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Development of Auditory Phase-Locked Activity for Music Sounds

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Shahin AJ, Trainor LJ, Roberts LE, Backer KC, Miller LM. Development of auditory phase-locked activity for music sounds. *J Neurophysiol* 103: 218–229, 2010. First published October 28, 2009; doi:10.1152/jn.00402.2009. The auditory cortex undergoes functional and anatomical development that reflects specialization for learned sounds. In humans, auditory maturation is evident in transient auditory-evoked potentials (AEPs) elicited by speech or music. However, neural oscillations at specific frequencies are also known to play an important role in perceptual processing. We hypothesized that, if oscillatory activity in different frequency bands reflects different aspects of sound processing, the development of phase-locking to stimulus attributes at these frequencies may have different trajectories. We examined the development of phase-locking of oscillatory responses to music sounds and to pure tones matched to the fundamental frequency of the music sounds. Phase-locking for theta (4–8 Hz), alpha (8–14 Hz), lower-to-mid beta (14–25 Hz), and upper-beta and gamma (25–70 Hz) bands strengthened with age. Phase-locking in the upper-beta and gamma range matured later than in lower frequencies and was stronger for music sounds than for pure tones, likely reflecting the maturation of neural networks that code spectral complexity. Phase-locking for theta, alpha, and lower-to-mid beta was sensitive to temporal onset (rise time) sound characteristics. The data were also consistent with phase-locked oscillatory effects of acoustic (spectro-temporal) complexity and timbre familiarity. Future studies are called for to evaluate developmental trajectories for oscillatory activity, using stimuli selected to address hypotheses related to familiarity and spectral and temporal encoding suggested by the current findings.

INTRODUCTION

The auditory cortex undergoes developmental changes that reflect structural and functional specialization for sound processing (Hyde et al. 2009; Moore and Guan 2001; Moore and Linthicum 2007; Picton and Taylor 2007; Shahin et al. 2004). Understanding the course of auditory maturation, in particular highlighting milestones of functional auditory development in healthy individuals, will likely facilitate the diagnosis of developmental delays in hearing-impaired children (Ponton et al. 1996; Sharma et al. 2002) and children with language deficits and learning disabilities (Dykman et al. 1982; Lubar et al. 1992; Marosi et al. 1990; Warrier et al. 2004). Auditory maturation is influenced by the acoustical environment, including the particular sound features present and the level of exposure during different maturational periods. Rhythmic sounds, for example, can entrain the auditory response to oscillate according to the stimulus repetition interval (Gao et al. 2009). Also, infants rats exposed to environmental noise have delayed emergence of tonotopic maps in the primary

auditory cortex (A1) compared with infant rats exposed to the more structured pure tone stimuli (Chang and Merzenich 2003). Similarly, in humans, maturation of the auditory cortex is enhanced as a result of exposure to ecologically relevant sounds; musically trained children exhibit more mature auditory evoked potentials (AEPs), structural enhancement (increase in size of gray and/or white matter), and linguistic abilities than age-matched children with no musical training (Fujioka et al. 2006; Hyde et al. 2009; Moreno et al. 2009; Shahin et al. 2004). Most of us are exposed to music throughout the period of cortical maturation, which leads to well-characterized auditory representations for these sounds.

The time course of functional and anatomical maturation for sound processing is reflected in age-related changes in the latencies and amplitudes of the characteristic AEPs time-locked to acoustic stimuli (He et al. 2009a,b; Pang and Taylor 2000; Ponton et al. 2000; Sharma et al. 1997). However, although stereotyped AEPs show changes with maturation, they do not capture some important aspects of auditory functioning, notably the spectral and temporal course of the oscillatory activity of neural ensembles. EEG oscillations can be grouped into the following frequency bands: theta 4–8 Hz, alpha 8–14 Hz, beta 14–30 Hz, and gamma 30–100 Hz. The activity in each band may reflect different aspects of sound processing. For example, theta and gamma band oscillations have been associated with processing the temporal and spectral attributes of sounds, respectively. Theta band phase patterns can track the temporal envelope of spoken sentences (Ahissar et al. 2001; Luo and Poeppel 2007). In contrast, enhanced phase-locking and power of oscillations in the gamma band have been associated with increased spectral complexity of sounds (Shahin et al. 2008), memory matching in auditory (Lenz et al. 2007; Shahin et al. 2008) and visual (Herrmann et al. 2004) modalities, selective attention (Fries et al. 2001; Polley et al. 2006; Snyder et al. 2006), and long-range synchrony during music processing (Bhattacharya et al. 2001).

A hallmark of the early stages of normal development is that the power of spontaneous oscillations tends to shift from lower to higher frequencies (Bell 1998; Clarke et al. 2001; Marshall et al. 2002; Taylor and Baldeweg 2002) as we develop; delta (2–4 Hz) and theta power decrease, whereas alpha and beta power increase with age. A decrease in the higher frequencies with development can indicate abnormal development, as in children with dyslexia (Fein et al. 1986) and attention deficit disorder (Bresnahan et al. 1999). Of particular interest is how oscillatory phase-locking develops for the different frequency bands in response to music sounds. Phase-locking, studied here, represents the degree of temporal alignment of auditory responses to stimulus characteristics. Hence it shows how well

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stimulus attributes drive the neural response. Thus phase-locked oscillatory activity may index low-level aspects of auditory processing and may differ from spontaneous or induced activity that can be associated with higher-order or top-down processes (Deiber et al. 2007).

In a recent study of adult musicians and nonmusicians, the phase-locking of gamma band activity (GBA) was enhanced for music tones compared with pure tones for both groups, consistent with the role of GBA in processing spectral complexity. GBA phase-locking strength was also enhanced in musicians compared with nonmusicians, consistent with gamma's role in auditory memory (Shahin et al. 2008). In this study, we measured EEG during the presentation of piano, violin, and pure tones of the same fundamental frequency (f_0) and intensity in individuals between 4 and 25 yr of age. Oscillatory EEG activity evoked by these tones was subjected to phase and spectral power analyses. Phase-locking index (PLI) and spectral power were contrasted among age groups and tone types (piano, violin, pure) for theta, alpha, beta, and gamma band activity. Finding that different frequency bands show distinct maturational trajectories for a given sound would suggest that these frequency bands represent different aspects of sound processing. Distinct developmental trajectories for responses to music tones and pure tones, on the other hand, would suggest sensitive periods for processing different sound features or aspects of sound processing such as temporal variations, spectral complexity, and/or familiarity with musical timbres. We also charted the developmental trajectories for the peak amplitudes and latencies of the AEP component waves P1, N1, and P2 to compare with prior AEP developmental accounts.

METHODS

Subjects

Forty-six individuals between the ages of 4 and 25 yr participated in the study. Six were measured twice, with the second measurement occurring 2 yr later. The subjects were categorized into the following age groups: 4–5 ($n = 10$), 6–7 ($n = 8$), 8–9 ($n = 8$), 10–13 ($n = 8$), 14–17 ($n = 8$), and 18–25 yr ($n = 10$). Subjects who were tested twice over the span of 2 yr were included in a different age group for each measurement. Subjects were recruited from the Hamilton community and McMaster University. Before the experiment, information about their musical skills, listening habits, and the musical interest of their parents and siblings were collected. None of the subjects were practicing musicians or had formal musical training. Subjects gave written informed consent in accordance with the Research Ethics Board of McMaster University. For children under age 16, consent was also obtained from a parent.

Stimuli

Violin, piano, and pure tones were presented over a speaker placed 1 m in front of the subject at eye level. Tones were 500 ms in duration, and the interstimulus interval was fixed at 2.5 s offset to onset. The violin tones were taken from Kyma software and pitched to the notes A3 ($f_0 = 220$ Hz) and C3 ($f_0 = 131$ Hz) (American notation). The piano tones, also at A3 and C3 fundamental frequencies, were obtained from a Korg 01W synthesizer. Pure tones were created with a cosine envelope and matched to the fundamental frequency of the A3 and C3 music tones. The three types of tones differed in their temporal properties, primarily the shape of the sound envelope, and spectral properties, as reflected in different harmonic composition. For instance, the pure and piano tones had faster temporal onsets (~ 10 ms) compared with violin tones (>50 ms), whereas piano and violin tones

had a long offset compared with the pure tone. Also, violin and piano tones had a more complex spectral profile compared with pure tones. The temporal and spectral characteristics of tones are shown in Fig. 1.

Procedure

EEG was recorded from a 20-channel EEG cap (Neuromedical Quick-Cap, 10–20 system) using a Neuroscan Synamps amplifier (DC to 100 Hz sampled at 1 kHz). Reference and ground were Cz and AFz, respectively. The electrode configuration included fronto-temporal channels (FP₁, FP₂, Fz, F₃, F₄, F₇, F₈), centro-temporal channels (C₃, C₄, T₇, T₈), parietal channels (Pz, P₃, P₄, P₇, P₈), occipital channels (O₃ and O₄), and mastoids (M1 and M2). Electrode impedances were reduced to <10 kOhms using electrogel conductant. A total of 720 tones, equally distributed among type and f_0 , were presented in a single experimental session that lasted ~ 45 min. A passive listening protocol was followed during which subjects watched a silent movie. The six tones were presented in a pseudorandom order that was identical for each subject. Sound pressure level was set to 70 dB for all stimuli over a noise floor of 29 dB. Stimuli were judged to be of similar perceived loudness by psychophysical measurements taken from an independent group ($n = 10$) of nonmusician adult subjects before the study.

Data analysis

Using EEGLAB and in-house MATLAB code, continuous EEG files for each subject were average-referenced and epoched according to the tone type into 1,200-ms segments, which included a 500-ms prestimulus baseline. Trials containing amplitudes of ± 200 μ V or greater in any channel were rejected. The average number of trials (mean \pm SD), collapsing over the three tone types for the six age groups was 127 ± 46 (age 4–5), 118 ± 32 (age 6–7), 162 ± 38 (age 8–9), 171 ± 32 (age 10–13), 199 ± 33 (age 14–17), and 198 ± 24 (age 18–25) trials. Thus the number of trials tended to increase with age. However, trial number differences between tone types (pure, violin, piano) were much smaller—the mean difference between any two tone types for any age group was less than six trials. Two analyses were carried out: time-frequency and AEP analyses. Although AEP and time-frequency techniques may analyze the same activity, they can be differentially sensitive to, and therefore offer complementary perspectives on, its temporal and frequency dynamics. Here, for both analyses, data were collapsed across A3 and C3 tones for each stimulus type and subject to enhance the signal-to-noise ratio. Analyses involved all channels, but we focused on channels Fz and Cz, where auditory activity is maximally exhibited.

TIME FREQUENCY. In the time-frequency analyses, as implemented by EEGLAB (Delorme and Makeig 2004), spectrograms of intertrial

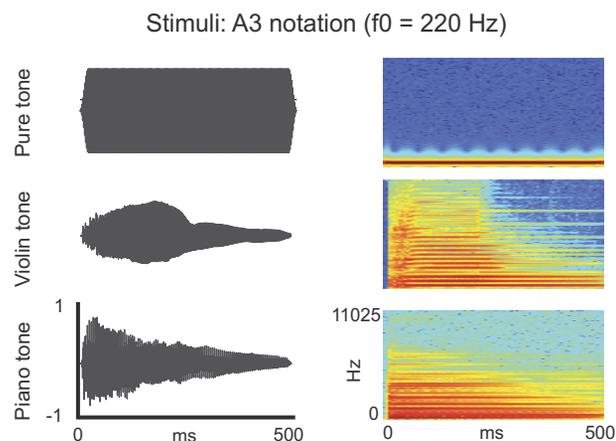


FIG. 1. The temporal profile and spectrograms of pure, violin, and piano tones matched in fundamental frequency (A3 American notation, $f_0 = 220$).

phase coherence (ITPC) and event-related spectral perturbation (ERSP) are generated. ITPC spectrograms represent the distribution of the phase-locking index (PLI) across time and frequency. It should be noted that PLI is a continuous measure ranging between perfect phase-locking (PLI = 1) or phase-independence (PLI = 0), although these limits are rarely reached. Enhanced phase-locking is indicative of the degree of temporal alignment of auditory responses to sound characteristics and does not imply enhanced neural population activity or enhanced synchrony between populations. The latter two factors can be indicated in the spectral power changes seen in the ERSP analyses. ERSP spectrograms represent the spectral power difference with respect to the time between poststimulus and prestimulus baseline activity, calculated as the log of the ratio of the two activities. In general and as specified here, ERSP refers to the average across spectrograms of all trials. Here, the ERSP analysis was conducted to show whether phase-locking changes were accompanied by spectral power changes.

Time-frequency (TF) analysis implemented by the *timef.m* function of EEGLAB spanned theta (4–8 Hz), alpha (8–14 Hz), lower-to-mid beta (14–25 Hz), and upper-beta and gamma (25–30 and 30–100 Hz, respectively) frequency bands. There were no significant gamma band effects >70 Hz, so gamma band examination was subsequently limited to the 70-Hz upper limit. Activities in the upper-beta and gamma bands, and similarly theta and alpha bands, were analyzed together because based on preliminary inspection they exhibited similar electrophysiological behavior. TF analyses used a sliding Hanning-windowed sinusoidal wavelet-based discrete Fourier transform (DFT) of the time-domain signal with a step size of ~5 ms and frequency increments of ~2 Hz. Poststimulus activity was baselined to the prestimulus interval of –500 to –150 ms to avoid smearing of prestimulus activity with the poststimulus activity. The sliding window was 256 samples (256 ms) in size at the lowest frequency (4 Hz, 1 cycle) and decreased in size, whereas number of cycles increased linearly with frequency, reaching 128 samples and nine cycles at the highest frequency (70 Hz). Given the 350-ms baseline duration (–500 to –150 ms), a one-cycle wavelet at the lowest frequency resulted in a floor frequency of 4 Hz (for a 256-ms window).

Peak analyses and permutation tests were used to compare age groups and tone types. Before further analysis, the ITPC activity was corrected for number of trials. PLIs tend to be higher for smaller number of trials (Fisher 1993). Here, the number of trials may especially become an issue when comparing activity from the youngest and oldest groups, which had an average trial difference of >70 trials. Effects caused by trial number can be remedied by baselining the poststimulus phase-locking activity to a prestimulus period equal in duration (Kolev et al. 2001) or by using the Rayleigh's *z* correction (Fisher 1993). For the current data, both of these methods yielded similar results, but we present the *z*-corrected data. To correct for number of trials, ITPC activity was *z*-transformed according to the following equation: $zPLI = n \times PLI^2$, where *n* is the number of trials and PLI is the phase-locking index for each time-frequency point of the ITPC spectrogram. Following the *z*-correction, the peaks of the *z*-corrected phase-locking index (zPLI), were obtained in four steps. 1) Individual zPLI time waveforms (zPLI temporal dynamics) were obtained for each subject by collapsing zPLI for each time point across all frequencies within each of the frequency bands. 2) The individual zPLI waveforms from *step 1* were averaged across all subjects in each of the age cohorts. 3) The zPLI peak latency from *step 2* was obtained for each age cohort at channel Cz. 4) The group zPLI peak latency values from *step 3* were used to obtain the zPLI peak amplitude values at these latencies for each subject, tone type, and frequency band. This way the individual zPLI values were driven by the age group maxima. A similar procedure was conducted for the spectral power (ERSP) analysis, with the exception that the spectral power peak values were based on the same peak latencies of the previous zPLI analysis. There was no need to correct for trial number

in the ERSP analysis, because it is always baselined to an average over the same number of trials.

AEPS. Individual data for each tone type were averaged, exported to MATLAB and filtered between 0.5 and 30 Hz using a zero-phase FIR filter. Latencies and amplitudes of the P1, N1, and P2 AEPs were measured at the frontal channel Fz where the P1 is known to reach its amplitude maximum (Shahin et al. 2004) and the vertex channel Cz where the N1 and P2 are known to reach their amplitude maxima (Shahin et al. 2003, 2004). First, each age group's mean data were plotted, and the peak latencies of the components of interest (P1, N1, P2) were chosen manually. These latency values were used in an automated windowing analysis, in which the latency and amplitude of the local maxima (P1, P2) or minima (N1) within ± 20 ms was determined for each individual's mean data and tone type at channels Cz for N1 and P2 and Fz for P1.

Statistical analysis

TIME FREQUENCY. zPLI and spectral power (ERSP) peak differences for each frequency band and across age and tone type were assessed by ANOVAs (Statistica v8, Statsoft) that were Greenhouse–Geisser corrected for sphericity violations. A group (6) \times tone type (3) design was implemented. Post hoc tests were based on Fisher's least significant difference (LSD) test.

In further analyses, permutation tests (Chau et al. 2004; Shahin et al. 2008) were used to identify time-frequency regions that showed significant differences between tone types for the *z*-corrected ITPC or ERSP spectrograms. Permutation-tested spectrograms have the advantage of showing differences between tone types across a range of frequency and time points and not just at the peak values as in the ANOVAs above. In this test, time-frequency points exceeding significance denoted time-frequency points where spectral power or phase-locking index values evoked by the first tone type (e.g., “piano” in “piano > pure” tone type) exceeded that evoked by the second tone type (depicted here with warm colors) or spectral power/zPLI evoked by the second tone type exceeded that evoked by the first tone type (cool colors). The threshold of significance was set at $P = 0.005$ and maximum resampling (2^n , where *n* equals the number of subjects in the comparison) was used (Good 2000).

AEPS. Latency and amplitude differences of AEPs were evaluated using ANOVAs that were Greenhouse–Geisser corrected for sphericity violations. ANOVAs were conducted for each AEP component (P1, N1, P2) and included the variables age group and tone type (piano, violin, pure). Post hoc tests were based on Fisher's LSD test.

RESULTS

The following analyses investigate the development of cortical representations for complex music tones with familiar timbres by examining the growth of oscillatory activity in different frequency bands between 4 yr of age and adulthood. In addition, we studied which frequency bands were sensitive to spectral information by comparing the activity in response to each music tone (containing many harmonics) to that of pure tones. We also studied the development of temporal onset encoding by contrasting responses to piano and pure tones, which have fast onsets, with responses to violin tones, which have relatively slow onsets (Fig. 1). Although the use of realistic music timbres precluded wide parametric control of acoustics, the contrasts outlined above provide beginning evidence on developmental trajectories for encoding temporal and spectral information.

Phase-locking analysis

Figure 2 shows the time-frequency developmental course for ITPC, using the piano tone condition as an example. Figure 2A shows z-corrected ITPC spectrograms at channel Cz for all age groups. Figure 2B shows the mean zPLI time course for each frequency band and age group at channel Cz and the corresponding scalp distribution at the zPLI peak latency. Notice from the spectrograms that phase-locked oscillations at the lower frequencies (approximately <20 Hz) exist for every age group and span a long time window after stimulus onset (~0–400 ms in the older groups). Higher frequency activity (>25 Hz) is mainly present in older age groups (>10 yr) and is confined to a short time window of 20–100 ms. Also shown in Fig. 2, and later in Fig. 5, maximum activity is confined to the fronto-central sites (e.g., Fz and Cz). There was also low-amplitude activity at inferior temporal electrodes in children, shifting posteriorly in adults. This response may reflect the same generator of the fronto-central (Fz, Cz) activity but of opposite polarity. Because of its low amplitude, it was not analyzed.

Figure 3A shows the permutation tested time-frequency spectrograms for tone type contrasts at channel Cz. In partic-

ular, the two music tones (violin and piano) are contrasted with pure tones and the piano and violin tones are contrasted.

LOWER BANDS (<25 HZ). For every age group, the zPLIs for theta, alpha, and to a lesser extent lower-to-mid beta (not as clear for the younger groups) were enhanced over the time period from about 100 to >200 ms for the spectrally complex music tones compared with pure tones, but these effects were strongest at ages >10–13 yr (Fig. 3A, *left 2 columns*). This suggests that spectral complexity influences activity in these bands. At the same time, differences can be seen between piano and violin tones in individuals 6 yr of age and older (Fig. 3A, *right column*). Because violin and piano tones differ in both temporal onset and details of the spectrum (see Fig. 1), and because piano tones are likely more familiar than violin tones, the cause of the enhanced responses to piano over violin tones, which seems to last from ~50 to 300 ms, is not clear. However, examination of the 0- to 100-ms time period of the piano/pure and violin/pure contrasts shows a clear temporal onset effect. In particular, phase-locking occurs earlier (~50 ms) for the pure tones (Fig. 3A, *middle column*, blue color) compared with the violin tones, the latter having much slower onsets than the former. Furthermore, the comparison of low-frequency phase-locking between piano and pure tones shows

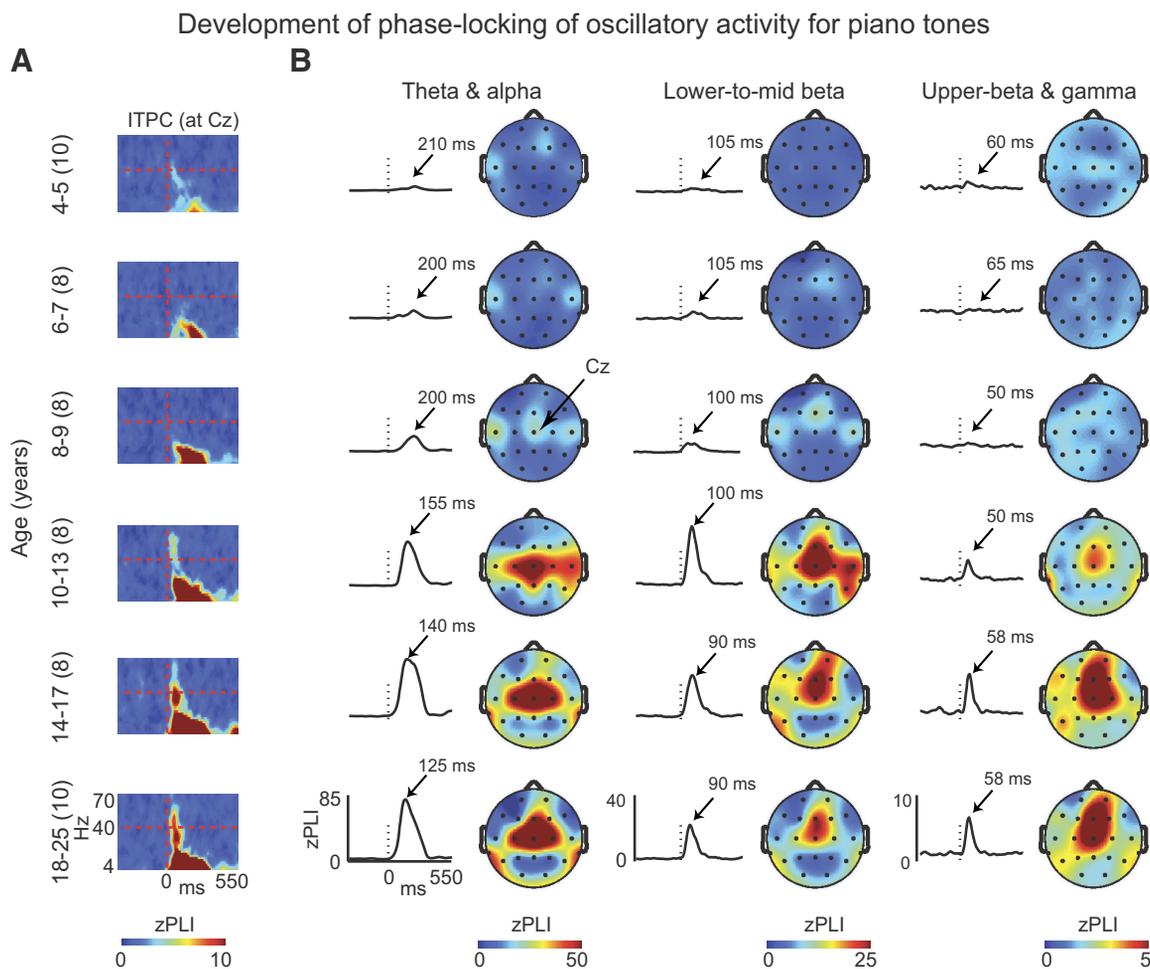


FIG. 2. *A*: mean z-corrected intertrial phase coherence (ITPC) spectrograms at channel Cz for each age group for piano tones. Horizontal lines represent the 40-Hz frequency mark. *B*: mean temporal course for z-corrected phase-locking index (zPLI) for each age group at channel Cz and frequency band and the corresponding scalp distribution at the peak latency values. Dashed vertical lines represent sound onset. Number of subjects per age group are $n(4-5) = 10$; $n(6-7) = 8$; $n(8-9) = 8$; $n(10-13) = 8$; $n(14-17) = 8$; $n(18-25) = 10$.

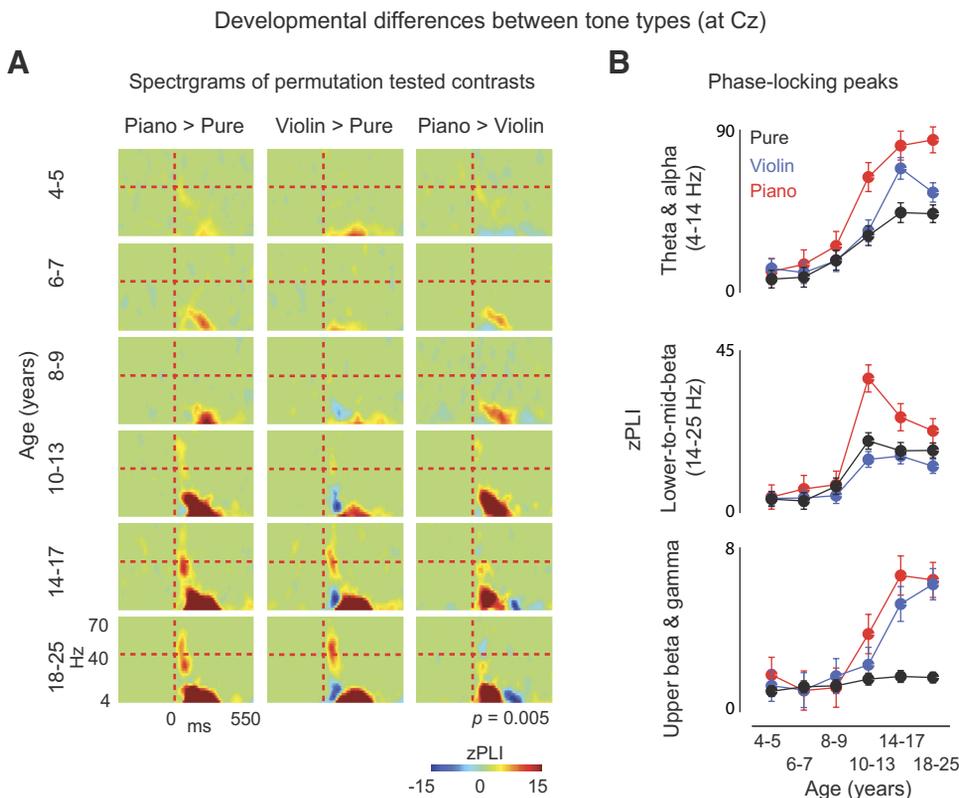


FIG. 3. *A*: mean permutation tested z-corrected ITPC spectrograms at channel Cz for each age group for piano > pure, violin > pure, and piano > violin tone contrasts. *B*: development of zPLI for theta and alpha, lower-to-mid beta, and upper-beta and gamma frequency bands at channel Cz, for piano, violin, and pure tones. Group means and SE are shown.

similar fast onsets. Together this suggests that low-frequency oscillations can be modulated by the temporal onset of the sound. In sum, for oscillations at the theta and alpha bands (<15 Hz), there is evidence that encoding of both spectral and temporal onset characteristics becomes enhanced with age.

HIGHER BANDS (<25 HZ). The permutation tests shown in Fig. 3*A* implicate spectral, but not temporal onset, encoding in high beta and gamma bands. Enhanced phase-locking for music tones relative to pure tones (Fig. 3*A*, left 2 columns) for upper-beta and gamma band (25–70 Hz) started at age 10–13 yr, was equally strong for violin and piano tones compared with pure tones, and occurred around the same time for both music tones. Furthermore, the direct contrast between piano and violin tones (Fig. 3*A*, right column) produced little activity in the upper beta and gamma frequencies, despite the different onset latencies and long-term temporal profiles of these tones (Fig. 1). Thus the permutation tests show little evidence for temporal encoding for high frequencies but strong evidence for spectral encoding.

A second analysis was done on the peak zPLI values shown in Fig. 3*B*. The time points of the peaks vary considerably across age and frequency, as can be seen for piano tones in Fig. 2*B*. Effects of tone type across age groups were examined by separate ANOVAs for each frequency band, with the amplitude at the zPLI peak as the dependent measure and age group and tone type as independent measures.

THETA/ALPHA BAND. An ANOVA on the zPLI peaks showed a main effect of age group ($F_{(5,46)} = 18.8, P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 62.7, P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 8.1, P < 0.0001$; Fig. 3*B*, top). Post hoc LSD tests ($P = 0.05$ or better) showed that significant age effects were mainly caused by enhanced phase-locking for the

oldest two groups (ages 14–17 and 18–25 yr) compared with the youngest two groups (4–5 and 6–7 yr). The middle age groups (8–9 and 10–13) exhibited transitional effects, with the age of transition dependent on tone type and frequency band. For example, the piano tones response transitioned to larger zPLI for ages 10–13 yr, whereas the response to violin and pure tones showed a transitional increase at ages 14–17 yr. Moreover, there was significant enhancement of zPLIs for piano tones compared with violin and pure tones for age groups older than 8–9 yr, whereas the violin tones zPLIs, compared with those of pure tones, were larger for the two older groups ($P < 0.05$). Thus at the peak of phase-locking activity, differentiation between tone types emerges after ~8–9 yr of age and seems to reflect primarily spectral characteristics, as activity is greater for music compared with pure tones, regardless of the onset rise time.

LOWER-TO-MID BETA BAND. An ANOVA on the zPLI peaks showed a main effect of age group ($F_{(5,46)} = 14, P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 33, P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 5.7, P < 0.0001$; Fig. 3*B*, middle). Post hoc LSD tests ($P = 0.05$ or better) showed that significant age effects were mainly caused by enhanced phase-locking for the oldest three groups compared with the youngest three groups, with the transition occurring between the 8–9- and 10–13-yr age period. The interaction was mainly caused by enhanced zPLIs for piano tones compared with violin and pure tones for age groups older than 8–9 yr, whereas the violin and pure tones did not differ in zPLIs at any age. Furthermore, zPLIs for piano tones peaked at age 10–13 yr, consistent with N1 and P2 AEP development. The enhanced response to piano tones compared with violin and pure tones is not consistent with either spectral or temporal enhancement alone. It might reflect an interaction between

these two sound characteristics, but it also could be caused by a familiarity bias for piano tones.

UPPER-BETA AND GAMMA BANDS. An ANOVA on the zPLI peaks showed a main effect of age group ($F_{(5,46)} = 8.4, P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 23.6, P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 5.7, P < 0.0001$). Post hoc LSD tests ($P = 0.05$ or better) showed enhanced zPLIs for piano and violin tones for the oldest age groups (>14 yr) compared with the younger age groups. The zPLIs for pure tones did not differ between any two age groups. The piano tones evoked larger zPLIs than pure tones for the oldest three age groups for piano and the oldest two age groups for violin tones. The piano and violin zPLIs only differed for the 10–13-yr age group, with piano evoking larger zPLIs. In sum, for upper-beta and gamma bands, spectral complexity seems to be the main feature that is encoded after age 8–9 yr.

Spectral power analysis

The spectral power (ERSP) of oscillatory activity was analyzed at channel Cz to see whether the enhanced phase-locking

seen in the ITPC analysis was accompanied by spectral power enhancement. Figure 4A shows the power spectrogram evolution with age for piano tones as an example. Note that most of the activity is <25 Hz, even for the older age groups, in contrast to the phase-locking analyses shown in Fig. 2A.

Figure 4B shows the permutation contrasts between tone types for each age group. Notice that piano tones exhibited larger spectral power for theta/alpha bands, and to a lesser extent lower-to-mid beta bands, compared with pure and violin tones for ages >10 yr. Violin tones exhibited larger spectral power for theta and alpha bands compared with pure tones for ages >14 yr (1 age group later than the piano $>$ pure comparison).

In a subsequent step, the spectral power peaks were contrasted for each frequency band in ANOVAs, with the independent variables being age group and tone type (Fig. 4C).

THETA/ALPHA BAND. An ANOVA on the spectral power peaks showed a main effect of age group ($F_{(5,46)} = 17.1, P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 40.6, P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 5.7, P < 0.0001$). Post hoc LSD tests ($P = 0.05$ or better) showed that significant age effects were mainly caused by

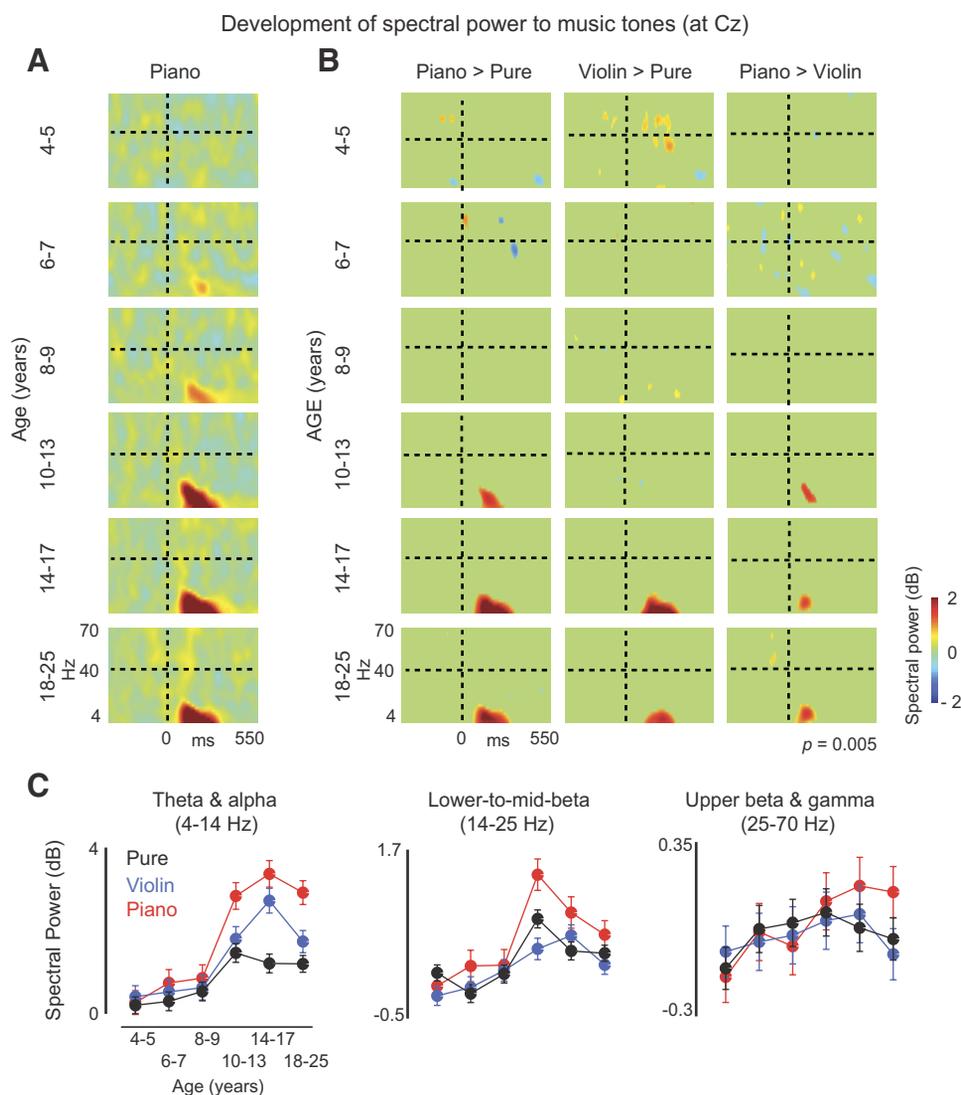


FIG. 4. *A*: mean event-related spectral perturbation (ERSP) spectrograms at channel Cz for each age group for piano tones. *B*: mean permutation tested ERSP spectrograms at channel Cz for each age group for piano $>$ pure, violin $>$ pure, and piano $>$ violin tone contrasts. *C*: development of peak spectral power for theta and alpha, lower-to-mid beta, and upper-beta and gamma frequency bands at channel Cz for pure, piano, and violin tones. The peak values for this analysis were taken at the same latencies as for the zPLI analysis (Fig. 2). Group means and SE are shown.

enhanced spectral power for the oldest three groups compared with the youngest three groups, with the largest transition occurring between the two periods: 8–9 and 10–13 yr. Moreover, there was a significant enhancement of spectral power of piano tones compared with violin and pure tones for age groups >8–9 yr (LSD test, $P = 0.05$ or better). The spectral power for violin tones, compared with that of pure tones, was larger for the two older groups (LSD test, $P = 0.05$ or better). Thus these results parallel those of the zPLI analyses.

LOWER-TO-MID BETA BAND. An ANOVA on the spectral power peaks showed a main effect of age group ($F_{(5,46)} = 9.7$, $P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 14.3$, $P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 2.6$, $P < 0.01$). Post hoc LSD tests ($P = 0.05$ or better) showed that significant age effects were mainly caused by enhanced spectral power for the oldest three groups compared with the youngest three groups, with the transition occurring between the periods of 8–9 and 10–13 yr. The interaction was mainly caused by enhanced spectral power for piano tones compared with pure tones for the 10–13- and 14–17-yr age groups and enhanced spectral power for piano tones compared with violin tones for the 10–13-yr age group. Spectral power for pure tones was larger than that of violin tones for the 10–13-yr age group. Peak power for piano tones was found at 10–13 yr of age. Again, these results largely parallel those of the zPLI analyses.

UPPER-BETA AND GAMMA BAND. The spectral power was quite low at all age groups, and an ANOVA on the spectral power peaks showed a borderline age effect ($P < 0.05$) and no main effect for tone type or an interaction between the variables ($F = 0.4$ or smaller). The age group effect was attributed to larger spectral power for age groups of 6 yr and older compared with the 4–5-yr age group. There were no differences between any two age groups above age 6 yr. This analysis contrasts the zPLI analyses, which showed large enhancements for the music tones compared with the pure tones above age 10–13 in the high-frequency range.

In short, this spectral power analysis showed that the enhanced phase-locking for the theta/alpha and lower-to-mid beta bands seen at older ages for music tones was also accompanied by enhanced spectral power. Furthermore, spectral power and phase-locking showed similar effects across pure, violin, and piano tones for these bands. However, the enhanced phase-locking in the upper beta and gamma bands was not accompanied by enhanced spectral power. Enhanced spectral power in the lower frequencies for music tones may indicate an increase in synaptic population (how many synapses are activated by the sound) or enhanced synchronicity in their firing (as with sharpening of the neural temporal response) within each trial. However, these two factors cannot be distinguished in EEG.

AEPs

Figure 5A shows the waveforms at channel Cz for piano, violin, and pure tones for all age groups. Topographies at the peak latencies for the P1, N1, and P2 components are shown for the piano tones as an example. Notice that the P1 was maximally exhibited frontally, whereas the N1 and P2 were maximally exhibited at the vertex. Figure 5B shows the evo-

lution of the peak latency and amplitude for each component and tone type.

P1. An ANOVA of the P1 latency showed an age group main effect attributed to decreased latencies with age for all tones ($F_{(5,46)} = 48.8$, $P < 0.0001$). There was also a tone type main effect ($F_{(2,92)} = 19.3$, $P < 0.0001$) and an interaction between age group and tone type ($F_{(10,92)} = 4.5$, $P < 0.0001$). The interaction was mainly linked to the P1 for violin tone occurring at longer latencies compared with P1 of piano tones for the 4–9-yr age group (post hoc LSD tests, $P = 0.05$ or better) with no differences for older groups. For the P1 amplitude, an ANOVA showed a main effect of age group ($F_{(5,46)} = 58.2$, $P < 0.0001$) related to decreased amplitude with age and a main effect of tone type ($F_{(2,92)} = 15.6$, $P < 0.0001$) caused by enhanced P1 amplitude for music tones compared with pure tones (Fig. 5B). There was no interaction between the variables ($F < 1.9$).

N1. An ANOVA of the N1 latency showed a main effect for age group ($F_{(5,46)} = 53.8$, $P < 0.0001$), a tone type main effect ($F_{(2,92)} = 24.9$, $P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 3.5$, $P < 0.001$). Post hoc LSD tests ($P = 0.0001$ or better) showed that the main effects were mainly caused by 1) a decrease of N1 latency with age across all tone types, with the largest difference occurring between the oldest and youngest two groups and 2) delayed N1 latency for the pure tones compared with piano or violin tones across all age groups. The interaction was attributed to longer N1 latency occurring for pure compared with music tones for the 4–9-yr age group (LSD tests, $P = 0.05$ or better) with no differences for older groups. For the N1 amplitude, an ANOVA showed a main effect of age group ($F_{(5,46)} = 195$, $P < 0.0001$), a main effect of tone type ($F_{(2,92)} = 15.6$, $P < 0.0001$), and an interaction between the variables ($F_{(10,92)} = 2.7$, $P < 0.01$). Post hoc LSD tests ($P = 0.0001$ or better) showed that main effect of age group was mainly attributed to enhanced N1 amplitude, across all tones, for the three oldest groups compared with the three youngest groups, with maximum amplitude occurring at age 10–13 yr. The main effect of tone type was caused by enhanced N1 amplitude for piano compared with violin tones (LSD test, $P < 0.0001$) across all age groups, with no difference between the N1 amplitude of the piano and pure tones. Finally, the interaction was mainly caused by larger N1 amplitudes occurring for piano and pure tones compared with violin tones for the youngest two age groups (LSD test, $P = 0.05$ or better). Also, the pure tones evoked larger N1s than violin tones for the 8–9-yr age group, whereas piano tones evoked larger N1s than violin tones for the 10–13-yr age group (LSD test, $P = 0.05$ or better).

P2. An ANOVA of the P2 latency showed an age group main effect ($F_{(5,46)} = 3.7$, $P < 0.01$), a tone type main effect ($F_{(2,92)} = 7.9$, $P < 0.001$), and an interaction between the variables ($F_{(10,92)} = 9.2$, $P < 0.0001$). Post hoc LSD tests ($P = 0.05$ or better) showed that the main effects were mainly caused by 1) a shorter P2 latency for the 4–5- and 8–9-yr age groups than for the other age groups across all tone types and 2) delayed P2 latency for the pure tones compared with piano or violin tones across all age groups. The interaction was mainly attributed to the pure tone P2 occurring at longer latencies compared with violin tones for ages 4–9 yr and shorter latencies for children

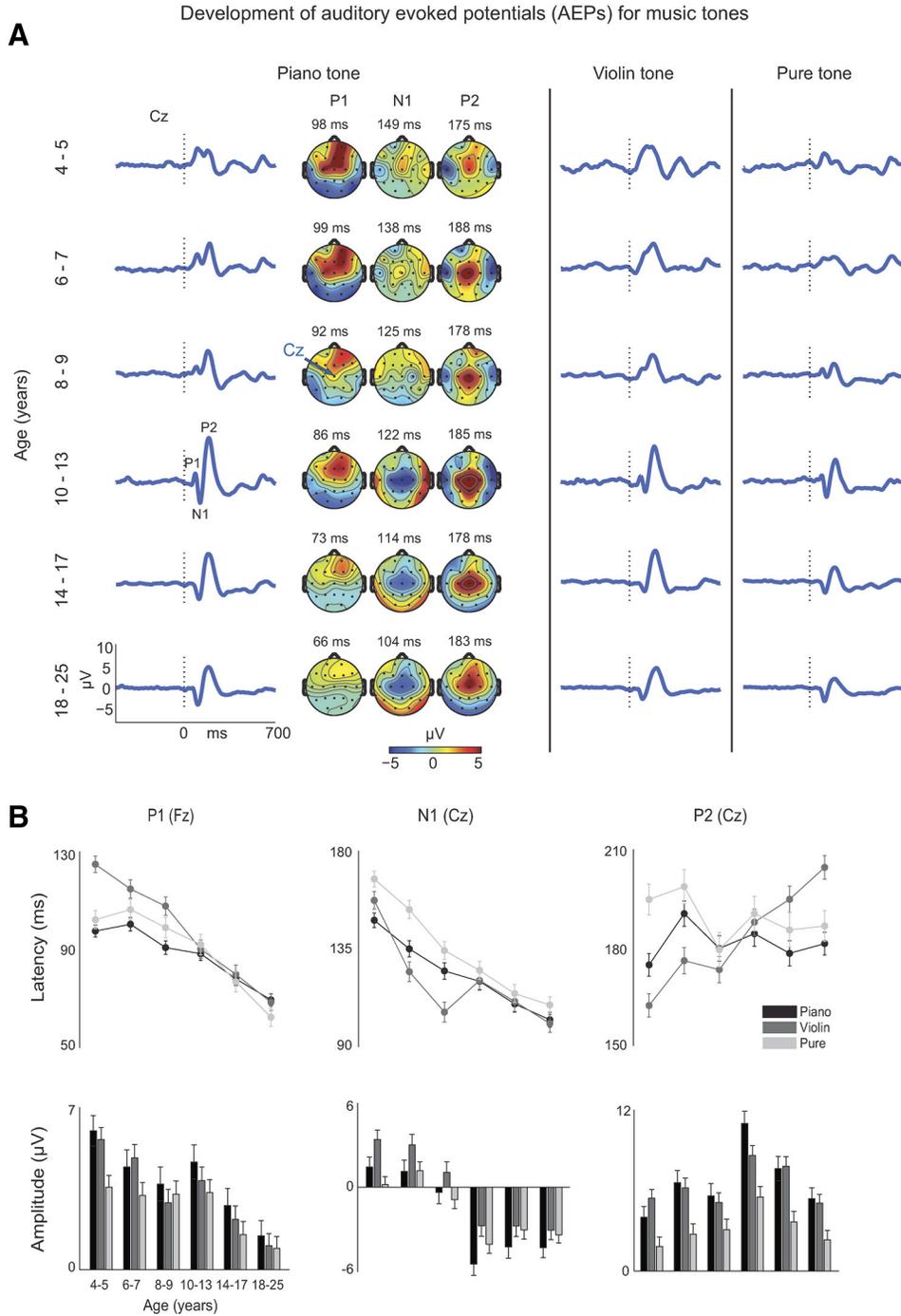


FIG. 5. *A*: *left*: group-averaged auditory-evoked potentials (AEPs) at channel Cz for piano tones and corresponding scalp distributions at the P1, N1, and P2 peak latency values. *Middle* and *right*: group-averaged AEPs at channel Cz for violin tones and pure tones, respectively. Dashed lines indicate sound onset. *B*: development of latency and amplitude of the P1, N1, and P2 peaks for all tone types at channels Fz for the P1 and at channel Cz for the N1 and P2 AEPs. Group means and SE are shown.

older than 14 yr (LSD tests, $P = 0.05$ or better). The piano tones evoked intermediate P2 latencies occurring between those of the pure and violin tones for the youngest two age groups (4–5 and 6–7 yr). However, piano tones had shorter latencies than violin tones for age groups older than 14 yr (LSD tests, $P = 0.05$ or better). In general, despite significant results for the development of the P2 latency, there was no clear latency trend with maturation for the pure and piano tones, whereas the P2 latency of the violin tone increased with age. For the P2 amplitude, an ANOVA showed a main effect of age group ($F_{(5,46)} = 6.5$, $P < 0.001$), a main effect of tone type ($F_{(2,92)} = 90.7$, $P < 0.0001$), and an interaction of age group and tone type ($F_{(10,92)} = 2.4$, $P < 0.02$). Post hoc LSD tests

($P = 0.05$ or better) showed that the main effects can be attributed to 1) larger P2 amplitude occurring for the 10–13- and 14–17-yr age group compared with the other groups across all tone types and 2) a greater P2 amplitude for music tones than pure tones across all ages. The interaction between the variables was attributed to the piano tones evoking larger P2 than violin tones only for the 10–13-yr age group (LSD test, $P < 0.0001$).

DISCUSSION

These findings showed that phase-locked brain responses for music sounds follow a well-defined course of development that

differs across oscillatory frequency bands. Across all frequency bands, phase-locking of oscillatory activity increased gradually through the youngest age groups, more rapidly across the mid-aged groups, and either remained constant or diminished slightly in the oldest age groups. The age of maximal increase was younger for the lower frequency (<25 Hz) bands (8–13 yr) and older for the higher frequency (>25 Hz) bands (10–17 yr). In general, the increase in phase-locking of oscillatory activity with age was larger for music tones than pure tones, suggesting that processing sounds with complex spectrotemporal structure becomes more refined with age.

The development of phase-locked activity followed different developmental trends in different frequency bands, likely reflecting functional differences in the sound properties encoded in these different bands. The lower-frequency bands (<25 Hz) showed sensitivity to the temporal onset of the sounds, manifested during the first 100 ms after sound onset. In particular, in age groups older than 7 yr, the tones with the fastest temporal onset slopes (piano and pure) showed earlier enhanced phase-locking in the theta, alpha, and low-to-mid beta bands compared with the tones with the slowest onset slope (violin; Fig. 3A), regardless of the sound frequency/spectral content. Theta's sensitivity to processing the temporal representations of sounds is noteworthy because it has been shown that theta band phase patterns can track the temporal outline of spoken sentences (Ahissar et al. 2001; Luo and Poeppel 2007). After 100 ms, violin and piano tones showed enhanced prolonged (~100–300 ms) phase-locking in the lower frequencies (<25 Hz) compared with the pure tones, and piano tones showed enhanced phase-locking compared with violin tones. These differences are more difficult to interpret. The enhancement for music tones suggests sensitivity to spectral content. However, the music tones also have more complex temporal envelopes (intensity) over time than the pure tones (Fig. 1), and the piano tones decay more rapidly than the violin tones. The contribution of temporal and spectral factors cannot be dissociated by the current stimuli and should be addressed parametrically in future studies with synthetic sounds.

Furthermore, the analyses of phase-locking peaks suggest differences between theta/alpha and low-to-mid beta bands. For theta/alpha in the older age groups, the greatest activity is seen for piano tones, followed by violin tones and then pure tones. However, for beta, only for piano tones is phase-locking greater than for pure tones; violin and pure tones do not differ. Although a definitive cause of these differences cannot be made, one possibility is that, with increasing age, lower-to-mid beta band phase-locking becomes particularly sensitive to familiar timbres. Piano tones are likely more familiar than violin tones. Also, although our participants were instructed to concentrate on the silent movie, the familiarity of piano sounds may have commanded the attention of participants to a greater degree than for violin or pure tones. Indeed, there is evidence that, if subjects exercise selective attention, oscillatory activity can become more temporally aligned to the attended stimulus (Bonte and Becker 2009; Kolev et al. 2001). For example, when individuals categorize stimuli based on type of vowel or the voice uttering the vowel, alpha band phase-locking is enhanced (Bonte and Becker 2009). At the same time, enhanced representations (e.g., phase-locking or spectral power here) in auditory memory in response to the familiar music tones can also occur without focused attention. For example,

out-of-tune or out-of-key tones can evoke a response in non-musicians with or without focused attention (Brattico et al. 2006; Trainor et al. 2002), suggesting that sound cues are matched to prior representations in auditory memory even during passive listening.

The development of phase locked oscillatory activity for higher frequencies (>25 Hz) followed a different trajectory than for the lower frequencies. First, compared with lower frequencies, phase-locking was much less evident in the higher bands before age 10–13, suggesting different underlying mechanisms. Second, phase-locked activity in the higher frequencies only lasted for ~100 ms after stimulus onset compared with 300 or 400 ms for lower frequencies. Third, phase-locking was greater for both piano and violin tones compared with pure tones, and there was no evidence that piano and violin tones differed. Given that violin and piano tones differ in their onset rise times and in their extended temporal envelopes, this strongly suggests that the phase-locked oscillatory activity that emerges >25 Hz in the older children is related to spectral complexity and not to temporal sound characteristics. It is unclear from these results whether the development of this functional role is more related to how the sound's spectral energy is structured ("harmonic structure"), the broadness of the frequency bandwidth, the presence of different frequencies in the sound, or all of the above. For example, there is evidence that high-frequency oscillations seen for music sounds are related to the identification of the "preferred" harmonic structure of the sounds. An animal study has shown that bat calls evoke gamma band activity in the auditory cortex that is attenuated when the calls are played backward in time (Medvedev and Kanwal 2008). Also, upper-beta and gamma oscillations may have been evoked by the high frequencies present in the music but not in the pure tones. Although N1 latency is known to decrease with increasing sound frequency, and also for music compared with pure tones (Shahin et al. 2004; Wunderlich 2001; and herein), the effects of higher frequencies on the phase-locking level for the upper-beta and gamma band oscillations remains to be tested in further studies. A robust evoked gamma band response is known to occur for 1,000-Hz pure tones (Pantev et al. 1991; cf. with our 130- and 220-Hz pure tones).

A remaining challenge is to explain the neural mechanisms that underlie these developmental changes in electrophysiology. Auditory maturation encompasses several neurodevelopmental processes that start prenatally and continue through various periods postnatally (Marsh et al. 2008). These processes are apoptosis (programmed cell death), synaptogenesis (the formation of new synapses), cortical myelination, and synaptic pruning. The onset and end of these processes varies between brain regions. Generally, apoptosis ends at about the same age as the youngest group of this study (4–5 yr), so it is unlikely that it contributes substantially to the developmental changes in phase locked oscillatory activity seen in these results. In contrast, synaptogenesis terminates around puberty, whereas myelination continues through adolescence (Marsh et al. 2008). Toward the end of synaptogenesis, a period of synaptic pruning begins and extends through adolescence (Bourgeois and Rakic 1993; Zecevic and Rakic 1991). Synaptic pruning is a process that can increase neural efficiency by eradicating "noisy" synapses that contribute to temporal jitter and synapses that are not useful.

The developmental trajectories seen here show the greatest increase in phase-locking of oscillatory activity around 10–13 yr of age for frequencies <25 Hz. This parallels the maturation of synaptic connections in the superficial layers of auditory cortex, which starts around age 5 and concludes at ~12 yr of age (Moore and Guan 2001; Moore and Linthicum 2007). This age span also corresponds with improvement in language abilities and may indicate sensitive periods for language development (Moore and Guan 2001; Moore and Linthicum 2007; Ponton et al. 2000). Effects of musical training on AEP components are also greatly reduced when the training begins after ~10–12 yr of age (Pantev et al. 1998; Trainor 2005), implying that there might also be a similar sensitive period for musical development (Trainor 2005). Enhanced phase-locking for the lower frequency (<25 Hz) bands in music compared with pure tones was accompanied by spectral power enhancement in older age groups (Fig. 4). Thus maturational changes in these frequency bands may also reflect functional tuning of a neural population to familiar sound characteristics (Okamoto et al. 2007) or even structural changes leading to an enhanced number of synapses across neural circuits (Hyde et al. 2009). Upper-beta and gamma band oscillations were less evident before age 10–13 yr (Figs. 2A and 3A), suggesting that the mechanisms underlying this activity are largely dependent on maturation of the superficial auditory layers.

Previous studies of AEP development suggest that the decrease in AEP latency with age is largely a result of enhanced myelination (Picton and Taylor 2007; Poulsen et al. 2007). The same may be true of the theta and alpha bands latency shifts seen in the present paper (Fig. 2), because activity at these frequencies may contribute to AEP responses. It should be noted that the latency shifts seen in the current AEPs, mainly the P1 and N1, persisted beyond age 18 yr. This is in contrast to the findings of Ponton et al. (2000), which show leveling off of the latency decrease around age 18. However, our results are in accordance with recent evidence for P1 and N1 latency shifts persisting well into middle age (Poulsen et al. 2007) and with evidence for continued myelination and increased white matter density beyond the fourth decade of life (Benes 1998; Good et al. 2001).

Whereas myelination may be responsible for decreases in latencies of P1 and N1 with age, changes in response amplitude or the strength of phase-locking may be more related to synaptogenesis and synaptic pruning. In this study, the N1 amplitude was much smaller in young children compared with those 10 yr and older, including adults. In young children, the AEP complex consisted mainly of the P1 and P2 components. A previous study (Moore and Guan 2001), summarized in Eggermont (2008), showed that layer II and III axons in the auditory cortex, which generate negative scalp polarities as for the N1, were immature in 5 yr olds but had matured by age 12. The axons in deeper cortical layers responsible for generating positive deflections, as in P1, were mature by age 5. Thus axonal maturation in superficial layers may explain the P1/N1 amplitude trade-off with age. The same process may contribute to enhanced phase-locking that occurred with age in all of the frequency bands studied here, reflecting factors such as (but not limited to) the number of synapses activated, spatial summation of synaptic activity, temporal synchronization of synapses, and how the activated neurons are aligned (Picton and Taylor 2007). Assuming that synaptic pruning removes asynchronous or inefficient synapses (Bourgeois and Rakic 1993; Zecevic and Rakic 1991), pruned neural networks

should fire more synchronously and show both increased AEP amplitude and increased phase-locking power (especially in higher frequencies) in response to music tones. Enhancement of the N1/P2 and phase-locking for all frequency bands seen for piano and violin tones between 8–9 and 10–13 yr may be correlates of a sensitive period for this maturational neuronal efficiency.

Because AEPs can be reflected in the slow oscillatory activity, the abrupt enhancement of N1 and P2 between age 8–9 and 10–13 yr may be partly attributed to the abrupt phase-locking enhancement for the low-frequency oscillatory bands seen for this age span. It is also noteworthy that the maturational trend of the lower-to-mid beta follows a similar trajectory as for the N1 and P2 amplitudes, in which activities peak around age 10–13 yr of age and diminish afterward. This raises the possibility that what we interpret as phase-locking for this frequency band may reflect lower temporal jitter of the N1/P2 peaks across trials. This trend was not clear for the other frequency bands.

Although we may attribute the development of AEPs and oscillatory activity to anatomical and functional changes in specific generators along the auditory thalamo-cortical pathway (Ponton et al. 2000), maturation of oscillatory dynamics may also reflect the evolution of how auditory networks communicate. Communication between assemblies is essential to binding of sensory information. A role in communication for upper-beta and gamma activity is favored by our finding that spectral power in the upper-beta/gamma range is not enhanced with age (Fig. 4), although phase-locking is (Fig. 3). Beta may be distinguished from gamma by its role in facilitating long-range synchrony between neocortical regions as opposed to gamma activity, which reflects synchrony between local assemblies (Kopell et al. 2000; Roelfsema et al. 1997). Long-range synchrony is especially essential during multimodal integration. Kopell et al. (2000) noted that beta oscillations have more tolerance for large conduction delays (~10 ms) than gamma band oscillations and hence may reflect improved synchronization between distant assemblies. Furthermore, changes in the oscillatory activity may also reflect the maturation of a hierarchical oscillatory system, in which lower frequency phase activity modulates higher frequency amplitudes to control neural excitability during stimulus processing (Lakatos et al. 2005). It has been shown that alpha and theta phase can enhance postsynaptic efficiency by controlling the co-occurrence of high-frequency (e.g., gamma band) spikes, thereby minimizing high-frequency adaptation (Canolty et al. 2006; Fries et al. 2001).

In summary, these findings offer strong evidence for maturational changes evoked by music sounds and suggest that developmental trajectories are influenced by the spectral and temporal profile and/or familiarity of sounds. Further studies using stimuli targeted at specific hypotheses raised by these findings should be conducted to assess the influence of sound parameters on the development of oscillatory brain activity.

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