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Neural processing of auditory temporal modulations in awake infants

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Abstract

The Amplitude Modulation Following Response is the steady-state auditory response signaling phase-locking to slow variations in the amplitude (AM) of auditory stimuli, that provide fundamental acoustic information. On a developmental perspective, the AMFR has been recorded in sleeping infants, compared to sleeping or awake adults. The lack of AMFR recordings in awake infants limits conclusions on the development of phase-locking to AM. Moreover, previous studies assessing phase-locking to AM using non-speech carriers have not included slow AM rates (<20 Hz), which are particularly important for speech processing. This study aimed at disentangling these issues by recording the AMFR with electroencephalography: in awake infants (3- and 10-month-olds) and awake young adults; for both slow and faster modulation rates (8 Hz and 40 Hz). The AMFR was observable at 8 Hz at all ages (40%, 60%, 33% of significant AMFR at 3 months, 10 months and adults, respectively), but only adults showed reliable responses at 40 Hz (6% of significant AMFR at both 3 and 10 months, 100% in adults), thus ruling out the possibility that sleep has a suppressing effect on the response. This pattern might be explained by developmental differences in the sources of neural processing of faster AM rates.

I. INTRODUCTION

Auditory processing is thought to result from the action of a series of filters extracting spectral information from high to low frequencies within the peripheral auditory system, the cochlea (Moore, 2004). At the output of cochlear filters, sounds are then modeled as a series of narrowband signals modulated in amplitude over time. In each narrowband signal, changes in amplitude can be further decomposed. Specifically, two important time scales have been identified: a relatively fast one, corresponding to frequency modulation (FM) cues, and a relatively slow one, amplitude modulation (AM) cues (Drullman, 1995; Shannon et al., 1995).

AM processing can be modeled as the operation of a central bank of modulation filters (Dau et al., 1997) organized in neural sites that are thought to be selectively tuned to specific AM rates (Giraud et al., 2000; Joris et al., 2004; Kim et al., 2020; Liégeois-Chauvel et al., 2004).

The processing of AM information is fundamental in auditory perception (e.g., Joris et al., 2004), crucial for speech perception (Drullmann, 1995; Shannon et al., 1995) and for the mechanics of cochlear implants. However, the early development of AM processing in humans is not yet fully characterized.

Behavioral studies have shown that young listeners always exhibit worse AM sensitivity when compared to adults (Hall and Grose, 1994; Walker et al., 2019). However, other studies also showed similar effects, in infants and adults, of AM rate on AM detection thresholds. Specifically, when measuring 10-Hz AM detection thresholds, 3-month-old infants have been shown to require about 10 dB more of AM depth than adults (Walker et al., 2019) when tested with a narrow-band noise carrier. This notwithstanding, the cut-off frequency of the Temporal Modulation Transfer function (TMTF, the empirical function relating AM detection to the modulation frequency of the stimulus), was not different between infants and adults, showing analogous temporal resolution (i.e., the limit in the auditory system's ability to follow AM fluctuations as these become faster). The finding of adult-like temporal resolution despite worse AM detection in very young listeners supports the hypothesis that developmental differences in AM detection may not preponderantly relate to the maturation of

sensory coding for AM cues (which seems to be early attained), but rather to ‘processing inefficiencies’, i.e., lesser efficiency in the use of successfully extracted AM information in younger listeners (Cabrera et al., 2019; Dau et al., 1997).

Electroencephalography (EEG) offers the opportunity to look into these processing differences at the neural level. In particular, EEG can measure the auditory brain activity following the modulation rate of sinusoidally amplitude modulated tones (Picton et al., 2003). This response, the so-called Amplitude-Modulation Following Response (AMFR), or Envelope-Following Response (EFR), is phase-locked to the amplitude envelope of auditory stimuli. As such, it describes the auditory response that encodes the periodicity of the temporal envelope.

The AMFR was measured in 1-month-old infants and adults in a series of pioneering studies (Levi et al., 1993, 1995). In particular, it was recorded for modulations ranging between 20 and 80 Hz, in sleeping infants as compared to awake adults. The largest response (i.e., the stronger AMFR relative to background neural noise) detected in sleeping infants and sleeping adults corresponded to modulations of 80 Hz; conversely, the largest responses detected in awake adults corresponded to modulations of 40 Hz. Thus, sleep, either natural or chemically induced, has a significant effect on the AMFR in adults (Levi et al., 1993, Picton et al., 2003).

A second study presented sleeping 1-month-old infants AM tones with carrier frequencies of 500, 1000, or 2000 Hz modulated at 80 Hz and the same tones modulated at 40 and 80 Hz to adults (Levi et al., 1995). The results showed no difference between infants and adults for 500 and 1000 Hz carrier frequencies. However, infant’s AMFRs relative to background neural noise was smaller than adults’ for the highest carrier frequency (2000 Hz). This suggests that, although robust phase locking to the sound envelope is observed by 1 month of age, age-related differences in the AMFR can be detected, depending on the carrier frequency.

Finally, a study comparing the AMFR evoked by AM-white noise (i.e., a broadband noise sinusoidally modulated in amplitude) obtained in naturally sleeping newborns versus sedated 2-year-olds showed developmental changes in response morphology and improvements in AMFR detectability against

background noise between the rates of 20-200 Hz (Nodarse et al., 2012). In fact, a 40Hz-AMFR was not reliably observed until 2 years of age in some studies, with its magnitude increasing with age (Nodarse et al., 2012; Pethe et al., 2004).

Crucially, in all EEG experiments mentioned above, infants were asleep. This was done to ensure cooperation during long experiments. However, knowing that sleep influences AMFR responses in adults (Levi et al., 1993), it is necessary to test the AMFR in awake infants, thus allowing a more reliable comparison of the responses observed at different ages. Furthermore, only AMFRs for high rates of modulations (> 20 Hz) have been recorded in infants, so far, in spite of the fact that slower AM rates are known to be particularly important for speech perception (Shannon et al., 1995). Cortical tracking to slower AM rates in infancy have been reported by studies assessing phase-locking to AM of the speech signal (ex., Ortiz Barrajas et al., 2021; Attaheri et al., 2022), which provided important evidence that infants track the envelope of continuous speech at different time scales (at least, at the level of sentence prosody ~ 2 Hz, and at the syllabic level ~ 4 Hz). These investigations, in particular, contributed clarifying the abilities of the infant's brain to track speech temporal cues. However, it is important to note that the underlying auditory mechanisms of this ability are not yet fully understood yet. Exploring the AMFR with non-speech sounds, on the other hand, allows to assess AM tracking for highly controlled acoustic stimuli. In fact, using pure tones as an AM-carrier entails only AM fluctuations specific to a given rate and stimulates only a given region on the basilar membrane. This allows to draw specific conclusions on the development of the auditory mechanisms involved in general AM tracking, whereas studies conducted with speech stimuli cannot, as speech carriers are more complex in their spectrum and contain temporal fluctuations at different rates (i.e., AM and FM).

To sum up, the aim of the present study was twofold: 1) to compare AMFRs in infants and in adults while using the same experimental conditions (all participants awake), and 2) to compare the AMFR obtained with slow versus faster modulation rates. Specifically, we measured AMFR in awake infants and adults at two modulation rates: 8 vs 40 Hz, using a pure tone carrier of 1000 Hz, carrier frequency which, based on the literature, should elicit a response in both infants and adults (Levi et

al., 1993; Savio et al., 2001). The (slow) modulation frequency of 8 Hz was selected because previous literature has shown strong links between this frequency range and speech perception. Indeed, strong degradation of performance in speech perception in quiet has been shown when speech stimuli are vocoded by filtering modulation frequencies including and above 8-10 Hz (Drullman, 1995). Moreover, evidence has been put forward of a relationship between AM detection thresholds as measured using non-speech stimuli modulated at 8 Hz and speech in noise perception abilities (Cabrera et al., 2019).

The present experiments focused on infants of 3 months because this is the earliest age at which infants have been shown (behaviorally) to have similar TMTF to those of adults (Walker et al., 2019), suggesting adult-like temporal resolution and AM processing. Additionally, we also recruited a group of 10-month-old infants, with the goal to investigate the maturation of the AMFR during the first year of life and, particularly, in a period of intense linguistic development (Werker et al., 1984). Indeed, between 3 and 10 months of life, infants undergo a process of perceptual reorganization resulting in the fact that they become, as adults, better able to process the speech sounds that belong to their native language(-s), while at the same time decreasing precision in processing speech sounds that do not belong to their native language. This process is crucial for linguistic development (Kuhl, 2004) and is underpinned by reorganization in the neurofunctional treatment of native versus non-native speech sounds (Minagawa-Kawai et al., 2007). Thus, observing the characteristics of the AMFR to a target frequency relatively to background noise (i.e., signal-to-noise ratio, SNR) in awake 10-month-olds can also shed light on the effectiveness of the AM processing skills that are available to human infants during such crucial tuning to the speech signal.

In a first experiment, three groups of participants (one group of 3-month-old infants, one group of 10-month-old infants, and one group of adults) were presented with AM tones played at 65 dB SPL (sound-pressure level) in free field. All participants were awake. In a second experiment, we manipulated the intensity level of stimulus presentation. Specifically, intensity was increased up to 75 dB SPL for a new group of 3-month-old awake infants to assess whether intensity levels could

influence the neural response to the target AM rates (Cone & Garinis, 2009). Apart from the intensity difference, the recording procedure was the same as in the first experiment. Our hypotheses were as follows. If the infant auditory system is sensitive to both slow and fast AM fluctuations from early on, we should observe similar AMFR-SNR in the three age groups (3-month-olds, 10-month-olds and adults), at both 8 and 40 Hz modulations. Inversely, if temporal auditory processing takes a long time to develop, we should observe an effect of age on the strength of AMFR (characterized by a higher SNR) at both rates. Specifically, if differences are observed between slower versus faster AM rates, this could relate to the development of sensory processing coding for temporal information. In other words, if smaller AMFR-SNR for faster AM rates are only observed in infants as compared to adults, this might be due to limited temporal resolution; but if smaller AMFR-SNR are observed in infants irrespectively of AM rate, this could rather relate to the development of higher stages of auditory temporal processing (e.g., changes in the neural transmission of temporal information along the auditory pathway enhancing processing efficiency with age).

II. EXPERIMENT 1

A. Methods

1. *Participants*

Three different age groups of 15 participants each took part in the present study: 3-month-old infants (aged between 2 months 16 days and 3 months 22 days, mean age = 3 months, sd = 12 days; 9 female); 10-month-old infants (aged between 9 months 11 days and 10 months 5 days, mean age = 9 months 22 days, sd = 8 days, 7 females); young adults (aged between 20 and 30 years; mean age = 23.2 years, sd = 2.8 years; 14 females). Group size was decided according to previous studies recording the AMFR in young infants (e.g. Cone & Garnis, 2009, Levi et al., 1993, Nodarse et al., 2012). Informed consent forms were obtained from all infants' legal guardians and adult participants.

All participants were raised in monolingual French families (exposed less than 10% of the time to an additional language than French). All infants were born full term (> 37 gestational weeks), with a birth weight over 2.5 kg, had no history of otitis media at testing, no risk factors for hearing loss nor language disorder, and had no history of health or developmental concerns. They also all passed the newborn-hearing screening. For adult participants, absolute auditory thresholds were assessed with pure tones for both ears at octave frequencies between 0.25 and 8 kHz prior to testing. The mean pure-tone average threshold was considered as normal if equal or below 20 dB Hearing Level.

Data from an additional two 3-month-olds were excluded because recordings were still too noisy after processing. Data from an additional six 10-month-olds were excluded because recordings were too noisy (N=4), the infant was too fussy to complete the task (N=1) and parents interfered during recording (N=1). Those data were excluded from the analyses.

2. Stimuli & Procedure

Two 100% sinusoidally amplitude modulated pure tones centered at 1027 Hz were used as stimulus (John et al., 2004; Levi et al., 1993). The AM rate was set either to 8 or to 40 Hz (as shown in **Figure 1.A**). Each sound was 4 min-long including 50-ms raised-cosine onset/offset ramps, and presented continuously through 2 loudspeakers (Bose ® Companion 20) positioned at 0-degree Azimuth on each side of a computer screen. Participants sat in front of the screen at a distance of ~ 1 meter. Infants were sat onto one of their parents' laps. In experiment 1, the intensity level was calibrated at 65 dB SPL at the place where participants were positioned.

Each participant was exposed to two 4-min long blocks of sounds, one for each modulation rate (8 and 40 Hz modulations), presented in a counterbalanced order between participants. After the first auditory stimulation, a short break was proposed and the second stimulation started soon after.

Participants watched a silent animated cartoon during the whole experiment. Infants were provided with toys and distraction when they were not interested in the cartoon in order to reduce movement.

All methods were carried out in accordance with relevant guidelines and regulations, Informed consent forms were obtained from all infants' legal guardians and adult participants as approved by the university ethic committee (CER-U Paris).

3. EEG setup, signal processing and analyses

The EEG system used for the recording was Brain Vision (version v1.0.9). Three active central electrodes (Fz, Cz, Pz from 10-20 system, the ground positioned at Fpz) were used, based on previous studies (John et al., 2004; Levi et al., 1993; Nodarse et al., 2012) were positioned on a cap with the ground and 2 external electrodes were positioned at mastoids (acting as online references) as represented in **Figure 1.B**. The sampling rate during recording was set to 10 kHz. The cap size was determined prior the experiment following each participant head size.

Signal processing was done in Matlab (version 2021b) using EEG lab (version 2021.0). For each electrode recording, the continuous EEG signal was first divided into 2 epochs: one containing the recording for the 8 Hz stimulation and one for the 40 Hz one. Then the signal was band-pass filtered from 6 to 46 Hz (using the FIR from EEGLAB). In each condition, a Fast Fourier Transform was used to calculate the complex frequency spectrum of each epoch, resulting in a frequency resolution of 0.0024 Hz.

For each participant, the maximum amplitude value of the EEG signal was measured between 7.8 and 8.2 Hz and between 39.8 and 40.2 Hz for the 8 and 40 Hz conditions, respectively. The noise floor was computed as the mean of squares at either side of the modulation frequency (± 3 Hz) not including portions of the target signal window itself (Cone and Garinis, 2009; Mepani et al., 2021; Vanvooren et al., 2015). The signal-to-noise ratio (SNR) was then defined as the ratio between the maximum amplitude at the target frequency and the noise floor. Note that we will not compare directly SNR values between the 8 and 40 Hz conditions as the EEG noise is significantly higher at lower frequencies (Cellier et al., 2021).

A visual inspection of the responses recorded in each condition revealed that the best responses (i.e., overall less noise) were observed at Fz electrodes for infants. Moreover, comparison of the SNR values between electrodes and combination of electrodes confirmed that the SNR was the highest at Fz for infants. Thus, the following analyses focused on comparing the responses at Fz between age groups.

In the analyses, the individual responses at each modulation rate were considered to be statistically significant using a F-ratio estimating the probability that the amplitude at the target frequency is significantly above the neighboring frequencies (noise calculated over > 120 points at each side of the signal frequency) at a level of $p < .05$. More precisely, the SNR of the AMFR was compared to the critical value of 2.9957 corresponding to a F value for $\alpha = 0.05$ with 2 and >120 degrees of freedom (John et al., 2004; Valdes et al., 1997). Then, age group comparisons were done. The AMFR-SNR in dB were normally distributed (Shapiro-Wilk test, $p > .05$ for all conditions/groups), but, as each group

amounted to 15 participants only, non-parametric tests (Kruskal-Wallis test for k independent samples and Mann-Whitney U for 2 independent samples) were used to evaluate the effect of Age group on the SNR data at 8 and 40 Hz independently.

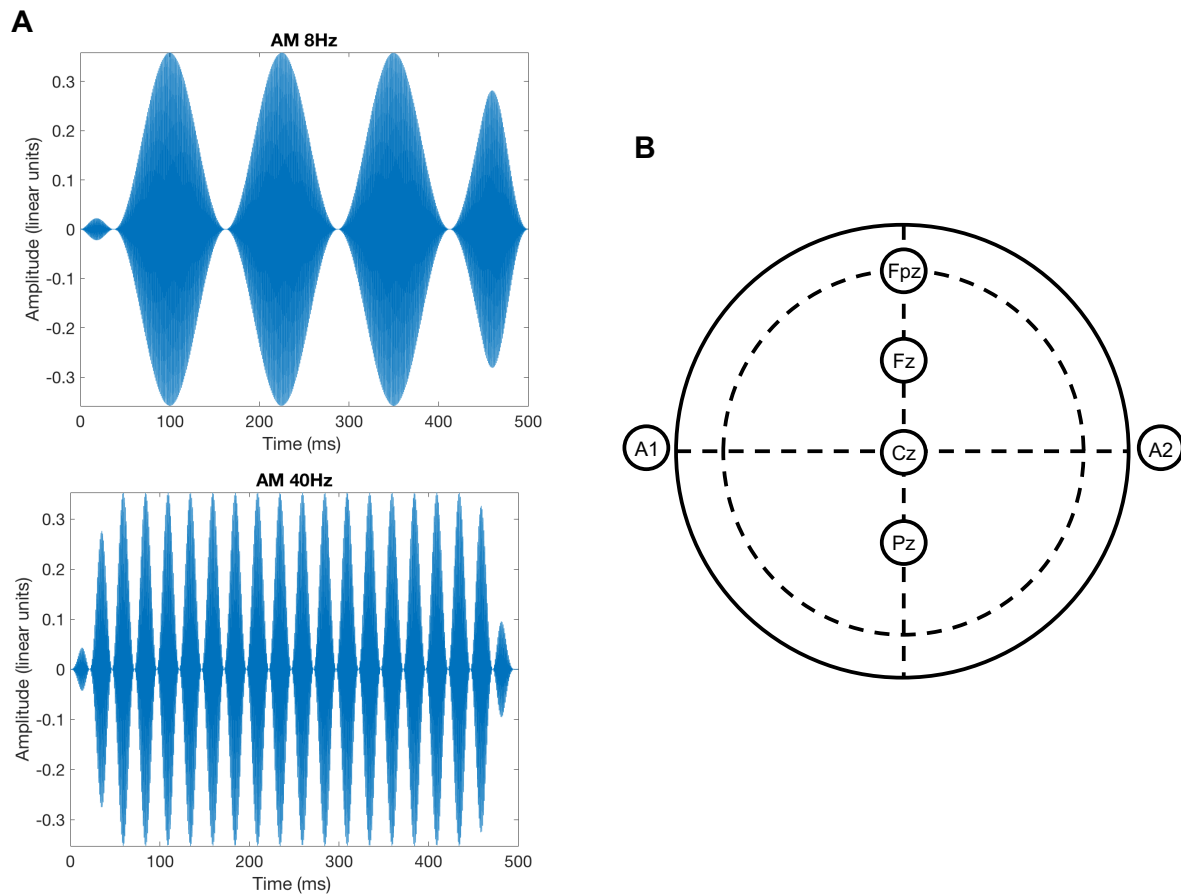


Figure 1. A. Waveforms of two pure tones representing the variations in amplitude over time of a tone modulated at 8 Hz (upper panel) and at 40 Hz (lower panel). A 50-ms on and off ramp was applied. **B.** Schematic representation of the EEG setup including: the 3 central electrodes used for AMFR measurement (Fz, Cz and Pz); the ground, as placed at Fpz; the 2-linked mastoids (A1, A2), used as online reference.

B. Results

The grand averages of the AMFR for the 8 Hz and 40 Hz conditions are shown in **Figure 2** for each group. As shown in the literature (Cellier et al., 2021), the level of noise was higher in the 8 Hz condition than in the 40 Hz condition for all groups as revealed by non-parametric Wilcoxon test for paired samples ($Z = -3.412, p = .001$; $Z = -3.416, p = .001$; $Z = -3.420, p = .001$; for 3-month-olds, 10-month-olds and adults, respectively). Moreover, infants showed significantly higher levels of noise than adults as shown by U test of Mann-Whitney ($U = 551.500, n \text{ adults} = 32, n \text{ infants} = 58, p = .001$). Note that, even though more noise was observed in infants than adults, this difference was taken into account by the SNR calculated for each participant (the ratio between the maximum amplitude at the target frequency and the noise floor). All three groups displayed a peak at 8 Hz in the average response, but only the group of adults showed a peak at 40 Hz.

Individual SNR of the AMFR in each group is represented in **Figure 3**. The percentage of significant AMFR (representing the proportion of participants whose AMFR was above chance level) at 8 Hz was 40%, 60% and 33% for 3-months, 10-months and adults, respectively. At 40 Hz, a different pattern was observed, as significant AMFR were observed only in 6% of the 3-month-olds and 6% of the 10-month-olds, but in 100% of the adult group.

The Kruskal-Wallis test for independent samples showed no effect of Age group on the AMFR-SNR values in the 8 Hz condition [$H(2, n = 45) = 1.573; p = .455$]. However, a significant effect of Age group was observed in the 40 Hz condition [$H(2, n = 45) = 29.799; p < .001$]. To further assess this main effect of Age, comparisons 2 by 2 were run using the U test of Mann-Whitney (i.e., 3-month-olds vs adults; 10-month-olds vs adults; 3-month-olds vs 10-month-olds). These comparisons confirmed that the AMFR-SNR values were significantly higher in the 40 Hz condition for adults than for 3-month-olds ($U=1.000, p < .001$) and for adults than for 10-month-olds ($U=0, p < .001$), but did not differ between 3- and 10-month-olds ($U=85.000, p = .233$)ⁱ.

In order to assess whether the absence of AMFR at 40 Hz in infants may be related to the intensity level of presentation (Cone and Garinis, 2009), we tested a second group of 3-month-old

infants in the exact same conditions, but the sound level was set to 75 dB SPL. Ten-month-old participants were not included in this second experiment because, as temporal resolution for AM information is mature by 3 months of life (Walker et al., 2019), if an increase in the AMFR at 40 Hz was detectable due to increased intensity in stimuli presentation, it should be observed starting from this early age. As adult listeners already showed a strong AMFR at 40 Hz when stimulated at 65 dB SPL, we did not include a new group of adults in this second experiment.

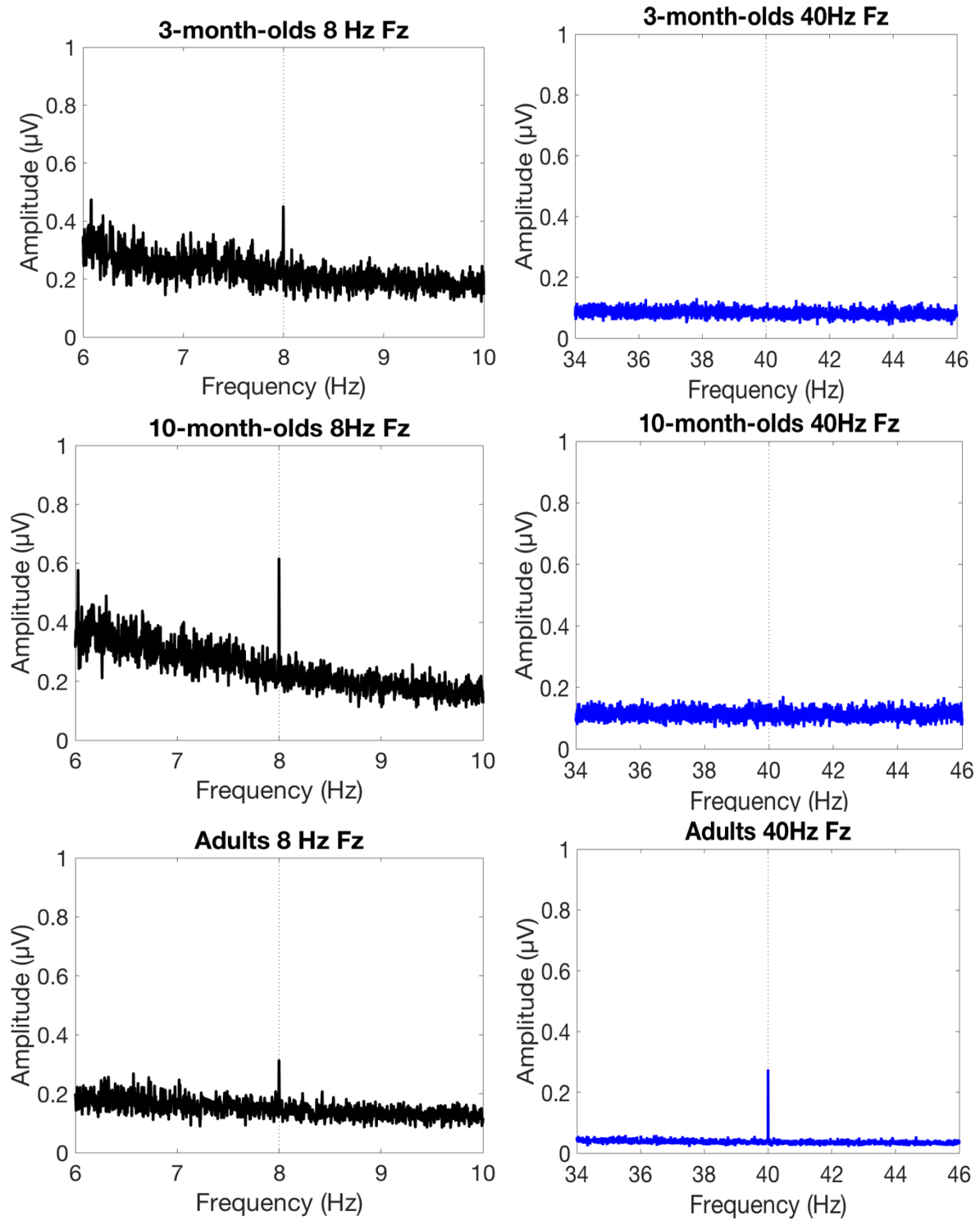


Figure 2. Grand average ($N=15$) of the AMFR (in μV) for the 8 Hz (left panels) and 40 Hz (right panels) conditions in the three age groups (3-month-olds, 10-month-olds and adults from the top panel to the bottom panel, respectively). The data are shown for the Fz channel.

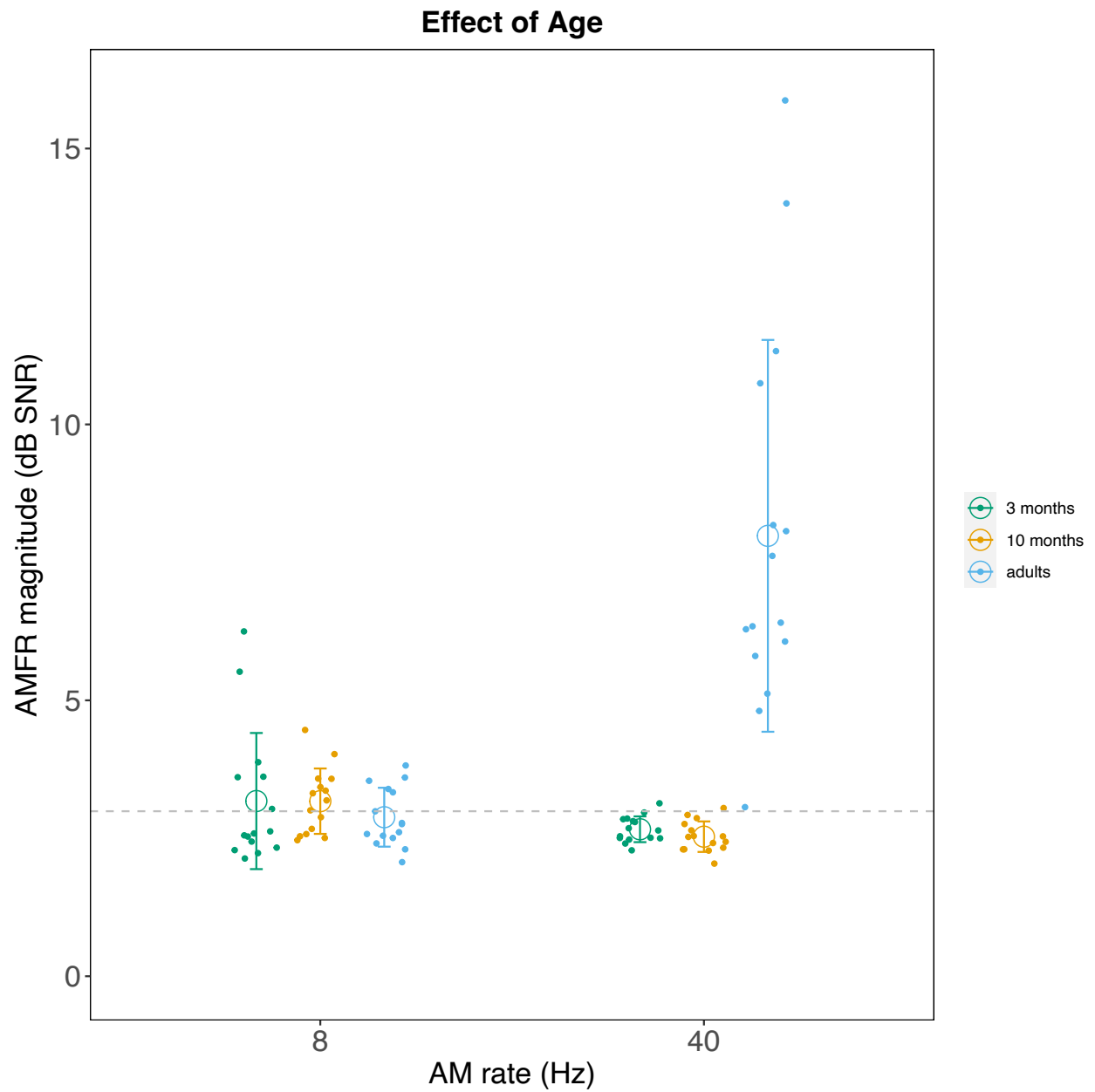


Figure 3. Individual AMFR magnitudes (in dB SNR) are represented in each group (closed circles in green, orange and blue for 3-, 10-month-olds and adults, respectively). Open circles represent the group averages in the 8 Hz and in the 40 Hz condition. The error bars represent the standard deviation. Higher magnitude corresponds to higher AMFR peaks. The horizontal grey dashed line represents the critical value for 0.05 level of significance for the F ratio.

III. EXPERIMENT 2

A. Methods

1. *Participants*

A second group of 15 3-month-old infants participated in the second control experiment (aged between 2 months 16 days and 3 months 22 days, mean age = 3 months, sd = 12 days, 9 girls). The inclusion/exclusion criteria were the same as in Experiment 1. One additional infant was not included in the final sample because s/he was too tired to complete the task.

2. *Stimuli, Procedure, EEG setup, signal processing and analyses*

Similar stimuli and procedure from Experiment 1 were used except that the presentation level was set at 75 dB SPL. Analogous EEG setup, signal processing and analyses were used.

B. Results

The grand average of the AMFR for the second group of 3-month-olds tested at 75 dB SPL is represented at each rate in **Figure 4.A**. At 8 Hz, significant AMFRs were observed in 93% of the 3-month-olds stimulated at 75 dB SPL, but only 6% showed a significant AMFR at 40 Hz. The individual SNR of the AMFR for the 2 groups of 3-month-olds (tested at 65 dB SPL in Experiment 1 and at 75 dB SPL in Experiment 2) is represented in **Figure 4.B**. The average response for the 8 Hz condition in Experiment 2 appears to be larger than the average response recorded in the 3-month-old group from Experiment 1, but there is still no observable averaged response at 40 Hz. The Mann-Whitney U test comparing 2 independent samples showed a significant effect of Intensity level (65 vs 75 dB SPL) between the two groups of 3-month-olds in the 8 Hz condition only ($U = 40.500, p = .002$). There was no significant difference in the 40 Hz condition ($U=95.000, p = .486$). Thus, the AMFR amplitude in 3-month-old infants was enhanced by the increase in presentation level but only at 8 Hz. The analysis of the phase locking value provided no further evidence of a significant response at 40 Hz (see Figure A in Supplementary Materials).

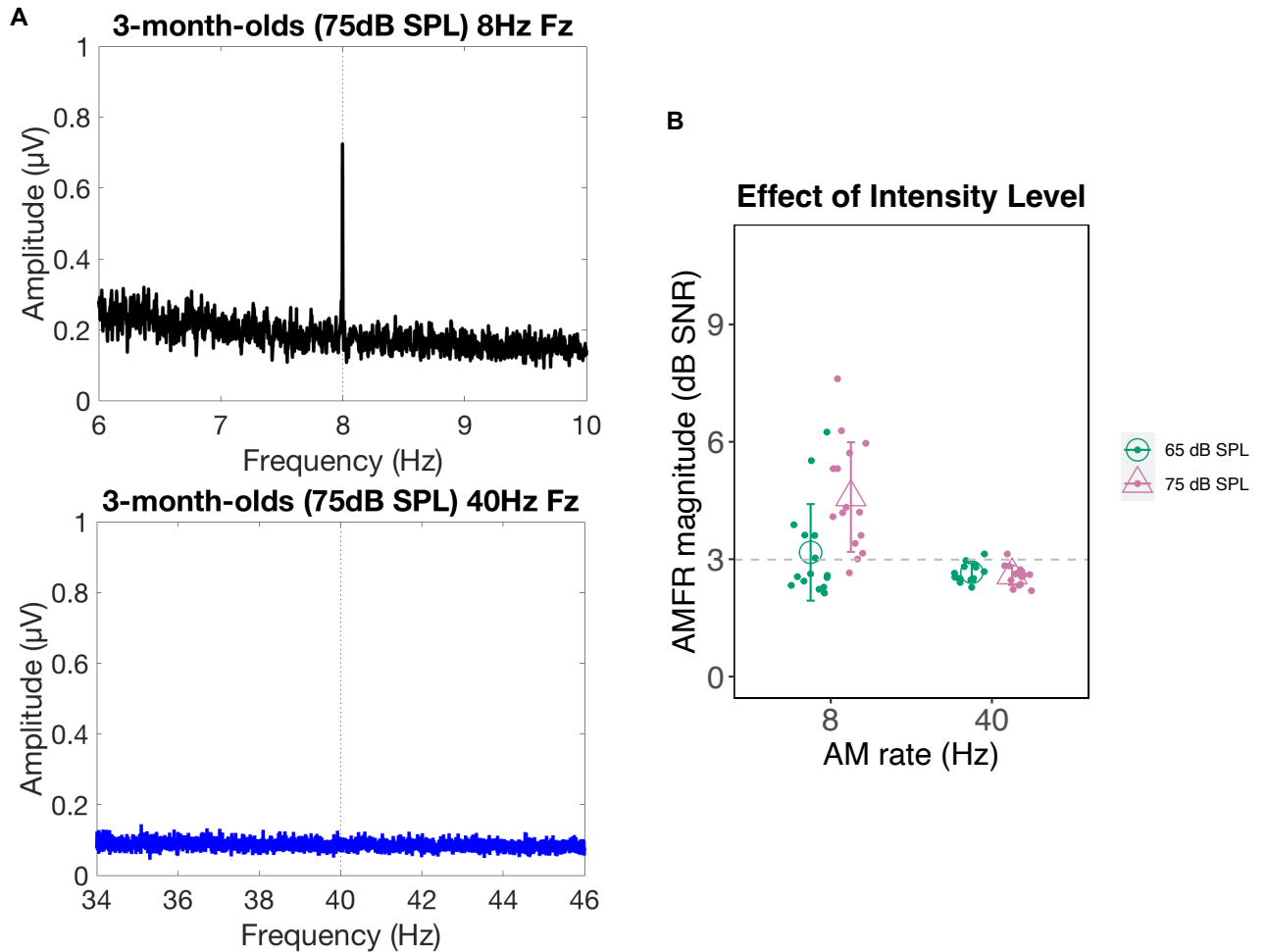


Figure 4. A. Grand average ($N=15$) of the AMFR (in μV) for the 8 and 40 Hz condition in the second group of 3-month-old infants stimulated at 75 dB SPL. The data are shown for the Fz channel. **B.** Individual AMFR magnitude (in dB SNR) in 3-month-olds as tested at 65 dB SPL in experiment 1 (filled green circles) and at 75 dB SPL in experiment 2 (filled pink circles). Open symbols represent the average of each group and the error bars represents the standard deviation. The horizontal grey dashed line represents the critical value for 0.05 level of significance for the F ratio.

IV. DISCUSSION

The goals of the present study were to measure the ability of the auditory system to follow AM cues during infancy while 1) comparing awake infants with awake adults, 2) comparing slow versus faster AM rates. AMFRs were observed in awake 3 and 10-month-old infants for a slow modulation rate of 8 Hz, while at 40 Hz modulation rate we failed to detect a significant AMFR.

Infants showed an adult-like AMFR to an 8 Hz sinusoidally modulated-tone. In particular, the percentage of significant AMFR at 8 Hz resulted in 44% of all participants stimulated at 65 dB SPL in Experiment 1. This value is consistent with previous studies in adult listeners (Gransier et al., 2020), observing that less than 50% of participants show a significant AMFR at a rate of 7.5 Hz when presented at 70 dB SPL. In Experiment 2, increasing the level of sound presentation by 10 dB increased the AMFR at 8 Hz in 3-month-old infants and increased the percentage of significant AMFR at 93%. This result reflects effective phase-locking to a modulation frequency which falls in the range of slow AM that are particularly relevant for speech perception by 3 months of age (Drullman, 1995; Shannon et al., 1995). Thus, with this finding, we encourage future investigations aiming at a better understanding of the interaction between auditory development in the AM domain and early language acquisition. More generally, further investigations are also needed to evaluate cortical tracking of AM in awake infants with different carriers, as we only used pure tones, and testing more AM rates.

At 40 Hz modulation rate, we failed to detect a significant AMFR in awake infants aged 3 and 10 months. Increasing the sound level presentation by 10 dB for an additional group of 3-month-olds did increase the AMFR for the AM rate of 8 Hz, but still no significant response was observed at 40 Hz. Importantly, as our participants were awake during sound presentation, our results suggest that the absence of AMFR at 40 Hz in infants is not related to the state of arousal, thus ruling out the hypothesis that infants' sleep has a suppressing effect on the AMFR at 40 Hz (Levi et al., 1993).

The immature phase-locking observed at 40 Hz in infants, as recorded with EEG, is consistent with previous developmental studies conducted with sleeping infants, that showed a protracted developmental trajectory for the 40 Hz neural response (Aoyagi et al., 1993; Levi et al., 1993). In particular, Levi et al. (1993), testing 1-month-old asleep infants at modulation rates between 10 and 80 Hz, showed that the AMFR was not consistently observed for the rates falling below (and comprising) 40 Hz (the AMFR at 40 Hz was only shown by 4 infants out of 12 tested with a 500 Hz carrier and by 4 infants out of 14 tested with a carrier of 2000 Hz).

One possible interpretation of this absence of AMFR at 40 Hz in young participants could be that young listeners do not process the faster AM cues as adults, and thus, that the upper limit of the neural TMTF grows over age. However, it is difficult to endorse this hypothesis. In the first place, it seems improbable in light of the fact that the Frequency Following Response (FFR) can be measured in infants (Lemos et al., 2021), implying that infants' temporal resolution must be high. Secondly, it is not supported by recent behavioral experiments showing similar TMTF in 3-month-old infants and adults (Walker et al., 2019): in this study, the maximal modulation rate that could be reliably detected by infants, as estimated using a broadband noise carrier, was 81.7 Hz and was not significantly different from adults' maximal rate (87.5 Hz). Even though the current experiment used a different kind of AM carrier than Walker and colleagues (that is, a pure tone, and not a noise carrier), we should expect higher cutoff frequency for the TMTF without the presence of the inherent envelope fluctuations carried by a noise carrier in infants and adults (Dau et al., 1997). It is important to note, though, that ASSR-measured hearing thresholds for a 40 Hz modulated tone have been shown to be about 10 dB above audiometric, behaviorally-measured hearing thresholds (see Picton et al., 2003). Nevertheless, our second experiment revealed that increasing by 10 dB stimulus presentation did not influence the AMFR at 40 Hz for 3-month-old, suggesting that the absence of 40 Hz AMFR observed here in infants is unlikely to reflect specific processing difficulties at this rate (e.g., hearing or detection thresholds effects).

Alternately, our results may be explained by the neural loci of AM processing for higher modulation rates changing over development, as a result of brain maturation.

In adults, experiments using functional Magnetic Resonance Imaging (fMRI) showed that, even though slow and faster AM rates activate similar cortical regions (Heschl Gyrus, superior temporal sulcus and associative areas), specific regions are also activated as a function of the AM rate. More precisely, fluctuations comprised between 32 and 256 Hz have been found to activate more the inferior colliculus of the auditory brainstem, while fluctuations of 8 Hz activated more the primary auditory cortices (Giraud et al., 2000). Using Magneto-Encephalography (MEG) (Weisz and Lithari,

2017) and EEG (Farahani et al., 2017), several studies suggested multiple sources of activation for 40 Hz modulations both at the brainstem and at the cortical level. As MEG and low-density EEG are more sensitive to cortical versus subcortical activity, the absence of 40 Hz AMFR in young listeners may then be related to the development of those cortical regions. Such perspective has been suggested by previous experiments using MEG between 5 and 52 years of age, detecting a significant developmental trend until adolescence for the AMFR at 40 Hz (Rojas et al., 2006). These results were interpreted by hypothesizing that the maturation of the cortical regions involved in the processing of 40 Hz modulations might develop over age, thus making the sources of the AMFR at 40 Hz out of reach for MEG recording. Similar results have also been observed comparing AMFR measured with MEG in 3-to-5-year-old children and adults (Tang et al., 2016). Moreover, EEG studies measuring brain oscillations for visual stimulations in infancy detected gamma band oscillations at precisely 40 Hz, by 8 months of age (Csibra et al., 2000), showing that such EEG rates can be recorded in the infant brain. Future longitudinal assessments of the AMFR should further evaluate the development of neural coding of temporal information at an individual level (allowing, among other things, to investigate its possible relationship with speech and language development)

Overall, our results corroborate the hypothesis that the immature auditory cortex (e.g. Moore, 2002) has a limited capacity, relatively to the adult brain, to process a 40 Hz modulation rate of sounds. This hypothesis needs to be tested in future studies granting localization of the source of the neural signal. A very simple EEG set-up was applied here, based on previous literature, that cannot shed light on this question. Further investigations using high density EEG are warranted to enable source localization of AMFR for slow versus faster AM rate during the early years of development.

Incidentally, this result (in line with previous studies, see John et al., 2004), also casts doubts on the appropriateness of using the modulation rate of 40 Hz for evoked potential audiometry in infants. Concerning the possible clinical applications of AMFR recording in awake infants, the present experiment showed that it is possible to measure AMFR for a 10-min stimulation period while presenting silent animated videos and toys to infants aged 3 and 10 months. The attrition rate was

higher for 10-month-olds as compared to 3-month-olds, due to lack of cooperation and signs of discomfort leading to noisy data (25% excluding parents' interference, vs 6% in 3-month-olds). The possibility to test awake infants might thus be considered, here circumventing the difficulty to get infants asleep when they come to the clinic.

Finally, the hypothesis of developmental changes in the neural transmission of temporal information along the auditory pathway (with a transition from relatively more subcortical to relatively more cortical responses) fits well with the hypothesis that developmental improvements in AM processing (Cabrera et al., 2019, 2022; Hall and Grose, 1994) might be triggered by increasing processing efficiency (the central ability to make efficient use of available AM information). In other words, thanks to a more distributed network, less sensory information might be lost along the auditory pathway. Higher neural noise (i.e., spikes that are unrelated to the stimulus, see (Sanes and Woolley, 2011), is indeed observed, in infants as compared to adults in the current study, further supporting this hypothesis. The relationship between processing efficiency and AMFR for higher versus low modulation rate in infancy deserves further exploration.

V. CONCLUSIONS

The present results show similar signal-to-noise ratio for the AMFR at a slow modulation rate (8 Hz) in both 3- and 10-month-old awake infants compared to adults. Conversely, we did not observe any response for faster modulations in both infant groups (40 Hz), even when the sound level was increased to 75 dB SPL for 3-month-old infants. We posit that 40 Hz modulation rates may be preponderantly processed by subcortical regions in awake infants, while they are processed by both cortical and subcortical regions in adulthood. This suggests different developmental trajectories of temporal processing in cortical and subcortical regions as a function of modulation rates.

Additional information

The authors declare no competing interests.

FIGURE LEGENDS

Figure 1. A. Waveforms of two pure tones representing the variations in amplitude over time of a tone modulated at 8 Hz (upper panel) and at 40 Hz (lower panel). A 50-ms on and off ramp was applied. **B.** Schematic representation of the EEG setup including: the 3 central electrodes used for AMFR measurement (Fz, Cz and Pz); the ground, as placed at Fpz; the 2-linked mastoids (A1, A2), used as online reference.

Figure 2. Grand average (N=15) of the AMFR (in μV) for the 8 Hz (left panels) and 40 Hz (right panels) conditions in the three age groups (3-month-olds, 10-month-olds and adults from the top panel to the bottom panel, respectively). The data are shown for the Fz channel.

Figure 3. Individual AMFR magnitudes (in dB SNR) are represented in each group (closed circles in green, orange and blue for 3-, 10-month-olds and adults, respectively). Open circles represent the group averages in the 8 Hz and in the 40 Hz condition. The error bars represents the standard deviation. Higher magnitude corresponds to higher AMFR peaks. The horizontal grey dashed line represents the critical value for 0.05 level of significance for the F ratio.

Figure 4. A. Grand average (N=15) of the AMFR (in μV) for the 8 and 40 Hz condition in the second group of 3-month-old infants stimulated at 75 dB SPL. The data are shown for the Fz channel. **B.** Individual AMFR magnitude (in dB SNR) in 3-month-olds as tested at 65 dB SPL in experiment 1 (filled green circles) and at 75 dB SPL in experiment 2 (filled pink circles). Open symbols represent the average of each group and the error bars represents the standard deviation. The horizontal grey dashed line represents the critical value for 0.05 level of significance for the F ratio.

SUPPLEMENTARY MATERIALS

See supplementary material at [URL will be inserted by AIP] for a supplementary analysis of phase locking to AM applied to our data (phase locking value calculated as the correlation between the phase of the EEG signal and the phase of the input auditory signal).

DATA AVAILABILITY

The raw data will be available upon request to the corresponding author.ⁱⁱ

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ⁱ Other measures can also be used to assess the ability of the auditory system to follow the variations of a sound. For instance, the phase locking value can be calculated as the correlation between the phase of the EEG signal and the phase of the input auditory signal (Lachaux et al., 1999; Zhu et al., 2013). However, we calculated those values in the current experiment and found the exact same results as for the AMFR, that is, a strong response in the adult group but an absence of response at 40 Hz in both infant groups (see Figure A in Supplementary Materials).