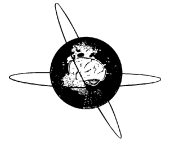




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Continued maturation of auditory brainstem function during adolescence: A longitudinal approach

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HIGHLIGHTS

- We longitudinally tracked subcortical speech encoding in adolescents from ages 14–17.
- Spectral representation, response consistency, and envelope tracking decreased. Peak latencies were stable.
- Subcortical auditory development continues through adolescence.

ABSTRACT

Objective: Considerable attention has been devoted to understanding development of the auditory system during the first few years of life, yet comparatively little is known about maturation during adolescence. Moreover, the few studies investigating auditory system maturation in late childhood have employed a cross-sectional approach.

Methods: To better understand auditory development in adolescence, we used a longitudinal design to measure the subcortical encoding of speech syllables in 74 adolescents at four time points from ages 14 through 17.

Results: We find a developmental decrease in the spectral representation of the evoking syllable, trial-by-trial response consistency, and tracking of the amplitude envelope, while timing of the evoked response appears to be stable over this age range.

Conclusions: Subcortical auditory development is a protracted process that continues throughout the first two decades of life. Specifically, our data suggest that adolescence represents a transitional point between the enhanced response during childhood and the mature, though smaller, response of adults.

Significance: That the auditory brainstem has not fully matured by the end of adolescence suggests that auditory enrichment begun later in childhood could lead to enhancements in auditory processing and alter developmental profiles.

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1. Introduction

Early studies on maturation of the auditory system found that cortical evoked activity changes throughout childhood and adolescence (Sharma et al., 1997; Cunningham et al., 2000; Ceponiene et al., 2002; Sussman et al., 2008; Mahajan and McArthur, 2012) whereas subcortical evoked responses approximate the response of young adults by age two (Hecox and Galambos, 1974). These results provided the basis for the widely held belief that auditory cortex

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maturation follows a protracted time course while auditory brainstem maturation occurs rapidly up to age two and then plateaus until senescence (Schulman-Galambos and Galambos, 1979; Salamy, 1984). Recent cross-sectional evidence, however, has challenged this view by showing that changes in auditory brainstem function continue throughout childhood and adolescence (Lauter and Oyler, 1992; Johnson et al., 2008; Skoe et al., 2013b; Spitzer et al., 2015). These cross-sectional investigations indicated that while responses at age 2–3 are comparable to the young adult response, between 3 and 18 years of age responses demonstrate continued maturational plasticity (Johnson et al., 2008; Skoe et al., 2013b).

In particular, brainstem responses during the ages 5–11 years are characterized by earlier latencies, heightened intertrial response consistency, and more robust spectral encoding relative to younger children or adults. Based on this difference between children aged 5–11 years and adults we hypothesize that auditory brainstem function continues to mature through adolescence. In support of this, cross-sectional evidence suggests that after responses reach their developmental apex, spectral encoding, stimulus envelope tracking, and neural response consistency decline and response timing slows as the response continues to take on more adult-like characteristics. However, conclusive evidence of these changes occurring during adolescence requires a longitudinal analysis of this age range. Thus, to understand the maturational time course of subcortical auditory function in adolescence, we longitudinally tracked within-subject changes in auditory brainstem processing from age 14 years to 17 years by examining the subcortical evoked response to a synthesized speech syllable.

2. Methods

2.1. Participants

Four years of longitudinal data were collected on 74 adolescents (40 female). Participants were recruited from three Chicago-area public high schools. Participants were enrolled in the study during the summer before their freshman year of high school (average age at first test = 14.6 ± 0.4 years) and returned once a year over the next 3 years (average test–retest interval 344 days). Parental/guardian informed consent and adolescent informed assent were obtained prior to testing. All protocols and procedures were approved by the Northwestern University Institutional Review Board, and the participants were compensated for their participation.

At each test point, participants were screened to ensure that they met the inclusionary criteria, which included having no diagnosis of a reading, learning or neurological disorder, normal IQ (defined as a standard score ≥ 85 on the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)), normal hearing as defined by air conduction thresholds < 20 dB nHL for octaves between 125 Hz and 8000 Hz (ANSI, 2009) and an 80 dB SPL click-evoked wave V auditory brainstem response latency within lab-internal normal limits (5.24–5.99 ms). Year 1 test data were collected on an additional 14 participants, but these data were not included because of hearing loss (3 participants), failed IQ screening (1 participant), external diagnosis of a reading (2 participants) or learning (4 participants) disorder, and failure to return for testing in any or all of the subsequent years (4 participants).

2.2. Recording parameters

During data collection, the participant sat in a comfortable reclining chair in a soundproof, electromagnetically-shielded booth. Ag–AgCl electrodes were applied to the participant in an ipsilateral vertical montage (active electrode at Cz, reference electrode on the right ear, and ground placed on the forehead).

Individual electrode impedance was kept at ≤ 5 k Ω and inter-electrode impedance differences were maintained below < 3 k Ω . Stimuli included two variants of a consonant vowel stimulus (referred to as “long-da” and “short-da”, collected separately using NeuroScan and Bio-logic systems, respectively, described below) presented in alternating polarity at 80 ± 1 dB SPL to the participant’s right ear at a rate of 3.9 Hz (long-da) and 10.9 Hz (short-da). During the recording sessions, the participant watched a self-selected movie with the movie’s soundtrack presented in free field at < 40 dB SPL. The left ear remained unoccluded so that the participant could hear the movie’s soundtrack (see Skoe and Kraus, 2010 and Kraus, 2011 for details about the auditory brainstem response to complex sounds (cABR)).

2.3. Stimulus characteristics and response processing

2.3.1. Long-da

The long-da is a 170 ms speech sound. This stimulus is a six-formant syllable stimulus synthesized with a Klatt synthesizer (Klatt, 1980) at a 20 kHz sampling rate. During the first 5 ms the onset of the sound is marked by a short burst of broadband energy. The consonant–vowel formant transition begins at 5 ms and continues for 45 ms, during which the fundamental frequency (F_0) remains at 100 Hz, while the first formant increases from 400 Hz to 720 Hz, and the second and third formants decline from 1700 Hz and 2580 Hz to 1240 Hz and 2500 Hz, respectively. The steady state vowel lasts from 50 ms to 170 ms, during which the first three formants (F_1 – F_3) are steady at 720, 1240, and 2500 Hz. From 5 ms to 170 ms the fourth, fifth, and sixth formants are constant at 3330, 3750, and 4900 Hz, respectively. The long-da was presented in NeuroScan Stim² software (Compumedics; Charlotte, NC).

Responses to the long-da were processed off-line. First, the responses were bandpass filtered in Neuroscan Edit from 70 Hz to 2000 Hz (12 dB/octave, zero phase-shift), which captures the limits of brainstem phase-locking (Liu et al., 2006; Chandrasekaran and Kraus, 2010). Responses were segmented into epochs –40 to 190 ms referenced to stimulus onset and baselined to average prestimulus amplitude. Epochs with amplitude exceeding ± 35 μ V were rejected as artifact, and 6000 of the remaining artifact free trials were averaged to create the final responses. Fig. 1(A) displays the stimulus and response waveforms, with labels for the formant transition and steady-state regions.

2.3.2. Short-da

To demonstrate the generalizability of the change in the auditory brainstem response as a function of age and to replicate previous cross-sectional results (Skoe et al., 2013b), a 40 ms speech sound, ‘da’ (short-da) was also presented to seventy-one of the seventy-four participants (Fig. 1B). The short-da is a five-formant synthesized speech sound (Klatt, 1980) beginning with a noise burst that is followed by a formant transition between the consonant ‘d’ and the vowel ‘a’. Although the stimulus does not contain a steady-state vowel, it is still perceived as the syllable ‘da’. Over the 40-ms duration of the stimulus, there is a linear change in the F_0 and the first three formants (F_1 , F_2 , F_3): F_0 from 103 to 125, F_1 from 220 to 720, F_2 from 1700 to 1240, and F_3 from 2580 to 2500 Hz. F_4 and F_5 remain constant at 3600 and 4500 Hz, respectively. For the short-da, stimuli were presented and responses were collected with the Bio-logic Navigator Pro System (Natus Medical Incorporated, Mundelein, IL).

Responses to this stimulus were processed online. The responses were bandpass filtered from 100 to 2000 Hz. The recording window spanned –15 to 70 ms. Trials beyond ± 23.8 μ V were considered artifact and so were excluded from the running average. Two sub-averages of 3000 trials were collected. Because the effects of maturation on the response to short-da were similar to

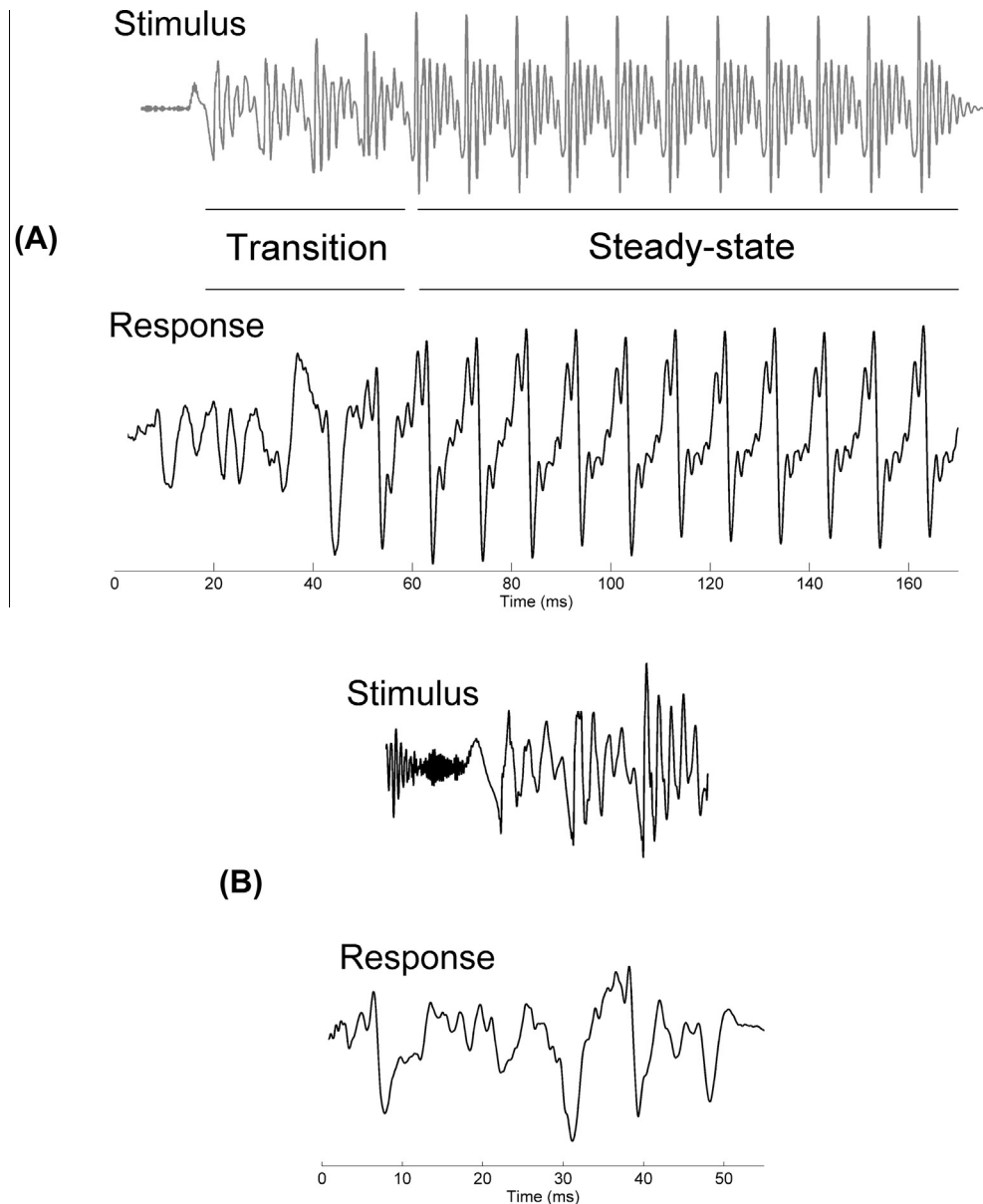


Fig. 1. (A) Long-da stimulus (top) and grand-average response across all participants in year 1 (bottom). Both the stimulus and response consist of a dynamic transition region followed by a static steady-state region. The stimulus was time-shifted to account for the time delay between presentation of the stimulus and generation of the response. (B) Short-da stimulus (top) and grand-average response across all participants in year 1 (bottom).

the maturation profile of long-da, descriptive and statistical values for the short-da analyses are presented in the text and tables, but figures demonstrating the developmental effect are shown for the long-da only. Three participants were not presented with the short-da and were, therefore, excluded.

2.4. Data analysis

2.4.1. Spectral amplitudes

2.4.1.1. Long-da. For the response to the long-da, a fast-Fourier transform (FFT) was run separately over the response to the transition (20–60 ms) and steady-state (60–180 ms). Over the transition, spectral amplitudes were calculated for 20-Hz bins centered on the fundamental frequency and its second (H_2) through sixth (H_6) harmonics (e.g. H_2 bin: 190–210 Hz), while 10 Hz bins were used over the vowel. The greater spectral stability that characterizes the response to the vowel allowed for a narrower sampling region to

be used for the steady-state relative to the transition (Fig. 2). Harmonic amplitudes beyond the sixth harmonic did not reliably exceed the noise floor and so were not considered in the analyses. The spectral amplitudes for H_2 through H_6 were averaged to create a composite harmonic amplitude value.

2.4.1.2. Short-da. In response to the short-da, an FFT was run over the 22–40 ms time range. This time range was chosen because it encompasses peaks D, E, and F, which occur during the frequency-following response to the transition. Two frequency bins were analyzed: 103–120 Hz, which includes the response to the fundamental frequency of the stimulus, and 455–720 Hz (Skoe et al., 2013b).

2.4.2. Inter-trial response consistency

Inter-trial response consistency was measured by calculating the Pearson product-moment correlation (r -value) between 3000

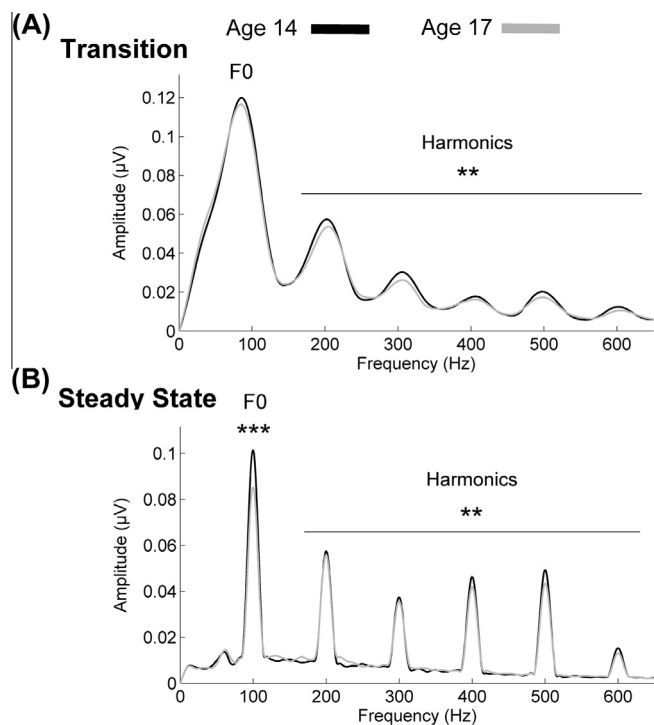


Fig. 2. (A) Spectral encoding in the response to the transition of long-da declined between age 14 (black) and age 17 (gray) as revealed through a longitudinal design. (B) Spectral encoding in the response to the steady-state vowel declined between ages 14 and 17. For each year, grand average data across all participants are plotted.

sweep sub-averages of the evoked response for each stimulus, where an r -value of 0 indicates that the sub-averages are entirely inconsistent, and an r -value of 1 indicates that the sub-averages are identical. For both stimuli, r -values were Fisher-transformed prior to data analysis to place the data on a normal distribution, while figures and tables display the actual r -values.

2.4.2.1. Long-da. Consistency of the response to the long-da for each subject was calculated by creating pairs of randomly-selected 3000-sweep averages. The mean correlation of 300 random pairs was computed for a composite response consistency score (Tierney et al., 2013). This procedure was run separately for the response to the transition (5–60 ms) and the steady-state vowel (60–180 ms).

2.4.2.2. Short-da. For the response to the short-da, inter-trial consistency was run by correlating a 3000-sweep sub-average of the first half of the recording with the 3000 sweep sub-average of the last half of the recording (Hornickel and Kraus, 2013) (this system does not save individual trial data, making the procedure used to calculate inter-trial consistency for the long-da not possible here). An inter-trial consistency value over the consonant–vowel transition (5–48 ms) was calculated.

2.4.3. Neural tracking of the stimulus amplitude envelope

The stimulus was filtered to match the brainstem response characteristics and recording parameters (70–2000 Hz) with a 12 dB/octave roll-off. The broadband envelopes of the stimulus and response were extracted using the Hilbert transform, and then these envelopes were low-pass filtered at 400 Hz. To calculate the similarity between the stimulus and participants' neural encoding of the envelope, a cross-correlation was performed by shifting the stimulus envelope relative to the response envelope to produce the maximum correlation. This procedure was only performed

for the long-da. Cross-correlation r -values were Fisher transformed prior to statistical analysis.

2.4.4. Response timing

Experienced, in-house peak-pickers used standardized peak-picking criteria (Hall, 2007) to identify latencies corresponding to peak maxima and minima for both stimuli.

2.4.4.1. Long-da. For the long-da, multiple positive peaks were identified in both the transition and the steady-state regions of the response. These peaks have previously been found to be highly replicable in individual participants and occur at approximately 43, 53, 63, 73, 83, 93, 103, 113, 123, 133, 143, 153, and 163 ms (Anderson et al., 2010).

2.4.4.2. Short-da. For the short-da, peaks occurring at 6.5, 7.5, 22, 32, 40, and 48 ms (labeled V, A, D, E, F, and O) were picked using methods described previously (Krizman et al., 2012). Peaks V and A correspond to the onset of the stimulus, peaks D, E, and F encode the consonant-to-vowel transition, and peak O is in response to the cessation of the stimulus. Except for V, all of the peaks of interest are local minima.

2.5. Statistical analyses

Analyses were carried out using customized software in MATLAB version R2012B (The MathWorks, Inc.; Natick, MA) and R (R Core Team, 2014, RStudio Team, 2014) using custom routines coded by AT, ES, and ABF. Year-to-year changes in neurophysiologic measures were determined for each dependent measure through repeated measures analysis of variance (RMANOVA) across the 4 years, using Huynh–Feldt-corrected p -values when Mauchly's test revealed that the assumption of sphericity was violated ($p < 0.05$). t -Tests between years 1 and 4 were conducted for all measures that showed a main effect of age in the RMANOVA. For all analyses, no interaction with sex was found (amplitude envelope $p = 0.081$, all other measures, $p > 0.1$), therefore, analyses were collapsed across males and females.

3. Results

3.1. Spectral amplitude

3.1.1. Fundamental frequency (F_0)

3.1.1.1. Long-da. Across adolescence, there was a change in fundamental frequency encoding in the steady-state response to the long-da ($F(3, 219) = 14.86$, $p < 0.001$). Paired t -tests comparing ages 14 and 17 confirmed that F_0 amplitude declined during adolescence ($t(73) = 6.268$; $p < 0.001$). However, in the transition region, the response to the F_0 did not change over the 4 years ($p > 0.2$) (Figs. 2 and 3). See Table 1 for mean F_0 amplitude across the 4 years.

3.1.1.2. Short-da. The response to the short-da F_0 amplitude also changed across the 4 years ($F(3, 210) = 6.064$, $p < 0.001$) showing a decline from age 14 to 17 ($t(70) = 3.704$, $p < 0.001$). See Table 1 for mean F_0 amplitude across the 4 years.

3.1.2. Harmonics

3.1.2.1. Long-da. Harmonic encoding changed over both the transition ($F(3, 219) = 5.42$, $p < 0.01$) and steady-state ($F(3, 219) = 5.89$, $p < 0.01$; Table 1, Figs. 2 and 3) response regions. Harmonic amplitudes decreased between ages 14 and 17 in both the transition ($t(73) = 3.410$, $p < 0.01$) and steady-state regions ($t(73) = 2.960$,

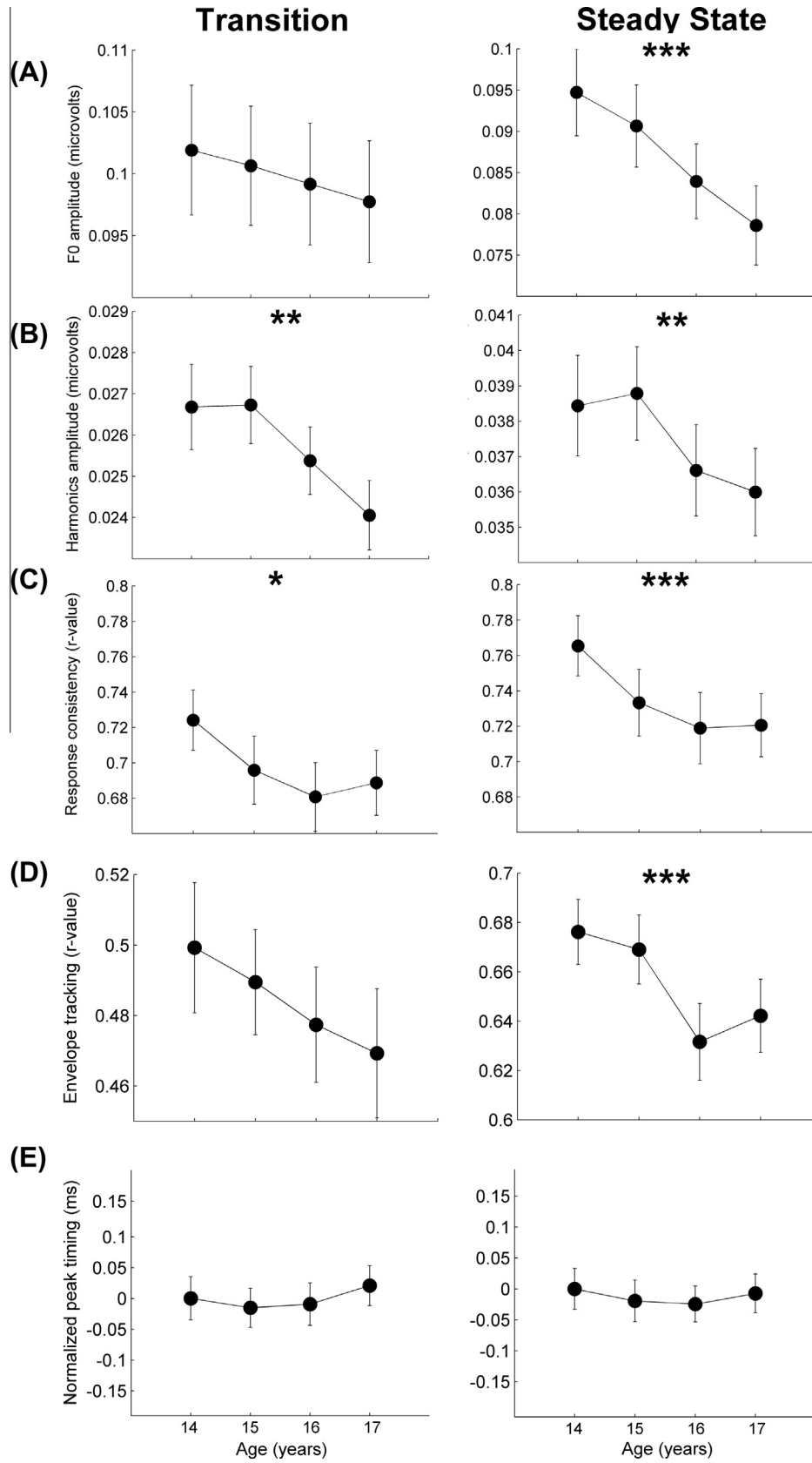


Fig. 3. Year-to-year changes in the response to the long-da transition (left) and steady-state (right). (A) Fundamental frequency encoding decreased with age in the response to the steady-state, but was more stable in the response to the transition. (B) Harmonic encoding decreased with age in both the steady-state and transition. (C) Consistency decreased with age in the response to the transition and steady-state. (D) Amplitude envelope tracking decreased with age for the steady-state only. (E) Response timing did not change with age. Error bars are one standard error of the mean. For data visualization, peak timing composite scores were calculated for the transition by averaging latencies for peaks 43, 53, and 63 and for the steady-state by averaging latencies for peaks 73, 83, 93, 103, 113, 123, 133, 143, 153, and 163. Composite timing scores were then normalized by subtracting the mean score for all participants in year 1.

Table 1
Mean spectral amplitudes (in microvolts) across years. Standard deviations are listed in parentheses.

	Spectral amplitudes (microvolts)			
	Year 1	Year 2	Year 3	Year 4
<i>Long-da</i>				
F ₀ transition	0.102 (0.045)	0.101 (0.041)	0.099 (0.042)	0.098 (0.042)
F ₀ steady-state	0.095 (0.045)	0.091 (0.043)	0.084 (0.039)	0.078 (0.041)
Harmonics transition	0.027 (0.009)	0.027 (0.008)	0.025 (0.007)	0.024 (0.007)
Harmonics steady-state	0.038 (0.012)	0.038 (0.011)	0.037 (0.011)	0.036 (0.011)
<i>Short-da</i>				
F ₀	0.104 (0.034)	0.096 (0.036)	0.095 (0.037)	0.091 (0.034)
Harmonics	0.014 (0.007)	0.014 (0.007)	0.013 (0.006)	0.013 (0.006)

Table 2
Mean response consistency (*r*) across years. Standard deviations are listed in parentheses.

	Response consistency (<i>r</i> -value)			
	Year 1	Year 2	Year 3	Year 4
Long-da transition	0.72 (0.14)	0.7 (0.16)	0.68 (0.16)	0.69 (0.15)
Long-da steady-state	0.76 (0.14)	0.73 (0.16)	0.72 (0.17)	0.72 (0.15)
Short-da	0.73 (0.13)	0.72 (0.14)	0.69 (0.14)	0.68 (0.17)

$p < 0.01$). See Table 1 for mean harmonic amplitude across the 4 years.

3.1.2.2. Short-da. For the short-da, harmonic encoding also changed across years ($F(3, 210) = 4.807, p < 0.01$). Consistent with the response to long-da, there was a decrease in harmonic spectral amplitude between ages 14 and 17 ($t(70) = 3.365, p < 0.01$). See Table 1 for mean harmonic amplitude across the 4 years.

3.2. Neural response consistency

3.2.1. Long-da

Consistency of the response to the transition of the long-da changed with age during adolescence ($F(3, 219) = 3.800, p < 0.05$, Fig. 3), decreasing between ages 14 and 17 ($t(73) = 2.773, p < 0.01$). Consistency of the response to the steady-state vowel also changed during adolescence ($F(3, 219) = 7.280, p < 0.001$), likewise dropping between age 14 and 17 ($t(73) = 4.43, p < 0.001$). See Table 2 for mean response consistency *r*-values.

3.2.2. Short-da

The consistency of the response to short-da showed a similar pattern to the long-da stimulus ($F(3, 210) = 2.774, p < 0.05$) such that response consistency declined from ages 14 to 17 ($t(70) = 2.734, p < 0.01$). See Table 2 for mean response consistency *r*-values.

3.3. Neural tracking of the amplitude envelope

3.3.1. Long-da

Neural tracking of the amplitude envelope in the transition of the long-da did not change with age during adolescence ($F(3, 219) = 1.26, p > 0.1$, Fig. 3). Neural tracking of the envelope in the steady-state vowel did change during adolescence ($F(3, 219) = 5.84, p < 0.001$), dropping between age 14 and 17 ($t(73) = 2.84, p < 0.01$). See Table 3 for mean envelope tracking *r*-values.

Table 3
Mean envelope tracking *r*-values across years. Standard deviations are listed in parentheses.

	Envelope tracking (<i>r</i> -value)			
	Year 1	Year 2	Year 3	Year 4
<i>Long-da</i>				
Transition	0.5 (0.159)	0.49 (0.12)	0.47 (0.14)	0.47 (0.15)
F ₀ steady-state	0.68 (0.113)	0.66 (0.12)	0.63 (0.13)	0.64 (0.12)

Table 4
Mean peak latencies across years. Standard deviations are listed in parentheses.

	Peak latencies (ms)			
	Year 1	Year 2	Year 3	Year 4
<i>Long-da</i>				
43	43.05 (0.49)	42.98 (0.37)	43.02 (0.43)	43.04 (0.37)
53	52.96 (0.27)	52.98 (0.25)	52.97 (0.27)	52.98 (0.29)
63	63.08 (0.31)	63.07 (0.24)	63.08 (0.27)	63.09 (0.25)
73	73.13 (0.29)	73.10 (0.25)	73.11 (0.27)	73.11 (0.25)
83	83.15 (0.28)	83.15 (0.27)	83.12 (0.23)	83.16 (0.28)
93	93.16 (0.28)	93.13 (0.26)	93.13 (0.27)	93.12 (0.27)
103	103.16 (0.28)	103.14 (0.25)	103.16 (0.27)	103.13 (0.31)
113	113.14 (0.27)	113.15 (0.29)	113.13 (0.26)	113.13 (0.27)
123	123.15 (0.28)	123.11 (0.27)	123.13 (0.26)	123.14 (0.28)
133	133.14 (0.27)	133.13 (0.31)	133.12 (0.26)	133.14 (0.27)
143	143.16 (0.29)	143.15 (0.33)	143.13 (0.26)	143.14 (0.27)
153	153.14 (0.28)	153.14 (0.31)	153.13 (0.29)	153.14 (0.28)
163	163.18 (0.29)	163.12 (0.34)	163.14 (0.29)	163.13 (0.29)
<i>Short-da</i>				
V	6.61 (0.25)	6.60 (0.25)	6.60 (0.25)	6.64 (0.25)
A	7.58 (0.33)	7.56 (0.33)	7.52 (0.29)	7.57 (0.31)
D	22.38 (0.44)	22.38 (0.46)	22.36 (0.39)	22.38 (0.44)
E	30.92 (0.42)	30.90 (0.37)	30.90 (0.39)	30.96 (0.41)
F	39.46 (0.41)	39.42 (0.33)	39.43 (0.38)	39.43 (0.35)
O	48.08 (0.31)	48.14 (0.35)	48.13 (0.27)	48.16 (0.35)

3.4. Peak Latency

3.4.1. Long-da

Latencies of the major peaks in the evoked response to long-da did not change with age for either the response to the transition or the steady-state vowel ($p > 0.1$, Fig. 3). See Table 4 for mean latency values across year for each peak in the response.

3.4.2. Short-da

Neural timing did not change with age in response to the short-da (all p 's > 0.1). See Table 4 for mean latency values across year for each peak in the response.

4. Discussion

We longitudinally tracked maturation of subcortical auditory function during adolescence. Cross-sectional evidence has shown that early childhood (i.e., 5–11 years of age) represents a period of heightened subcortical auditory processing relative to adulthood, where the early childhood evoked response is larger in amplitude, earlier in latency, and more consistent relative to the response seen in young adults (Skoe et al., 2013b). That the response seen in the child differs from the response seen in the adult led to the hypothesis that auditory brainstem function continues to mature through adolescence. Specifically, this cross-sectional finding suggests that adolescence represents a developmental period in which the larger, earlier, and more consistent child's response matures into a smaller, later, and less consistent response that is typically observed in adults. In line with this hypothesis, we demonstrate age-related changes in the frequency encoding, trial-by-trial consistency, and

speech envelope tracking of the evoked response over a short time frame during adolescence. Both the reduction in spectral encoding and decline in response consistency were pervasive, with effects observed across both stimuli tested. While a significant decline in spectral encoding in response to the transition of the long-da was only seen for the harmonics and not the F_0 , we still interpret this decline in encoding as pervasive given that the trend was for transition F_0 amplitude to decline with age and that F_0 amplitude significantly declined in response to the short-da (which consists of only a transition). An effect similar to that seen for F_0 encoding of the long-da was observed for the amplitude envelope tracking of this syllable. In contrast, changes in response latency during adolescence were not observed. Thus, our data provide nuance to the hypothesis that auditory brainstem function continues to mature during late childhood (i.e., 14–17 years), establishing that the malleability of auditory processing during this age range occurs for some aspects of the response (i.e., spectral encoding, consistency, envelope tracking), while other aspects appear stable (i.e., timing). The finding that not all features of the subcortical response are in flux during this age range suggests that the auditory brainstem response to complex sounds (cABR) contains components that can yield non-overlapping information about the development of auditory processing.

Early in development, maturation of the auditory system is characterized by increased myelination (Moore et al., 1995; Moore and Linthicum, 2007) and an over-proliferation of synapses (Kral and Sharma, 2012). These changes are presumed to drive developmental plasticity in the evoked response between birth and early childhood, leading to a response that is earlier, more consistent, and more robust in its spectral encoding relative to both the infant and young adult responses (Skoe et al., 2013b). We show that adolescence is a period of transition in which the response, over time, changes from one that is more child-like into a response that is more adult-like in that it is smaller in spectral amplitude and reduced in consistency. These changes in the evoked response likely reflect continued maturation of the structural and functional connectivity of auditory circuits during adolescence.

Changes in functional connectivity can occur through changes in myelination (white matter) and/or synaptic density (gray matter). However, within the 14–17 year old age range, gross measures of white matter volume appear to be stable (Pfefferbaum et al., 1994) suggesting that changes in white matter volume are not implicated in the changes observed here. Moreover, though subtle changes in white matter density can occur during adolescence (e.g., see Yeatman et al., 2014), these changes have been shown to enhance synchronicity and speed of the neural response (Zatorre et al., 2012), yet, as evidenced by a lack of change in latency during adolescence, our results suggest that speed of the response is unchanging over this age. Given that the auditory brainstem measures reported here are declining or unchanging, it is unlikely that these maturational effects are the consequence of changes in white matter density either. Instead, our results most likely reflect changes in gray matter. Specifically we suggest that the reduced consistency and amplitude of the response result from a reduction in synaptic density, as a result of synaptic pruning within the auditory system. Pruning of synapses is known to occur from late childhood through young adulthood (Chechik et al., 1998, 1999; Giedd et al., 1999; Paus, 2005; Kral, 2013) including within the auditory system (Kral and Sharma, 2012; Holcomb et al., 2013). While fewer extraneous cellular connections would produce a more temporally-synced pool of dendritic potentials, synaptic pruning could also remove redundant connections, which may then lead to a net reduction in response consistency and amplitude. Future work should test the possibility that synaptic pruning underlies the decrease in response consistency present in adolescence through the use of an animal model or investigate these changes in humans by using a combination of structural MRI and electrophysiology.

Moreover, it has been shown that performing a concurrent task can influence the subcortical evoked response (Hairston et al., 2013) and it is also known that attentional control mechanisms are developing over this age range (Anderson et al., 2001). Therefore, because the participants were doing a concurrent task (i.e., watching a movie), it is possible that maturation of online attentional control is also contributing to the changes in neural processing observed here. While the influence of maturation of attention cannot be conclusively ruled out from the present study, we would argue that the influence would be minimal since it has also been previously shown that the brainstem response is an obligatory evoked response that is relatively insensitive to subject state and can demonstrate inter-subject differences even when recorded on sleeping (e.g., Krishnan et al., 2005) or otherwise-engaged participants (e.g., Hornickel and Kraus, 2013). Nevertheless, future work that systematically investigates how the effects of movie-watching on the brainstem response change with age can specifically address this question.

In addition to arguing for a reevaluation of the maturational time course of the auditory brainstem, our results also suggest that enriched or diminished experiences later in childhood can have a larger effect on auditory function than previously believed (Skoe and Kraus, 2013a; Tierney et al., 2013). Given the assumption that plasticity of the nervous system declines dramatically beyond mid-childhood, previous studies of the auditory system have suggested an age of 7–10 years as the closing of a heightened period of malleability in response to experience. It has therefore been argued that exposure to certain experiences such as music or second-language learning must begin early in life for a child to realize the full potential of those skills (Asher and Garcia, 1969; Watanabe et al., 2007). That the auditory brainstem has not fully matured until the end of adolescence suggests that auditory enrichment begun later in childhood (e.g., ~14 years) could still lead to sizeable enhancements in auditory processing and alter developmental profiles. Future work assessing enrichment or impoverishment during adolescence can test this hypothesis.

Alternatively, or additionally to the proposed influence of gray matter plasticity, the reduction in neural response consistency and spectral amplitude with increasing age could result from increases in head size and skull thickness. Indeed, differences in head size have been shown to affect auditory-evoked potentials; however, these expected effects of head size are inconsistent with the pattern of results observed in the current study. Increasing head size has been shown to decrease the amplitude of the response and increase the response latency (Trune et al., 1988; Durrant et al., 1990). We do not observe changes in latency in the current study; moreover, there is no evidence to suggest that increases in head size would decrease inter-trial response consistency. Furthermore, changes in head size and skull thickness are relatively minor during normal adolescent development. Head growth has been shown to reach 90% of adult mass by age 6 (Eichorn and Bayley, 1962), while head growth is <1 cm in circumference from age 14 to 17 for both males and females (Eichorn and Bayley, 1962; Nellhaus, 1968). This change in circumference would result in a <0.0001% increase in total head volume over this time period. Therefore, it is unlikely that change in head size is a major contributor to these developmental changes; rather, we contend that these differences in the evoked response are the result of changes in the functional and structural connectivity of the auditory system during adolescence.

5. Conclusions

We demonstrate continued changes in auditory brainstem function between ages 14 and 17, which suggest continued

maturation of the auditory brainstem through adolescence. This finding is in contrast to the previously held belief that the auditory brainstem reaches functional and structural maturity by age 2 (e.g., Hecox and Galambos, 1974), but is consistent with recent cross-sectional evidence of a prolonged maturational time course of the auditory brainstem using coarser age sampling (Skoe et al., 2013b). We show that adolescent maturation of subcortical function is characterized by reductions in spectral amplitude, neural consistency, and speech envelope tracking but no change in peak latency. That not all aspects of the response change during this age range suggests that the auditory brainstem response to complex sounds (cABR) contains components that can yield non-overlapping information about the development of auditory processing. We propose that these changes result from refinement of functional circuits within the auditory system, most likely by pruning of irrelevant or redundant synapses. Future work in animal models can test this proposed model of adolescent development and future work in humans can identify if this extended maturational time course has implications for experience-based plasticity and perceptual abilities.

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