982; Chu 1985; Rosenhall et al. 1985; Thivierge and Cote 1990). Consequently, few studies have systematically examined developmental trends of the ABR across preschool and school-age children; however, those that have suggest that the developmental time course for the auditory brainstem is in fact more protracted (Lauter and Oyler 1992; Johnson et al. 2008).

To test the hypothesis that developmental changes in the auditory brainstem extend beyond age 2, we recorded ABRs over the lifespan using a cross-sectional design. Employing a large dataset with nearly continuous sampling over the life course and a complex auditory stimulus (speech syllable), we aimed to uncover subtle age-dependent variations in the ABR that might be cloaked by coarser sampling, simpler stimuli and/or smaller datasets (Rosenhall et al. 1985; Thivierge and Cote 1990). By adopting a complex auditory stimulus, we also had access to multiple measures of brainstem function (including latency, amplitude of frequency encoding, response consistency, nonstimulus activity), allowing us to determine whether these subcomponents of auditory brainstem function undergo a single common developmental trajectory or multiple maturational timelines (Insanally et al. 2009; Eggermont and Moore 2012). To date, there have been no direct comparisons between infants, children, adolescents, and adults of various ages for ABRs to complex stimuli.

## Materials and Methods

All procedures were approved by the Northwestern University Institutional Review Board. Adult participants gave their written informed consent to participate. For infant and child participants, informed consent was obtained from the parent or guardian. Verbal assent was obtained from 3 to 7 year olds, and written assent was collected from 8 to 17 year olds using age-appropriate language. All participants were paid for their participation.

## Participants

The dataset comprises 586 healthy subjects (293 females) ages 0.25–72.40 years, divided into 12 age groups (Table 1). The data were gathered, to a large extent, as part of past or ongoing studies in our laboratory, and this analysis represents a meta-analysis of these smaller studies. Subsets of the entire dataset have been published previously (Johnson et al. 2008; Banai et al. 2009; Dhar et al. 2009; Hornickel, Skoe and Kraus 2009; Russo et al. 2009; Krizman et al. 2010, 2012; Song et al. 2011; Anderson et al. 2012b).

**Table 1**  
Subject and group characteristics<sup>a</sup>

Age range (years)	N	Mean	Standard deviation	Min	Max	Females (%)
0–1	23	0.47	0.14	0.26	0.77	30.4
3–5	53	4.03	0.63	3.10	4.95	49.1
5–8	26	5.73	0.57	5.12	7.28	50
8–11	40	9.31	0.84	8.10	10.83	50
11–14	49	12.30	0.83	11.00	13.73	49
14–17	105	15.06	0.62	14.01	16.79	47.5
17–21	54	19.63	0.98	17.13	20.96	51.9
21–30	143	24.27	2.30	21.11	29.95	50.3
30–40	32	33.49	2.83	30.03	39.30	78.1
40–50	11	46.20	3.12	40.30	49.90	45.5
50–60	26	54.27	3.16	50.15	59.55	50
60–73	24	64.36	3.43	60.42	72.41	50
Total	586					50

<sup>a</sup>Subjects were divided into 12 age groups. The number of subjects and percentage of female subjects is reported along with age statistics (mean, standard deviation, youngest age in group, and oldest age in group). Throughout the article, the age ranges are labeled “X–Y” where X refers to the youngest possible age in the group and Y refers to the next integer value after the maximum age cutoff for the group. For example, for the “3- to 5-” year-old range, 3.00 is the youngest possible age and 4.99 is the oldest possible age. Thus, there is no overlap between the 3–5 and 5–8 groups.

The retrospective nature of this study afforded us the benefits of working with a large dataset; however, it also placed limitations on the study, including the number of subjects included in each age group. Across our dataset, each age group is relatively well represented, with the exception of 1–2 year olds. This age range can be difficult to test using electrophysiology methods. For this reason, 1–2 year olds have not been actively recruited by our laboratory, and they were not included in the smaller studies from which our meta-analysis drew.

None of the subjects included in this analysis had a history of learning disabilities or neurological dysfunction, and all subjects had normal audiometric profiles. Normal hearing was confirmed by air-conduction thresholds (<20 dB HL for 500, 1000, 2000, 4000 Hz) for participants older than 5 years or an audiological screen (pass/fail based on distortion product otoacoustic emissions and/or behavioral response at 20 dB HL) for participants 5 and under.

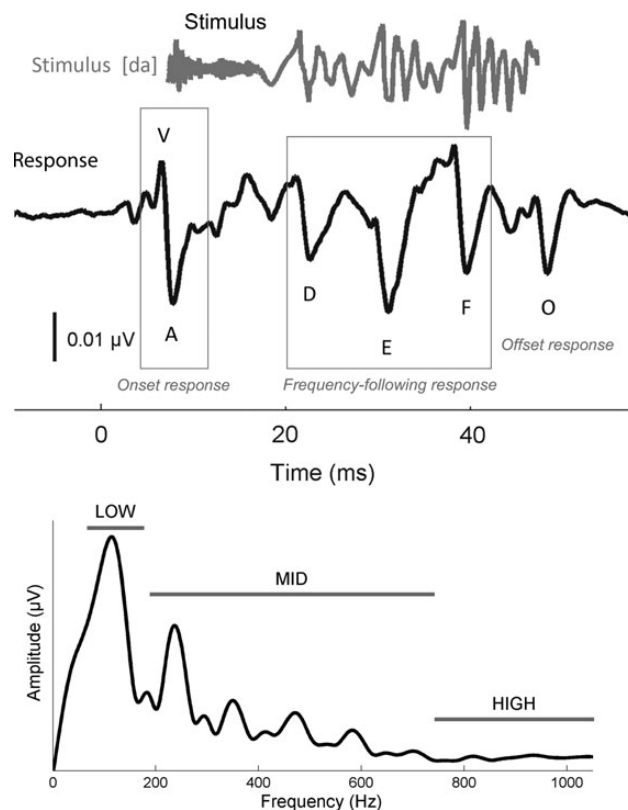
### Stimuli

Brainstem responses were recorded to a 100- $\mu$ s square-wave click stimulus and a 40-ms speech syllable, da. For the past 30 years, brief stimuli, such as clicks and tone bursts, have been the primary stimulus for ABRs in clinical and research settings; however, there has been a recent movement to adopt more naturalistic and, therefore, more complex stimuli to achieve greater functional sensitivity when probing brainstem function in impaired, normal, and expert populations (Skoe and Kraus 2010). ABRs to complex sounds (e.g., speech and music) will be henceforth referred to as complex-ABRs or cABRs for short. The cABR evoked to this speech stimulus includes transient responses to the onset and offset of the syllable, as well as a tonic frequency-following response (FFR) that entrains to the fundamental frequency of the stimulus and its harmonics up to ~1200 Hz. (Fig. 1).

### Electrophysiological Techniques

The collection protocol lasted roughly 20 min, during which subjects sat comfortably while watching a movie. In the case of infants, they were awake and seated on a parent’s lap, while a second tester engaged their interest with colorful toys. Stimuli were delivered at 80 dB SPL to the right ear through an insert earphone (ER-3A, Etymotic Research, Inc.). The speech stimulus was presented in alternating polarities at a rate of 10.9/s. The click stimulus was presented with rarefaction stimulus phase at a rate of 31/s.

Evoked potentials were recorded using the Navigator Pro AEP System (Natus Medical, Inc.) using 3 Ag/AgCl plated electrodes that were placed in a vertical recording montage on the head, with the active electrode at the vertex. The recordings were referenced to the right (ipsilateral) ear, and grounded using an electrode placed on



**Figure 1.** Characteristics of the speech-evoked auditory brainstem response. (Top) The complex stimulus [da] (gray) elicits a stereotyped auditory brainstem response (black) with 6 characteristic peaks (V, A, D, E, F, O). Waves V and A, which occur around 6.5 and 7.5 ms, respectively, represent the response to the onset of sound. Waves D, E, and F, which fall within the frequency-following response (FFR), occur roughly 9 ms apart. Wave O, the offset response, appears roughly 6–8 ms after the stimulus terminates. The stimulus waveform is shifted by ~6.8 ms to maximize the visual coherence between the 2 signals in this figure. (Bottom) Frequency domain representation of the FFR (19.5–44.2 ms). Spectral amplitudes were calculated over 3 ranges of frequencies: Low (75–175), mid (175–750), and high (750–1050 Hz).

the high forehead. Electrode impedance was <5 k $\Omega$ . The speech-evoked responses were bandpass filtered online from 100 to 2000 Hz, with a slightly narrower bandpass being used for the click-evoked response (100–1500 Hz). In the case of the speech stimulus, the recording window began 15 ms prior to the stimulus onset and extended to 58 ms. For the click stimulus, the recording window was –8 to 9.8 ms. Trials exceeding  $\pm 23.8$   $\mu$ V were considered artifact and were excluded from the running average. To gauge the repeatability of the response over the course of the recording, 2 subaverages were collected. In total, 6000 artifact-free trials were collected. For more information on the general recording techniques and stimulus, consult Skoe and Kraus, (2010).

### Analysis

The cABR was analyzed in the time and frequency domains to derive measures of latency, FFR amplitude, response consistency, and nonstimulus activity. With the exception of latency measurements, which were made via the AEP system, all data reduction occurred in the MATLAB programming environment (Mathworks, Inc.) using custom processing routines coded by the first author.

### Peak Latency

One of the most striking features of cABRs is their fidelity to the stimulus (Skoe and Kraus 2010). As seen in Figure 1, cABRs capture many of the temporal and spectral characteristics of the stimulus. The voiced /da/ stimulus evokes 6 characteristic response peaks (V, A, D, E, F, O) that relate to major acoustic landmarks in the stimulus, with each peak

occurring roughly 6–8 ms after its corresponding stimulus landmark, a timeframe consistent with the neural transmission time between the cochlea and rostral brainstem. (For more information on the neural origins of the cABR, we refer the reader to [Chandrasekaran and Kraus \(2010\)](#) where this topic is reviewed.) Waves V and A are transient responses to the energy burst at the onset of the sound, Wave O is an offset response that marks the cessation of sound, and the interval spanning D–E–F is the FFR to the fundamental frequency of the stimulus and its harmonics.

In addition to the 6 cABR peaks, the latency of wave V of the click-evoked ABR was also analyzed. Wave V of the cABR is analogous to Wave V of the click-evoked ABR ([King et al. 2002](#)), although the speech-evoked wave V has been shown, in multiple cases, to be a more sensitive marker of auditory function ([Song et al. 2008](#); [Banai et al. 2009](#); [Krizman et al. 2010, 2012](#)). Peak identification was confirmed by a team of experienced peak pickers. In ambiguous cases, such as when the amplitude was equivalent at 2 adjacent points, the earlier latency was chosen. To aid in peak identification and confirm that the response was replicable, the average waveform (6000 trials) was compared against the subaverages. If the peak was not present in both subaverages, or if it was consistently smaller than the baseline, it was excluded from the analyses.

cABR latencies have been previously shown to change as a function of age. Using a subset of the data presented here, [Johnson et al. \(2008\)](#) reported that school-age kids (5–12 year olds) had earlier latencies than preschoolers (3–5 year olds), with the effect being most pronounced for the onset peaks. Looking at the other end of the age spectrum, [Vander Werff and Burns](#) found that cABR latencies become prolonged in older subjects, especially for the offset peak ([Vander Werff and Burns 2011](#)). Aging-related changes in latency have since been replicated ([Anderson et al. 2012a](#); [Parbery-Clark et al. 2012](#)).

#### Frequency-Following Response Amplitude

The FFR of the cABR was defined as 19.5–44.2 ms. This time window encompasses the range of latencies observed for peaks D, E, and F across the lifespan. Response consistency measurements were also performed over this time range. The amplitude of the FFR was measured for 3 frequency bins that encapsulate the fundamental frequency (F0: 75–175 Hz), the first formant of the stimulus (F1: 175–750 Hz), and the higher frequencies that are within the phase-locking limits (~1200 Hz) of the inferior colliculus ([Langner and Schreiner 1988](#)), the putative primary generator of the FFR ([Liu et al. 2006](#); [Chandrasekaran and Kraus 2010](#)), that fall between the first and second formants of the stimulus (HF: 750–1050). These 3 ranges will hereafter be referred to as: low, mid, and high, respectively (Fig. 1).

Age-related changes in the FFR to speech or other tonal stimuli have in general received little attention. Several small studies have demonstrated that FFRs can be identified in neonates and infants but that the responses do not differ significantly from normal-hearing adults ([Gardi et al. 1979](#); [Jeng et al. 2010](#)). [Johnson et al. \(2008\)](#) reported smaller FFR amplitudes in preschool compared with older children at low and high response frequencies. Comparisons between older and younger adults further revealed that FFR amplitude diminishes in older adults ([Anderson et al. 2012a](#); [Clinard et al. 2010](#)).

#### Within-session Response Consistency

Neural variability is known to decrease over the course of childhood for both auditory and visual evoked potentials ([Callaway and Halliday 1973](#)). In line with this, [Lauter and coworkers](#) reported that the click-evoked ABR is more replicable across sessions in adults compared with school-age children ([Lauter and Oyler 1992](#); [Lauter et al. 1993](#)). However, in older adults, within-session cABR response stability has been shown to decrease with age ([Anderson et al. 2012a](#)). In our study, response consistency of the FFR was computed by comparing the subaverages via a Pearson product-moment correlation, with  $r$ -values closer to 1 representing more repeatable subaverages. To increase the normality of the data, all data points were Fisher transformed prior to statistical analyses; for graphing purposes, values are reported as  $r$ -values.

#### Nonstimulus Activity

To measure the magnitude of the response in the absence of stimulation, the root-mean-square amplitude of the 15-ms interval preceding the stimulus was taken. Little is known about how nonstimulus activity changes as a function of age within cABR recordings; there is currently only one study to date that has examined this question. [Anderson et al. \(2012a\)](#) recently reported that older adults have greater neural activity during the interstimulus period for cABR recordings compared with younger adults, similar to what has been observed previously in a click-ABR design ([Spivak and Malinoff 1990](#)).

#### Statistical Comparisons

For each of the dependent measures, we conducted a one-way ANOVA in SPSS (version 20, IBM) using age group (12 levels) as the independent variable. For significant main effects, Bonferroni-corrected post hoc comparisons were made. To provide a benchmark for both the maturational and aging-related changes to the ABR, we chose the 21- to 30-year-old group ( $n = 143$ ) as the “young adult” reference for subsequent post hoc comparisons with the other 11 age groups. This (approximate) age range has served as the reference point in previous investigation, and it represents a time point of relative stability in ABR development ([Ponton et al. 2000](#); [Vander Werff and Burns 2011](#); [Anderson et al. 2012a](#)). To counteract the problem of multiple comparisons,  $P$ -values have been Bonferroni-corrected by multiplying all values by 12 and then applying an  $\alpha$  of 0.05 to the result.

## Results

### Peak Latency

#### Click-Evoked ABR

For the click stimulus, wave V latency changes as a function of age, even when restricting the analysis to 3–30, where the trajectory has been previously assumed to be stable. For statistics, see Table 2 (Fig. 2).

#### cABR

The time-domain waveform of the cABR is plotted for each of the 12 groups in Figure 3. For each peak, latency changes as a function of age (see Table 2 for statistics, all peaks  $P < 0.001$ ). The same general pattern is observed across the 6 peaks (Fig. 4): latencies become progressively earlier between infancy and 3–5 years, with the nadir (i.e., fastest latencies) occurring across the 5–8 and 8–11-year-old window. Beginning around age 11, latencies then progressively elongate into adulthood, after which they stabilize for a period followed by a gradual slowing in the later decades. While the overall pattern of change is similar for all peaks, the slope of the latency trajectory is sharpest for wave O, and shallowest for waves E and F, with waves, V, A, and D being intermediate. This finding is consistent with the idea that offset responses are more variable than onset responses ([Elfner and Barnes 1983](#)).

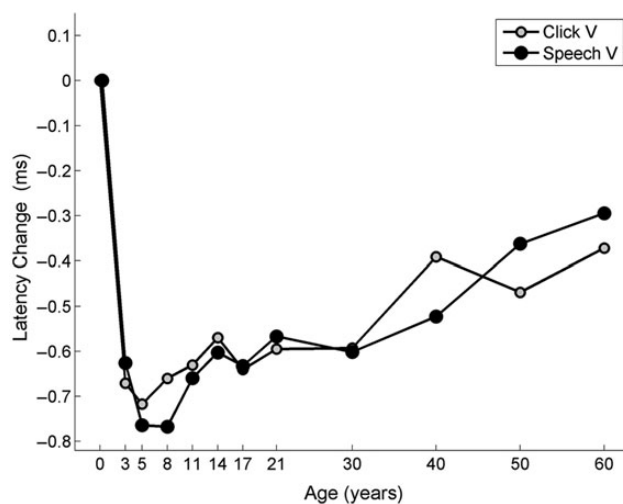
The striking latency changes seen in Figure 4 that occur within the first years of life are not unexpected based on what has been previously reported about the click-evoked ABR ([Salamy et al. 1975](#); [Salamy and McKean 1976](#); [Gorga et al. 1989](#)). A follow-up analysis narrowed in on the 3–30 age range, a time period where the click-evoked response is thought to be relatively stable ([Hall 2007](#)). However, within this range, neither click or cABR latencies are stable for our dataset. In fact, all peaks undergo extensive changes between ages 3 and 30 (Figs 3 and 4; see Table 2 for statistics, all peaks  $P < 0.001$ ). Post hoc analysis indicates that the 21–30 year old group does not differ from the 3- to 5-year-old group, which is



**Table 2**  
Latencies for the click- and speech-evoked auditory brainstem response as a function of age<sup>a</sup>

Group (age)	Click-V			V			A			D			E			F			O				
	Mean	Standard	Detect	Mean	Standard	Detect	Mean	Standard	Detect	Mean	Standard	Detect	Mean	Standard	Detect	Mean	Standard	Detect	Mean	Standard	Detect		
0-1	<b>6.32**</b>	0.35	100%	<b>7.22**</b>	0.42	86.9	<b>8.22*</b>	0.43	86.96	<b>23.14**</b>	0.66	91.30	31.51	0.49	91.30	39.91	0.45	82.61	<b>49.64**</b>	1.32	65.22		
3-5	5.64	0.18	100	6.59	0.26	100	7.56	0.35	88.67	22.36	0.38	88.67	30.90	0.37	98.11	39.34~	0.32	100	48.14	0.42	90.57		
5-8	<b>5.53**</b>	0.23	100	<b>6.45*</b>	0.21	100	<b>7.39</b>	0.28	100	<b>22.16*</b>	0.28	100	30.82	0.45	100	<b>39.23*</b>	0.27	100	<b>47.88*</b>	0.31	84.62		
8-11	5.60	0.23	100	<b>6.45**</b>	0.25	100	<b>7.37*</b>	0.36	95.00	<b>22.27~</b>	0.56	95.00	30.79~	0.44	100	<b>39.34</b>	0.52	100	48.10	0.48	92.50		
11-13	5.65	0.17	100	6.56	0.23	100	7.53	0.34	100	22.45	0.60	91.84	<b>30.82~</b>	0.46	98.00	39.40	0.42	100	48.08	0.29	98.00		
14-17	5.72	0.20	100	6.62	0.27	100	7.59	0.33	100	22.53	0.54	93.33	31.07	0.43	97.14	39.50	0.43	98.10	48.15	0.45	95.28		
17-21	5.69	0.21	100	6.58	0.23	100	7.53	0.31	96.30	22.41	0.40	92.60	31.02	0.44	94.44	39.50	0.46	98.15	48.26	0.34	98.15		
21-30	5.71	0.22	100	6.65	0.26	100	7.60	0.34	100	22.60	0.67	95.80	31.12	0.71	100	39.61	0.62	99.30	48.33	0.73	97.90		
30-40	5.68	0.19	100	6.61	0.33	100	7.53	0.43	100	22.52	0.56	96.88	31.09	0.50	96.88	39.54	0.42	96.88	48.21	0.46	93.75		
40-50	5.89	0.23	100	6.67	0.19	90.90	7.64	0.29	100	22.84	0.71	90.90	31.26	0.30	100	39.49	0.22	100	48.30	0.65	90.90		
50-60	<b>5.99**</b>	0.26	100	<b>6.86~</b>	0.32	88.46	<b>7.89*</b>	0.44	92.31	<b>23.08*</b>	0.71	76.92	<b>31.57*</b>	0.70	96.15	39.92	0.77	92.31	48.72	1.00	88.46		
60-73	<b>5.94**</b>	0.33	100	<b>6.92**</b>	0.38	91.67	<b>7.89*</b>	0.46	91.67	<b>23.05~</b>	0.61	83.33	31.37	0.55	83.33	39.68	0.46	83.33	<b>48.84**</b>	0.59	100		
ANOVA	<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>		<i>F</i>	<i>P</i>
Age: All subjects	<b>24.93</b>	<0.001		<b>15.46</b>	<0.001		<b>11.23</b>	<0.001		<b>8.12</b>	<0.001		<b>6.59</b>	<0.001		<b>5.25</b>	<0.001		<b>13.05</b>	<0.001		<b>4.03</b>	<0.001
Age: 3-30	<b>4.92</b>	<0.001		<b>4.90</b>	<0.001		<b>3.69</b>	0.001		<b>4.23</b>	0.001		<b>3.98</b>	0.001		<b>4.09</b>	0.001		<b>4.03</b>	0.001			

<sup>a</sup>Group mean and standard deviation are reported (ms), along with the percent detectability for each peak. Omnibus statistics appear at the bottom of the table. There is a main effect of age for each peak, when considering the entire dataset and when restricting the analysis to 3 to 30 year olds. Groups that are statistically different from the 21- to 30-year-old group are bolded (\* $<0.01$ , \*\* $<0.001$ , ~ $<0.05$ , ~ $<0.1$ , corrected for multiple comparisons).



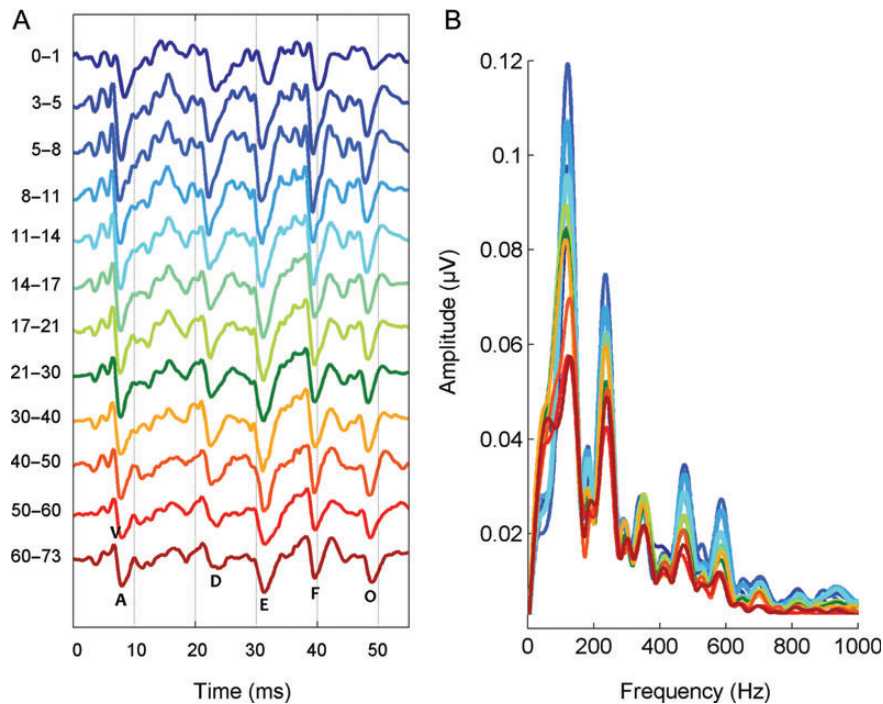
**Figure 2.** Developmental comparisons between click- and speech-evoked wave V of the auditory brainstem response (ABR). Age-dependent changes in latency are plotted for the click- (gray) and speech-evoked ABR (black). To graphically compare the developmental trajectories for these stimuli, the latency trajectories have been normalized such that the infant group is plotted at 0, with the y-axis representing the amount of change (ms) from the infants. The value reported on the x-axis represents the youngest age for each group; for example, 3 represents 3–5.

consistent with the conventional notion that the ABR is “adult-like” by around age 2 (Table 2) (Hall 2007). However, the 5- to 8-year-old group has significantly earlier latencies than the adults for all peaks, except A and E, suggesting that the response undergoes further maturational changes beyond age 5. In further support of a protracted development of the auditory brainstem, the 8- to 11-year-old group also differs from the adults in the latencies of peaks V and A, with trends observed for D and E.

#### Frequency-Following Response Amplitude

For the low-, middle, and high-frequency regions the amplitude of the response changes with age (see Table 3 for statistics, all ranges  $P < 0.001$ ) (Fig. 5). Amplitudes increase sharply during the first few years of life, with the maximum amplitude occurring in the 5- to 8-year-old range for the low and mid frequencies, and in the 8- to 11-year-old range for the higher frequencies. After reaching this maximum, the amplitudes decrease steadily with the slope being steepest for the mid- and high-frequency ranges. In this regard, the general developmental trajectory of the frequency measures is similar but not identical to that observed for the latency measures.

When restricting the analyses to ages 3–30, main effects of age are found for the mid- and high-frequency ranges but not the low range (see Table 3 for statistics). Post hoc comparisons revealed extensive differences between the child groups and the young adult value for both the mid and high frequencies, but not the low range. For the mid range, the 3–5, 5–8, and 8–11 age groups each differ from the 21- to 30-year-old group (all,  $P < 0.001$ ), suggesting that the developmental trajectory begins to take on a more adult-like configuration around age 11–13, where the difference from the 21- to 30-year-old group is trending ( $P = 0.07$ ). In the case of the high frequencies, development is somewhat longer, extending through age 11–14. In contrast, for the low frequencies, the only groups that differ from the 21–30 range are the 50–60- and 60–73-year-old groups.



**Figure 3.** (A) Time- and (B) frequency- domain representations of the speech-evoked auditory brainstem response for each age group represented as different colors.

#### *Within-Session Response Consistency*

In this sample of infants to older adults, response consistency changes with age (see Table 3 for statistics) (Fig. 6A). The trajectory follows an inverted U-shaped curve, such that consistency initially increases with age then stabilizes before declining with senescence. In this case, the 2 youngest groups and the 2 oldest groups differed significantly from the 21 to 30 year old, with maintained stability between the ages of 8 and 40.

#### *Nonstimulus Activity*

The extent of nonstimulus activity is age-dependent (see Table 3 for statistics), with the amplitude decreasing early in life, followed by a period of stabilization (Fig. 6B). For this measure, the 21–30 group had smaller amplitudes than the 3 youngest age groups, but they did not differ from the 8–11 year olds, suggesting that the trajectory stabilizes during that window. Although there appear to be increases in nonstimulus activity in the older age groups, the older adults do not differ statistically from the younger adults, perhaps because of the large variability in the older groups.

#### *Summary*

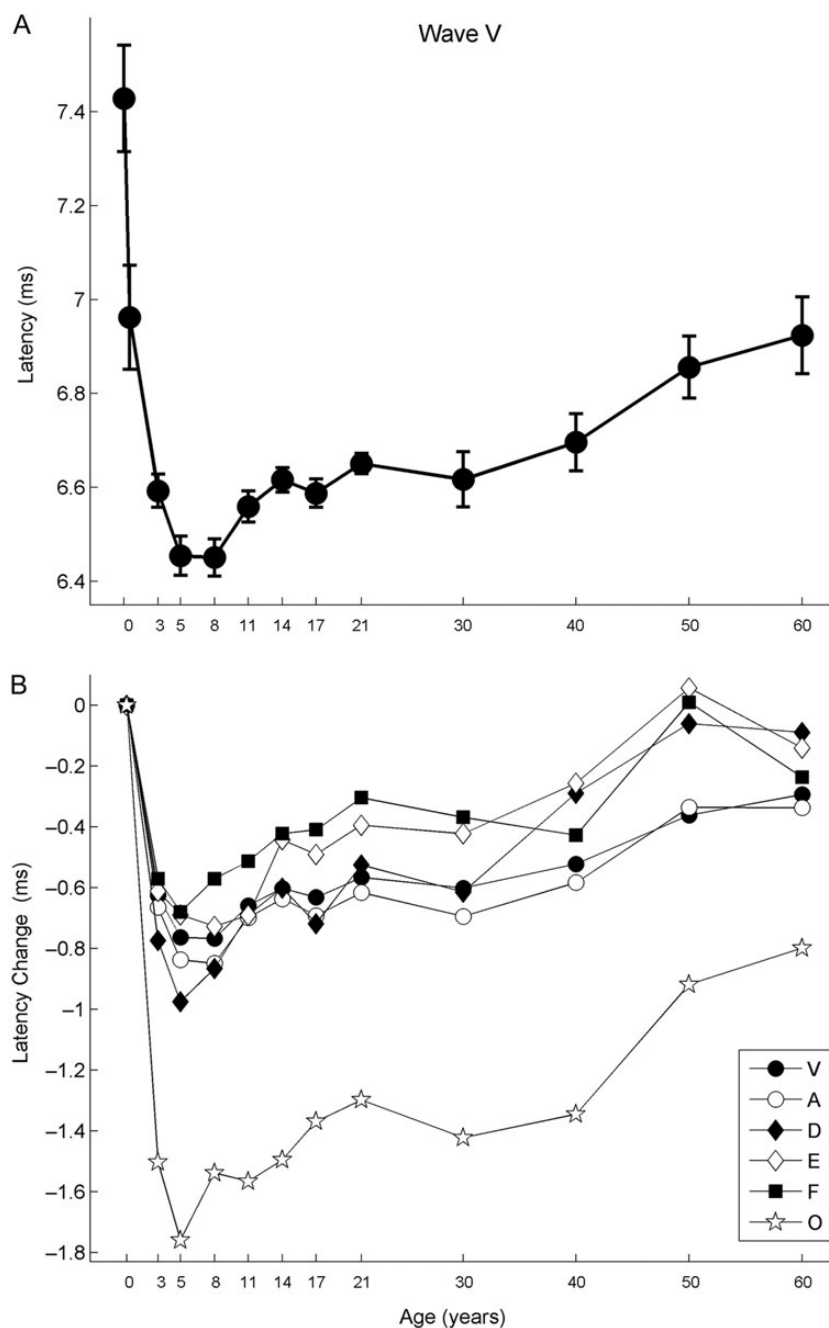
The subcomponents of the ABR mature at different rates, with the response to the low frequencies maturing first. By the 8–11 age window, the latency trajectories for the waves F and O, as well as response consistency and the nonstimulus activity have stabilized. During this same time window, the click-evoked wave V latency trajectory also begins to stabilize. For the cABR, the latency of onset peaks (V, A) and the first peak of the FFR (D) appear mature around ages 11–13, the same time that the mid frequencies do. High frequencies and peak E are the last to mature, with the trajectory remaining in flux until ages 14–17.

#### **Discussion**

In this study, we examined how auditory brainstem activity changes across the lifespan with the goal of understanding when activity is dynamic and when it is stable. We observed a common trend for developmental changes to continue well past age 2, the age generally attributed to maturational stabilization of the auditory brainstem. In addition to challenging the well-entrenched idea that the auditory brainstem matures early in life, a finding which on its own has significant implications for clinical applications of the ABR, the outcomes of this study provide a conceptual advance to understanding auditory development in general. As we discuss below, this dataset provides insight into the juxtaposition of multiple developmental timelines, the interplay between plasticity and stability within the developing auditory brainstem, and the tolerance limits for experience-dependent brainstem plasticity throughout life.

#### ***Localizing the Effects to the Auditory Brainstem***

We demonstrate developmental patterns that have not previously been shown for the auditory brainstem. This raises the question of whether our findings might reflect nonbrainstem components. By presenting the stimuli at a fast rate and filtering out low-frequency information, our recording techniques are optimized to isolate synchronized neural activity from auditory brainstem nuclei, while at the same time dampening auditory cortical activity, which has lower phase-locking capabilities, overall lower temporal precision, and longer neural transmission times (>12 ms) (Chandrasekaran and Kraus 2010). However, because cortical activity may not be completely removed, we acknowledge that a small proportion of the activity recorded at longer latencies within our recordings may have cortical origins. That said, we assert that our specific set of measurements, especially the peak and FFR amplitude measures, have predominantly subcortical origins. First, for



**Figure 4.** Latency trajectories for the 6 characteristic peaks of the speech-evoked auditory brainstem response (cABR). (A) Latency trajectory for wave V plotted as a function of age. Error bars represent 1 standard deviation of the mean. (B) Latency trajectory for the 6 characteristic peaks of the cABR. To compare across peaks, the trajectories have been normalized such that the infant group is plotted at 0, with the y-axis representing the amount of change (ms) from the infants. Across all peaks, the minimum latency occurs within the 5- to 11-year-old window.

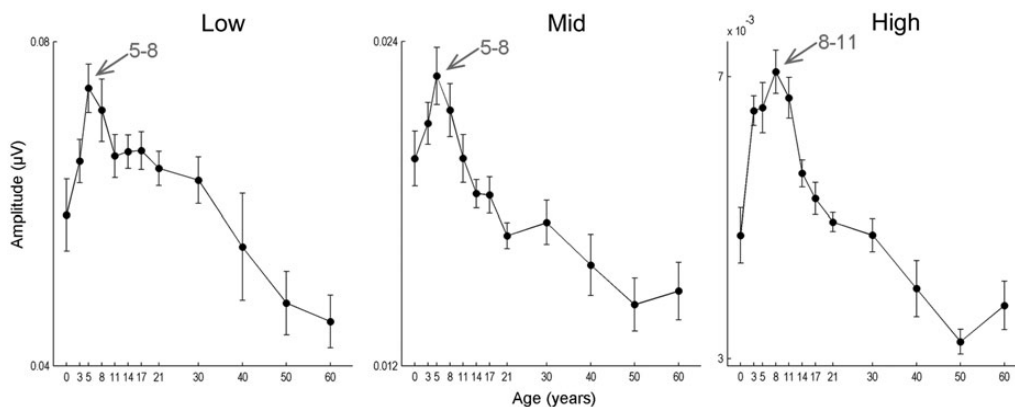
the mid- and high-frequency FFR measures, where developmental effects are most prevalent, we are capturing phase-locked activity that exceeds the very upper limits of cortical phase-locking ( $\sim 250$  Hz) (Steinschneider et al. 1980). Second, peaks V-A-D-E-F-O, emerge roughly 6–8 ms after the stimulus feature that evoked it, which is within the typical time frame for neural activity arising from the lateral lemniscus and inferior colliculus. As an example, within the stimulus, there are 3 large negative deflections occurring at 15, 23, and 30 ms that reflect the pulsing of the vocal chords. These pulses give rise to peaks D,

E, and F, with each peak occurring roughly 6–8 ms after the corresponding stimulus feature (i.e.,  $\sim 21$ ,  $\sim 30$ , and  $\sim 28$  ms, Fig. 1). Thus, while we measure their latency relative to time 0—the stimulus onset—these peaks are not in fact “long latency” responses, and so their origins are more likely subcortical than cortical. Owing to their more broadband nature, the origin or origins of the response consistency and nonstimulus activity measurements may be more difficult to pinpoint, although because of how the responses were filtered we can be confident that the dominant component is subcortical.

**Table 3**Age-dependent changes in frequency response amplitude, response consistency, and nonstimulus activity<sup>a</sup>

Group (age)	Frequency response amplitude ( $\mu\text{V}$ )						Response consistency (r-value)		Nonstimulus activity ( $\mu\text{V}$ )	
	Low		Mid		High		Mean	Standard	Mean	Standard
	Mean	Standard	Mean	Standard	Mean	Standard				
0–1	0.055	0.020	0.019	0.005	0.004	0.002	<b>0.585**</b>	0.177	<b>0.052**</b>	0.017
3–5	0.060	0.018	<b>0.020**</b>	0.005	<b>0.006**</b>	0.001	<b>0.659**</b>	0.161	<b>0.041**</b>	0.012
5–8	0.069	0.013	<b>0.022**</b>	0.005	<b>0.006**</b>	0.002	0.741	0.184	<b>0.041~</b>	0.010
8–11	0.066	0.023	<b>0.020**</b>	0.006	<b>0.006**</b>	0.002	0.761	0.185	0.038	0.012
11–14	0.061	0.017	<b>0.019~</b>	0.006	<b>0.006**</b>	0.002	0.782	0.145	0.033	0.011
14–17	0.061	0.019	0.017	0.005	0.005	0.002	0.824	0.099	0.034	0.011
17–21	0.061	0.016	0.017	0.005	0.005	0.001	0.782	0.157	0.032	0.012
21–30	0.059	0.025	0.016	0.005	0.004	0.001	0.776	0.154	0.032	0.010
30–40	0.057	0.015	0.016	0.004	0.004	0.001	0.794	0.120	0.033	0.011
40–50	0.050	0.019	0.015	0.004	0.004	0.001	0.666	0.184	0.035	0.014
50–60	<b>0.044**</b>	0.018	0.013	0.005	0.003	0.001	0.669*	0.182	0.038	0.013
60–73	<b>0.042**</b>	0.015	0.014	0.005	0.003	0.001	0.627**	0.213	0.036	0.015
ANOVA	F	P	F	P	F	P	F	P	F	P
Age: All subjects	<b>4.52</b>	<b>&lt;0.001</b>	<b>8.19</b>	<b>&lt;0.001</b>	<b>17.3</b>	<b>&lt;0.001</b>	<b>9.76</b>	<b>&lt;0.001</b>	<b>7.50</b>	<b>&lt;0.001</b>
Age: 3–30	1.4	0.213	<b>8.82</b>	<b>&lt;0.001</b>	<b>14.71</b>	<b>&lt;0.001</b>	<b>7.23</b>	<b>&lt;0.001</b>	<b>6.30</b>	<b>&lt;0.001</b>

<sup>a</sup>The group mean and standard deviation are reported with omnibus statistics provided at the bottom of the table. There is a main effect of age for each measure when considering the entire dataset. All measures, except the low frequencies, show an age-dependent effect when restricting the analysis to 3 to 30 year olds. Groups that are statistically different from the 21- to 30-year-old group are bolded (\*\*<0.01, \*<0.05, ~<0.1, corrected for multiple comparisons).



**Figure 5.** Developmental trajectories for the low-, mid-, and high-frequency components of the frequency-following response of the speech-evoked auditory brainstem response. In all 3 frequency bands, the response amplitude peaks transiently during school-age years.

### Evidence for 2 Distinct Developmental Trajectories

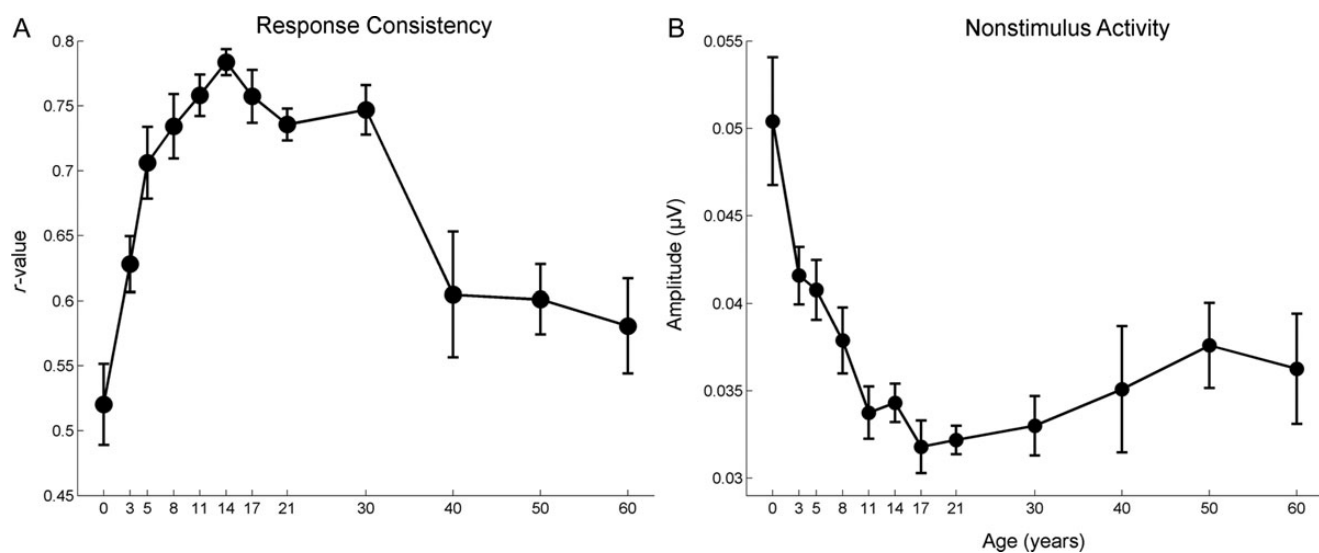
Our data provide evidence for multiple development trajectories of the auditory brainstem that are accessible via the cABR. From our constellation of findings, we conclude that there are at least 2 unique and complex developmental trajectories in the auditory brainstem: One has a transitory crest during school-age years that briefly “overshoots” the adult pattern (Transitory Crest) and is seen in both the speech and click stimuli. The other developmental pattern has a more symmetrical, broader trajectory that exhibits a longer plateau (Prolonged Apex) (Fig. 7). The ABR components that reflect exogenous measures (i.e., stimulus-driven measures) follow a Transitory Crest (latency and amplitudes) whereas the other measures (nonstimulus activity, response consistency), which are less dictated by the specific stimulus, display a Prolonged Apex.

#### Transitory Crest in Auditory Brainstem Function: Response Latency and Amplitude

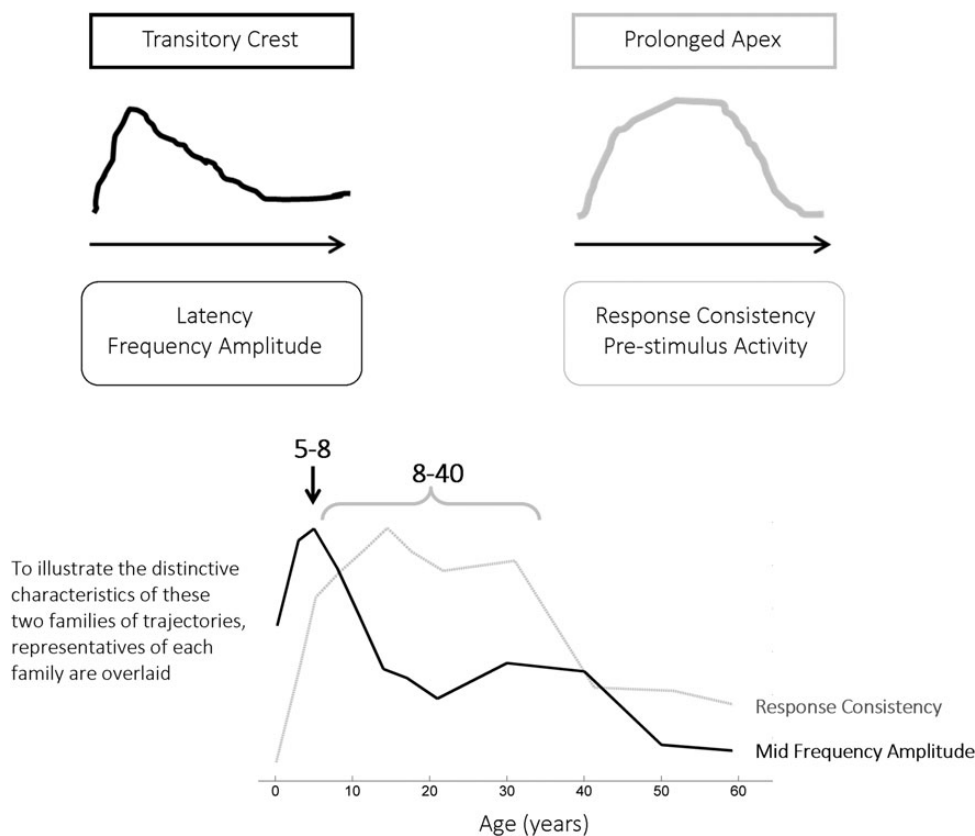
The developmental profile for the latency and spectral amplitude measures is marked by a brief period during childhood

(occurring within the 5–8 and/or 8–11-year-old range depending on the measure) when brainstem function is heightened, as evidenced by a brief decrease in response latencies and an upturn in response amplitude that surpasses the adult profile. Earlier latencies and larger amplitudes are considered telltale signs of a robustly functioning typically developing auditory system (Hall 2007). Leading up to this functional crest, latencies become progressively earlier and response amplitude becomes progressively more robust with age. By ages 3–5, the values match those of an adult. However, this adult-like state is only temporary; by ages 5–8, the latencies and amplitudes have overshoot the adult value. This overshoot is followed by a gradual increase in latency and decrease in amplitude during adolescence into early adulthood when the trajectory stabilizes. Beginning in the sixth decade of life, continuous changes in latency and frequency encoding are again evident.

Overshoot is observed across the frequency spectrum of the response and in the time domain across each of the major peaks of the cABR. Importantly, this overshoot can also be observed in the click-evoked ABR suggesting that this phenomenon generalizes across stimuli. While the general shape of the



**Figure 6.** Developmental trajectories for the measures of within-session response consistency (A) and nonstimulus activity (B) of the speech-evoked auditory brainstem response. Compared with the latency and amplitude measures, the developmental trajectories are more symmetrical.



**Figure 7.** Two distinct developmental trajectories are evidenced in the auditory brainstem response: As illustrated in this stylized schematic, one has a brief apex (Transitory Crest) during school-age years that overshoots the adult pattern (Transitory Crest), and the other has a more symmetrical and broader trajectory that exhibits a longer plateau (Prolonged Apex).

trajectories is similar, the extent of the overshoot and the “drop-off” from the overshoot is greater for some measures than others. For example, the drop-off is more gradual for the latency compared with the amplitude measures (especially the mid-frequency range), which show a sharper decay. Moreover, while the general trajectory is similar for the different frequency ranges, high frequencies take slightly longer to develop (Folsom

and Wynne 1986; Shahin et al. 2010), consistent with a bias toward low frequencies in the immature system and a progressive change in the tuning of auditory nerve fibers, with high-frequency characteristic fibers being initially tuned to low frequencies or being more broadly tuned (Lippe and Rubel 1983). In addition, while the developmental trajectory is similar for the latency and amplitude measures in that both demonstrate



a transient apex, the morphology and timelines of the trajectories are not identical, suggesting that the neural circuitry for these measures is overlapping but not mutually inclusive (Folsom and Wynne 1986). From our data, we conclude that the “Transient Apex” describes a general property of auditory brainstem development, with different latency and amplitude components of the ABR reflecting distinct developmental processes tethered together by a common overarching mechanism that culminates in an overshoot. In this regard, while we have grouped the latency and amplitude measures under the common umbrella of Transient Apex, our findings suggest that this broad category is composed of developmental subcategories.

To the best of our knowledge, we are the first to report a developmental overshoot in auditory brainstem function. Given the large body of literature on the ABR, this raises the question of why this overshoot has never before been documented, especially if this overshoot is a pervasive and generalizable phenomenon. The most parsimonious explanation is that there are notable differences in subject sampling between our study and its predecessors. In addition to being larger than other datasets, our dataset included a generous sampling of preadolescents and adolescents, 2 age groups that have been largely overlooked in previous investigations of the ABR which often simply compared infants and toddlers to adults. Another limitation of previous studies is that individuals spanning many ages were collapsed into single groups, permitting only broad generalizations, and masking subtle variations with age and fueling the belief that developmental processes do not extend into later childhood. Yet, while the notion that the auditory brainstem matures early is well entrenched in the literature and has become boilerplate in most textbooks and review articles (for example see Hall 2007; Moore and Linthicum 2007), there have been some hints in the literature that brainstem development is more complex and protracted (Lauter and Oyler 1992; Lauter et al. 1993; Johnson et al. 2008). Indeed, when reviewing decades-old data through the lens of our discovery, evidence of an overshoot can be observed (Mochizuki et al. 1982; Salamy 1984).

Although the discovery of an overshoot in brainstem function was surprising given the extant ABR literature, it was not wholly unprecedented given that overshoot phenomena are prevalent in the developmental literature (Giedd et al. 1999; Johnson 2001; Neville and Bavelier 2001). Similar to what we report, Shahin et al. (2004) found that auditory-evoked N1 and P2 hit their maximum amplitude around ages 10–12 and then subsequently decrease in amplitude. Functional overshoots, which are characteristic features of CNS development and hallmarks of sensitive periods, have been linked to the overproduction and subsequent elimination of synapses, a process that occurs on different timescales within different neural regions (Huttenlocher 1979; Huttenlocher and Dabholkar 1997; Giedd et al. 1999; Kral and Sharma 2012). For example, a similar transitory overshoot in auditory-evoked activity has been observed in the developing cat auditory cortex (Kral and O’Donoghue 2010). This functional overshoot in the cat coincided with a brief period of heightened synaptic density resulting from synaptogenesis that was followed by synaptic pruning. This synaptic overshoot process, which can be observed across the CNS, can be compared with a multistage rocket which takes flight with a full payload of resources, but then to maintain efficiency throughout its flight path eliminates materials at each successive stage. Kral and Eggermont (2007) have theorized

that synaptic overshoot endows flexibility to the developing auditory system, such that the auditory system is protected against maladaptive auditory experiences, including auditory deprivation, and primed to take advantage of enriched auditory environments during this period of development.

If we interpret our data in this light, the transitory peak in auditory brainstem function, occurring during school-age years, could be the outcome of synaptic overshoot. The sharp changes in auditory brainstem latency and amplitude leading up to the crest in the developmental trajectory may reflect a time of heightened gray-matter density reflecting a surplus of synapses which then, over time, are pruned as the auditory brainstem circuitry begins to stabilize and specialize (Kral and Sharma 2012). Synaptic changes are, however, only one of many possible neural mechanisms that could account for the overall shape of the trajectory. For example, rapid decreases in ABR latency and increases in amplitude that occur during the first years of life have previously been attributed to increases in white matter (myelination) that produce more efficient signal transmission along the auditory pathway (Shah et al. 1978; Wilkinson and Jiang 2006). Thus, synergistic increases in white and gray matter may account for the rapid decreases in latency and increases in amplitude seen during the first 5–8 years of life. Although increases in gray and white matter may occur in tandem, the developmental timelines may not be identical. For example, myelin levels may climax and then remain constant while net decreases in gray matter are underway. We speculate that the transient crest, occurring within the 5- to 11-year-old window, marks a tipping point in development where white- and gray-matter development are working in juxtaposition, leading to a change in slope in the developmental profile. Other explanations for the downturn in latency and amplitude cannot be dismissed. They include, but are not limited to, anatomical changes to the inner ear and head size (see however Sabo et al. 1992). To understand the numerous biological factors that may underlie this complex developmental trajectory, cellular, pharmacological, and genetic factors must also be considered across both human and animal models of development.

#### *Prolonged Apex: Response Consistency and Nonstimulus Activity*

In contrast to the trajectories that follow a transitory crest, the sustained trajectory displays a shallower decay between preadolescence into the fifth decade of life that gives it a relatively more symmetric appearance. The trajectory resembles the developmental timeline of gray matter within auditory cortex, which also takes roughly a decade to mature (Moore and Linthicum 2007). Given the similar time course, and the vast network of efferents that connect cortical structures to subcortical ones (Bajo and King 2012), one possible interpretation is that the sustained trajectory reflects the developmental timeline of the efferent auditory pathway. Within the auditory system, there is an extensive set of descending cortical projections, known as the corticofugal pathway, that connects the primary auditory cortex with all of the major nuclei within the subcortical auditory system (Bajo and King 2012). Through this communication link, the auditory cortex can optimize how sensory information is processed subcortically (Suga et al. 2000). Effective usage of sensory signals by high-order centers of the brain is limited by the reliability of the sensory input (Deneve and Pouget 2004; Faisal et al. 2008). Thus, the

establishment of an efficient and reliable sensory representation that is stable from one instance to the next may facilitate the development and retention of cognitive function (Skoe et al. 2013; Krizman et al. in press). In support of this idea, stable ABRs are associated with heightened language abilities (Hornickel and Kraus 2013). Moreover, declines in response consistency occur during the same time window when aging-related declines in cognitive function begin to accelerate (Salthouse 2009; Anderson et al. 2012a). Increased trial-by-trial response consistency coupled with decreased nonstimulus-related activity also creates a state of lower neural noise. Given that neural noise can interfere with the transfer of information within and between neural networks (Faisal et al. 2008), the auditory cortex has a vested interest in cleaning up and stabilizing the input it receives. While hypothetical at this point, we propose that the corticofugal system nears a maturational stabilization point around ages 8–11, allowing the auditory system to optimize signal transmission between the auditory brainstem and auditory cortex by promoting homeostasis of the mechanisms underlying cABR latencies and amplitudes. This raises the possibility that the 2 developmental profiles—Transitory Crest and Prolonged Apex—reflect neural processes that interact despite having different developmental profiles. This explanation also raises the possibility that the extended developmental time course, which is common to both the Transitory Crest and Prolonged Apex, may be influenced by protracted developmental processes occurring within non-brainstem components, including the efferent auditory system and the auditory cortex. This is not to imply that we are directly measuring the developmental trajectory of the auditory cortex or the efferent pathway but instead that we are measuring how neural processes within the auditory brainstem have been shaped by developmental processes occurring or that have occurred elsewhere in the brain.

Compared with the afferent auditory pathway, far less is known about the development of the efferent pathway in humans, especially the corticofugal pathway, or about the interaction between the afferent and efferent system during development. We view this as a topic ripe for further investigation as it may unlock the answers to many developmental questions and provide insight into specific developmental disorders (Hornickel, Skoe, Nicol, et al. 2009).

### ***Implications for Experience-Dependent Plasticity***

Humans have structurally well-formed auditory systems at birth, reflective of extensive, precocious development of the central auditory pathway prior to hearing onset that is largely preprogrammed (Gordon et al. 2011; Tillein et al. 2012). Although the general shape and time course of the Transitory Crest and Prolonged Apex trajectories may be biologically predetermined, we theorize that experience may guide how the trajectories are expressed, such that enriched or deprived sound experiences may produce slightly different patterns of development (Shahin et al. 2004; Shafer et al. 2010; Kral et al. 2013; Skoe et al. 2013). We further theorize that although the auditory brainstem undergoes experience-dependent changes throughout life (Kraus and Chandrasekaran 2010; Carcagno and Plack 2011; Hornickel et al. 2012; Song et al. 2012; Anderson et al. 2013), the potential for experience-dependent plasticity may be greater during periods when the underlying developmental trajectory is in flux, such that experience-

dependent processes may capitalize on the inherent developmental malleability at a particular time point in life (Johnson 2001; Bengtsson et al. 2005). Thus, we view the complex morphology of the developmental curves as supporting the possibility that enriched (music, multilingualism, etc.) or deprived (e.g., hearing loss, low-socioeconomic conditions) auditory experiences may influence the auditory brainstem differently depending on the developmental trajectory at the time that the experience occurs.

### ***Clinical Implications***

This study has important clinical implications given that ABRs are used in clinical settings to measure audiometric thresholds and to monitor neurological status during surgery (Hall 2007). Accurate normative data are required for clinical interpretation of ABRs. Because ABR latencies are assumed to be stable, and therefore mature, after age 18 months, it has become common clinical practice to use the same normative dataset for children (18 months plus) and adults (Hood 1998). Our findings suggest that this approach must be reconsidered. Applying a common set of norms to children and adults, or even between children of different ages, could increase the incidence of false negatives for children, especially for children in the 5–10 age range. For example, for an 8-year-old child, click-evoked wave V may not be delayed relative to adult norms but would be delayed if age-specific norms were available. It is well known that latency deviations on the order of fractions of milliseconds are clinically meaningful, so if a child was found to deviate even just slightly from the age-appropriate norms this could be indicative of a tumor along the auditory pathway, neuropathy, demyelination, or possibly a neurodevelopmental disorder such as dyslexia (Musiek et al. 2007; Banai et al. 2009).

To date, little work has been done to evaluate the cABR in infants. We validate that cABRs can be successfully recorded in awake infants and that the morphology of the response bears resemblance to the adult waveform, in both the time and frequency domain. However, it is also clear that the response undergoes substantial changes between infancy and adulthood that may not be evident in smaller datasets (e.g., Jeng et al. 2010), once again emphasizing the importance of large and diverse normative datasets in making claims about development. We, therefore, acknowledge that one of the limitations of this study is the lack of data from 1 to 2 year olds, a range that is undoubtedly developmentally important. That caveat aside, by validating that interpretable cABRs can indeed be measured from infant populations, this paves the way for using cABR technology in the early detection of dyslexia and other auditory processing and neurodevelopmental disorders (Choudhury and Benasich 2011; Cohen et al. 2013; Hornickel and Kraus 2013).

### ***Conclusion and Future Directions***

This study establishes that developmental plasticity of the auditory brainstem continues well past age 2, calling into question the conventional wisdom of the developmental timeline of the auditory brainstem. Through the use of a large dataset, more fine-grained groups in the pediatric age ranges, employing a more complex stimulus, and assessing multiple dimensions of brainstem function, it was possible to pull out subtle yet seemingly systematic variations that occur normally over the lifespan.

This dataset provides a springboard for many future investigations. Future studies should measure neurophysiological and behavioral development in parallel to assess whether the developmental trajectories of the ABR track with specific perceptual or linguistic skills (Sanes and Woolley 2011). At present, such a parallel study is difficult given that the same behavioral test cannot be easily applied to infant, pediatric, adult, and geriatric populations; this is in contrast to ABRs, where the same testing protocol can be used in humans and animals of all developmental stages. To gain insight into how developmental plasticity constrains or promotes experience-dependent plasticity, future experiments should also address how auditory impoverishment and auditory enrichment alters the developmental trajectory of the ABR using both cross-sectional and longitudinal approaches.

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### Notes

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### References

- Anderson S, Parbery-Clark A, White-Schwoch T, Kraus N. 2012a. Aging affects neural precision of speech encoding. *J Neurosci*. 32:14156–14164.
- Anderson S, Parbery-Clark A, White-Schwoch T, Kraus N. 2012b. Auditory brainstem response to complex sounds predicts self-reported speech-in-noise performance. *J Speech Lang Hear Res*. 56:31–43.
- Anderson S, White-Schwoch T, Parbery-Clark A, Kraus N. 2013. Reversal of age-related neural timing delays with training. *Proc Natl Acad Sci USA*. 110:4357–4362.
- Bajo VM, King AJ. 2012. Cortical modulation of auditory processing in the midbrain. *Front Neural Circuits*. 6:114.
- Banai K, Hornickel J, Skoe E, Nicol T, Zecker S, Kraus N. 2009. Reading and subcortical auditory function. *Cereb Cortex*. 19:2699–2707.
- Bengtsson SL, Nagy Z, Skare S, Forsman L, Forsberg H, Ullen F. 2005. Extensive piano practicing has regionally specific effects on white matter development. *Nat Neurosci*. 8:1148–1150.
- Callaway E, Halliday RA. 1973. Evoked potential variability: effects of age, amplitude and methods of measurement. *Electroencephalogr Clin Neurophysiol*. 34:125–133.
- Carcagno S, Plack CJ. 2011. Subcortical plasticity following perceptual learning in a pitch discrimination task. *J Assoc Res Otolaryngol*. 12:89–100.
- Chandrasekaran B, Kraus N. 2010. The scalp-recorded brainstem response to speech: neural origins and plasticity. *Psychophysiol*. 47:236–246.
- Choudhury N, Benasich AA. 2011. Maturation of auditory evoked potentials from 6 to 48 months: prediction to 3 and 4 year language and cognitive abilities. *Clin Neurophysiol*. 122:320–338.
- Chu NS. 1985. Age-related latency changes in the brain-stem auditory evoked potentials. *Electroencephalogr Clin Neurophysiol*. 62:431–436.
- Clinard CG, Tremblay KL, Krishnan AR. 2010. Aging alters the perception and physiological representation of frequency: evidence from human frequency-following response recordings. *Hear Res*. 264:48–55.
- Cohen IL, Gardner JM, Karmel BZ, Phan HT, Kittler P, Gomez TR, Gonzalez MG, Lennon EM, Parab S, Barone A. 2013. Neonatal brainstem function and 4-month arousal-modulated attention are jointly associated with autism. *Autism Res*. 6:11–22.
- Davis GW, Bezprozvanny I. 2001. Maintaining the stability of neural function: a homeostatic hypothesis. *Annu Rev Physiol*. 63:847–869.
- Deneve S, Pouget A. 2004. Bayesian multisensory integration and cross-modal spatial links. *J Physiol Paris*. 98:249–258.
- Dhar S, Abel R, Hornickel J, Nicol T, Skoe E, Zhao W, Kraus N. 2009. Exploring the relationship between physiological measures of cochlear and brainstem function. *Clin Neurophysiol*. 120:959–966.
- Eggermont J, Moore J. 2012. Morphological and functional development of the auditory nervous system. In: Werner L, Fay RR, Popper AN, editors. *Human auditory development*. New York: Springer. p. 61–105.
- Elfner LF, Barnes AR. 1983. Onset-offset effects of the human brainstem auditory-evoked response. *J Aud Res*. 23:101–107.
- Faisal AA, Selen LPJ, Wolpert DM. 2008. Noise in the nervous system. *Nat Rev Neurosci*. 9:292–303.
- Folsom RC, Wynne MK. 1986. Auditory brain stem responses from human adults and infants: restriction of frequency contribution by notched-noise masking. *J Acoust Soc Am*. 80:1057–1064.
- Gardi J, Salamy A, Mendelson T. 1979. Scalp-recorded frequency-following responses in neonates. *Audiology*. 18:494–506.
- Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. 1999. Brain development during childhood and adolescence: a longitudinal MRI study. *Nat Neurosci*. 2:861–863.
- Gordon KA, Wong DD, Valero J, Jewell SF, Yoo P, Papsin BC. 2011. Use it or lose it? Lessons learned from the developing brains of children who are deaf and use cochlear implants to hear. *Brain Topogr*. 24:204–219.
- 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*. 32:281–288.
- Hall JW. 2006. *New Handbook of auditory evoked responses*. Boston (MA): Allyn and Bacon.
- Hood LJ. 1998. *Clinical applications of the auditory brainstem response*. San Diego (CA): Singular Publishing Group.
- Hornickel J, Kraus N. 2013. Unstable representation of sound: a biological marker of dyslexia. *J Neurosci*. 33:3500–3504.
- Hornickel J, Skoe E, Kraus N. 2009. Subcortical laterality of speech encoding. *Audiol Neurootol*. 14:198–207.
- Hornickel J, Skoe E, Nicol T, Zecker S, Kraus N. 2009. Subcortical differentiation of stop consonants relates to reading and speech-in-noise perception. *Proc Natl Acad Sci USA*. 106:13022–13027.
- Hornickel J, Zecker SG, Bradlow AR, Kraus N. 2012. Assistive listening devices drive neuroplasticity in children with dyslexia. *Proc Natl Acad Sci USA*. 109:16731–16736.
- Hua JY, Smith SJ. 2004. Neural activity and the dynamics of central nervous system development. *Nat Neurosci*. 7:327–332.
- Huttenlocher PR. 1979. Synaptic density in human frontal cortex—developmental changes and effects of aging. *Brain Res*. 163:195–205.
- Huttenlocher PR, Dabholkar AS. 1997. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol*. 387:167–178.
- Insanally MN, Kover H, Kim H, Bao S. 2009. Feature-dependent sensitive periods in the development of complex sound representation. *J Neurosci*. 29:5456–5462.
- Jeng FC, Schnabel EA, Dickman BM, Hu J, Li X, Lin CD, Chung HK. 2010. Early maturation of frequency-following responses to voice pitch in infants with normal hearing. *Percept Mot Skills*. 111:765–784.
- Jerger J, Hall J. 1980. Effects of age and sex on auditory brainstem response. *Arch Otolaryngol*. 106:387–391.
- Johnson KL, Nicol T, Zecker SG, Kraus N. 2008. Developmental plasticity in the human auditory brainstem. *J Neurosci*. 28:4000–4007.



- Johnson MH. 2001. Functional brain development in humans. *Nat Rev Neurosci*. 2:475–483.
- King C, Warrior CM, Hayes E, Kraus N. 2002. Deficits in auditory brainstem pathway encoding of speech sounds in children with learning problems. *Neurosci Lett*. 319:111–115.
- Kral A, Eggermont JJ. 2007. What's to lose and what's to learn: development under auditory deprivation, cochlear implants and limits of cortical plasticity. *Brain Res Rev*. 56:259–269.
- Kral A, Hubka P, Heid S, Tillein J. 2013. Single-sided deafness leads to unilateral aural preference within an early sensitive period. *Brain*. 136:180–193.
- Kral A, O'Donoghue GM. 2010. Profound deafness in childhood. *N Engl J Med*. 363:1438–1450.
- Kral A, Sharma A. 2012. Developmental neuroplasticity after cochlear implantation. *Trends Neurosci*. 35:111–122.
- Kraus N, Chandrasekaran B. 2010. Music training for the development of auditory skills. *Nat Rev Neurosci*. 11:599–605.
- Krizman J, Skoe E, Kraus N. 2012. Sex differences in auditory subcortical function. *Clin Neurophysiol*. 123:590–597.
- Krizman JL, Skoe E, Kraus N. 2010. Stimulus rate and subcortical auditory processing of speech. *Audiol Neurootol*. 15:332–342.
- Krizman J, Skoe E, Marian V, Kraus N. Bilingualism increases neural response consistency and attentional control: Evidence for sensory and cognitive coupling. *Brain Lang*. in press.
- Krumholz A, Felix JK, Goldstein PJ, McKenzie E. 1985. Maturation of the brain-stem auditory evoked potential in premature infants. *Electroencephalogr Clin Neurophysiol*. 62:124–134.
- Langner G, Schreiner CE. 1988. Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. *J Neurophysiol*. 60:1799–1822.
- Lauter JL, Oyler RF. 1992. Latency stability of auditory brainstem responses in children aged 10–12 years compared with younger children and adults. *Br J Audiol*. 26:245–253.
- Lauter JL, Oyler RF, Lord-Maes J. 1993. Amplitude stability of auditory brainstem responses in two groups of children compared with adults. *Br J Audiol*. 27:263–271.
- Lippe W, Rubel EW. 1983. Development of the place principle: tonotopic organization. *Science*. 219:514–516.
- Liu LF, Palmer AR, Wallace MN. 2006. Phase-locked responses to pure tones in the inferior colliculus. *J Neurophysiol*. 95:1926–1935.
- 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*. 4:127–136.
- Moore JK, Linthicum FH Jr. 2007. The human auditory system: a timeline of development. *Int J Audiol*. 46:460–478.
- Musiek F, Shinn J, Jirsa R. 2007. The auditory brainstem response in auditory nerve and brainstem dysfunction. In: Burkard R, Eggermont J, Don M, editors. *Auditory evoked potentials: basic principles and clinical application*. Baltimore (MD): Lippincott, Williams & Wilkins. p. 291–312.
- Neville HJ, Bavelier D. 2001. Effects of auditory and visual deprivation on human brain development. *Clin Neurosci Res*. 1:248–257.
- Otto WC, McCandless GA. 1982. Aging and the auditory brain stem response. *Audiology*. 21:466–473.
- Parbery-Clark A, Anderson S, Hittner E, Kraus N. 2012. Musical experience offsets age-related delays in neural timing. *Neurobiol Aging*. 33:1483.e1. –1483.e4.
- Ponton CW, Eggermont JJ, Kwong B, Don M. 2000. Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clin Neurophysiol*. 111:220–236.
- Rosenhall U, Björkman G, Pedersen K, Kall A. 1985. Brain-stem auditory evoked potentials in different age groups. *Electroencephalogr Clin Neurophysiol*. 62:426–430.
- Rubel EW, Hyson RL, Durham D. 1990. Afferent regulation of neurons in the brain stem auditory system. *J Neurobiol*. 21:169–196.
- Russo N, Nicol T, Trommer B, Zecker S, Kraus N. 2009. Brainstem transcription of speech is disrupted in children with autism spectrum disorders. *Dev Sci*. 12:557–567.
- Sabo DL, Durrant JD, Curtin H, Boston JR, Rood S. 1992. Correlations of neuroanatomical measures to auditory brain stem response latencies. *Ear Hear*. 13:213–222.
- Salamy A. 1984. Maturation of the auditory brainstem response from birth through early childhood. *J Clin Neurophysiol*. 1:293–329.
- Salamy A, McKean CM. 1976. Postnatal development of human brainstem potentials during the first year of life. *Electroencephalogr Clin Neurophysiol*. 40:418–426.
- Salamy A, McKean CM, Buda FB. 1975. Maturation changes in auditory transmission as reflected in human brain stem potentials. *Brain Res*. 96:361–366.
- Salthouse TA. 2009. When does age-related cognitive decline begin? *Neurobiol Aging*. 30:507–514.
- Sanes DH, Woolley SM. 2011. A behavioral framework to guide research on central auditory development and plasticity. *Neuron*. 72:912–929.
- Shafer VL, Yu YH, Datta H. 2010. Maturation of speech discrimination in 4- to 7-yr-old children as indexed by event-related potential mismatch responses. *Ear Hear*. 31:735–745.
- Shah SN, Bhargava VK, Johnson RC, McKean CM. 1978. Latency changes in brain stem auditory evoked potentials associated with impaired brain myelination. *Exp Neurol*. 58:111–118.
- Shahin A, Roberts LE, Trainor LJ. 2004. Enhancement of auditory cortical development by musical experience in children. *Neuroreport*. 15:1917–1921.
- Shahin AJ, Trainor LJ, Roberts LE, Backer KC, Miller LM. 2010. Development of auditory phase-locked activity for music sounds. *J Neurophysiol*. 103:218–229.
- Skoe E, Kraus N. 2010. Auditory brain stem response to complex sounds: a tutorial. *Ear Hear*. 31:302–324.
- Skoe E, Krizman J, Kraus N. Forthcoming. The impoverished brain: disparities in maternal education affect the neural response to sound. *J Neurosci*. 33:17221–17231.
- Song JH, Banai K, Kraus N. 2008. Brainstem timing deficits in children with learning impairment may result from corticofugal origins. *Audiol Neurootol*. 13:335–344.
- Song JH, Nicol T, Kraus N. 2011. Test-retest reliability of the speech-evoked auditory brainstem response. *Clin Neurophysiol*. 122:346–355.
- Song JH, Skoe E, Banai K, Kraus N. 2012. Training to improve hearing speech in noise: biological mechanisms. *Cereb Cortex*. 22:1180–1190.
- Spivak LG, Malinoff R. 1990. Spectral differences in the ABRs of old and young subjects. *Ear Hear*. 11:351–358.
- Steinschneider M, Arezzo J, Vaughan HG Jr. 1980. Phase-locked cortical responses to a human speech sound and low-frequency tones in the monkey. *Brain Res*. 198:75–84.
- Stockard JE, Stockard JJ, Westmoreland BF, Corfits JL. 1979. Brainstem auditory-evoked responses. Normal variation as a function of stimulus and subject characteristics. *Arch Neurol*. 36:823–831.
- Suga N, Gao E, Zhang Y, Ma X, Olsen JF. 2000. The corticofugal system for hearing: recent progress. *Proc Natl Acad Sci USA*. 97:11807–11814.
- Thivierge J, Cote R. 1990. Brain-stem auditory evoked response: normative values in children. *Electroencephalogr Clin Neurophysiol*. 77:309–313.
- Tillein J, Heid S, Lang E, Hartmann R, Kral A. 2012. Development of brainstem-evoked responses in congenital auditory deprivation. *Neural Plast*. 2012:182767.
- Vander Werff KR, Burns KS. 2011. Brain stem responses to speech in younger and older adults. *Ear Hear*. 32:168. –180.
- Wilkinson AR, Jiang ZD. 2006. Brainstem auditory evoked response in neonatal neurology. *Semin Fetal Neonatal Med*. 11:444–451.