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Research Paper

Auditory cortex responses to interaural time differences in the envelope of low-frequency sound, recorded with MEG in young and older listeners

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ABSTRACT

Interaural time and intensity differences (ITD and IID) are important cues in binaural hearing and allow for sound localization, improving speech understanding in noise and reverberation, and integrating sound sources in the auditory scene. Whereas previous research showed that the upper-frequency limit for ITD detection in the fine structure of sound declines in aging, the processing of envelope ITD in low-frequency amplitude modulated (AM) sound and the related brain responses are less understood. This study investigated the cortical processing of envelope ITD and compared the results with previous findings about the fine-structure ITD. In two experiments, participants listened to 40-Hz AM tones containing sudden changes in the envelope ITD. Multiple MEG responses were analyzed, including the auditory evoked N1 responses, elicited both by sound onsets and ITD changes, and 40-Hz responses, elicited by the AM. The first experiment with healthy young adults revealed a substantial decline in the magnitudes of the ITD change N1 response, and the 40-Hz phase resets at higher carrier frequencies, suggesting a similar frequency characteristic as observed for fine structure ITD. The amplitude of the 40-Hz ASSR declined only gradually with increasing carrier frequency, and it was excluded as a confounding factor in the decline in the ITD response. Larger responses to outward ITD changes than inward changes, here first reported for envelope ITD, were another characteristics that were similar to fine-structure ITD. A second experiment with groups of young and older listeners examined the effects of aging and concurrent noise on the cortical envelope ITD responses. One important research question was, whether binaural cues are accessible in noise. Behavioural tests showed an age-related hearing loss in the older group and decreased performance in envelope ITD detection and speech-in-noise (SIN) understanding. Binaural hearing and SIN performance were correlated with one other, but not with hearing loss. The frequency limit for envelope ITD was reduced in older listeners similarly as previously found for fine structure ITD, and older listeners were more susceptible to concurrent multi-talker noise. The similarities between responses to envelope ITD and to fine structure ITD suggest that a common cortical code exists for the envelope and fine structure ITD. The dependency on the carrier frequency suggests that envelope ITD processing at the subcortical level requires stimulus phase locking, which might be reduced in aging.

1. Introduction

Interaural time and level differences (ITD and ILD) are major cues for binaural hearing (Akeroyd, 2006; Konishi, 2003; Middlebrooks and Green, 1991). The neural mechanism underlying ITD detection has been explained with coincidence detectors and a set of delay lines (Jeffress, 1948; Joris et al., 1998), which were found in the barn owl (Carr, 1993). The mammalian auditory system evolved differently and detects fine structure ITD using a single channel coincidence detector and a balance between inhibitory and excitatory synaptic connection for precise control of delay times (Grothe et al., 2010). However, how ITD in the envelope of sound is detected and processed is less understood. The current study investigates auditory cortex responses, elicited by temporal changes in the envelope ITD, to contribute to the understanding of the

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underlying neural mechanisms.

The study was motivated by findings that, binaural hearing beyond sound localization improves speech understanding in noise and reverberation. ITD is an effective cue for release from speech-in-noise (SIN) masking when listening in a multi-speaker environment (Kidd et al., 2010). In the challenging situation of listening to speech at an intensity just above the interfering noise, listeners could accept up to 10 dB higher noise level when speech and noise sources were separated in space (Hawley et al., 2004). Speech understanding can improve by 20% for each dB increase in the signal-to-noise ratio (SNR) (Duquesnoy, 1983). Moreover, listeners can allocate attention to a target sound when they can spatially separate the sound sources, which helps understanding speech while ignoring concurrent noise (Arbogast et al., 2005; Kidd et al., 2005). In reverberation, listeners integrate multiple sound images into a single image and suppress irrelevant information (Cosentino et al., 2014). Hearing-impaired listeners benefit less from binaural cues than normal hearing listeners (Bronkhorst and Plomp, 1992), and the ability to tolerate reverberating environments decreases with aging (Harris and Reitz, 1985) and hearing loss (Duquesnoy and Plomp, 1980). However, improving binaural hearing mitigates the SIN understanding deficit in aging (de Taillez et al., 2018; Hartley and Isaiah, 2014), and hearing-impaired listeners perform better with bilateral hearing aids (McArdle et al., 2012). Moreover, cochlear implant users may benefit from restoring binaural hearing through bilateral implantation (Brown and Balkany, 2007; Dietz and McAlpine, 2015; Gordon et al., 2014).

Binaural hearing abilities decrease with advancing age (King et al., 2014; Moore et al., 2018). Previous studies showed that the upper-frequency limit at which a change in the fine structure ITD elicited a brain response, could serve as an objective measure of ITD detection (Ross, 2008; Ross et al., 2007b). Similarly, the primary outcome measure for this study was the upper-frequency limit for eliciting brain responses to changes in the envelope ITD.

Listeners benefit from ITD dominantly at low frequencies and from ILD at higher frequencies above 1500 Hz according to the duplex theory of sound localization (Stevens and Newman, 1936). Several experimental studies confirmed this upper-frequency limit for ITD sensation (Brughera et al., 2013; Klumpp and Eady, 1956; Nordmark, 1976; Zwislocki and Feldman, 1956). Some have suggested that the 1500-Hz limit is determined by the path length difference between left and right ear of about 23 cm (Algazi et al., 2001) and the velocity of sound, resulting in a maximum ITD of about 660 μs, equivalent to the period of a 1500 Hz sine wave. A larger phase difference at higher frequencies would confuse the ear of the leading sound. However, a study of the sound localization abilities of mammals of different head sizes did not find any systematic relationship between the ITD frequency limit and the head size (Heffner and Heffner, 1992). Instead, a lower sensitivity for ITD at higher frequency could be beneficial for suppressing the ambiguity caused by large interaural phase differences (Hartmann and Macaulay, 2014).

Studies about long ITD have mainly concerned sound localization, often using pure tones. However, localization performance is best for the short ITD of sources close to the frontal midline. Turning the head toward the source improves localization while minimizing the ITD. Longer ITD becomes relevant in reverberation and for integration of multiple sources such as in listening to ensemble music. ITD in the envelope of common amplitude modulation may become the cue for broadband noise stimuli with long ITD, even beyond the range for sound localization. Moreover, sounds with long ITD can be fused into a single object, which is perceived as lateralized toward the ear receiving the earlier version of the sound (Leakey et al., 1958; Schubert and Wernick, 1969). Robust lateralization has been shown for long ITD of up to 20 ms (Blodgett et al., 1956). However, lateralization with such a long delay was possible only with spectral components below 1500 Hz, while lateralization of higher frequencies was limited to about 4 ms (Mossop and Culling, 1998). Neurophysiological recordings in owls and behavioural tests in humans have shown that both species could detect an ITD, five times longer than the maximum naturally occurring delay (Saberi et al., 2002). Binaural cross-correlation, which does not require long delay lines, has been proposed as a neural mechanism underlying this ability. These findings emphasize that ITD, longer than physiologically relevant for localization, plays a role in binaural hearing.

Envelope ITD serves as a cue for amplitude modulated (AM) sound above 1500 Hz (Henning and Ashton, 1981). However, long envelope ITD of 2 ms also contributed to lateralization of low-frequency 500-Hz sound with 25 Hz or 50 Hz AM (Bernstein and Trahiotis, 1985), indicating that envelope ITD is not exclusive to high frequencies. In this case, the envelope ITD of several milliseconds was substantially longer than the physiologically relevant ITD range. The effect of lateralization was subjectively equivalent to an ILD of a few dB. A recent study confirmed thresholds for envelope ITD detection of about 2 ms in 250 Hz or 500 Hz tones, amplitude modulated at 25 Hz, and in the 1-ms range for 50 Hz AM (Moore et al., 2018).

A model for discriminating envelope ITDs at high frequencies suggests that rectifying the high-frequency AM signal at the auditory nerve provides envelope information for further processing in the central auditory system, which is otherwise not contained in the low-frequency spectrum (Colburn and Esquissaud, 1976). Subsequent studies of envelope ITD have used the 'transposed stimulus' (Van De Par and Kohlrausch, 1997) which enhances the contrast of the modulation envelope in the time domain and adds multiple sidelines to the modulation spectrum. The ITD detection thresholds were shorter for the transposed stimulus compared to sinusoidal AM tones (Bernstein, 2001). However, envelope ITD thresholds were still multiple times longer than for ITD in pure tones with the same frequency as the AM frequency. The results suggest a central mechanism of binaural hearing, which is common for low and high-frequency ITD discrimination, while properties of the auditory periphery explain the differences between high and low frequencies (Bernstein and Trahiotis, 2002).

Low-frequency masking sound below 1300 Hz has been applied in most experiments about high-frequency envelope ITD discrimination to ensure that the observations are specific to the high-frequency sound (Bernstein and Trahiotis, 2002). However, the relevant information in speech is conveyed mainly at spectral frequencies below 1500 Hz (Warren et al., 1995). SIN understanding depends on binaural hearing at low frequencies and may not benefit from binaural cues at high frequencies. Therefore, the focus of the current study was on envelope ITD processing at low frequencies. Evidence for specific sensitivity for sound envelopes has come from recent findings that low-frequency neurons in the inferior colliculus and the dorsal nucleus of the lateral lemniscus in guinea pigs are sensitive to envelope ITD (Agapiou and McAlpine, 2008).

A focus of previous research at the level of the auditory cortex was on the question of how binaural cues find their representation in a spatial map (Lee and Middlebrooks, 2013; Razak, 2011). However, the role of cortical ITD responses beyond sound localization is less understood. The general aim of this study was investigating the cortical processing of envelope ITD and compare the results with previous findings of processing the fine-structure ITD. Multiple types of changes in interaural time disparities have been used to elicit auditory evoked responses or changes in steady-state responses. Some stimuli used temporal structures such as sudden change in interaural correlation (Chait et al., 2005; Dajani and

Picton, 2006) and interaural coherence in noise (Jones et al., 1991). Others used a sudden change in the time delay of the fine structure of noise (Magezi and Krumbholz, 2010; McEvoy et al., 1990; Ozmeral et al., 2016), a click series (Sams et al., 1993), and AM tones (Vercammen et al., 2017). Moreover, periodic ITD changes at a rate of seven changes per second could be detected as a peak in the frequency domain at the periodicity of ITD changes even when the magnitude of ITD was close to the physiological threshold (Undurraga et al., 2016).

The primary objective of the first experiment was to investigate how the cortical responses elicited by envelope ITD changes depend on the stimulus carrier frequency and ruling out potential confounds of effects of the carrier frequency on the AM envelope processing. The results were expected to inform us about common mechanisms underlying envelope and fine structure ITD processing. The experimental approach was similar to previous studies of the effects of ITD changes in the fine structure of AM sound (Ross et al., 2007a,b). MEG responses were analyzed with respect to transient changes in the interaural time difference of the envelope of 40-Hz AM sounds while preserving the fine structure of the bilateral sounds with zero phase difference in the carrier signals. The experimental parameter carrier frequency was varied between 250 Hz and 4000 Hz. Equal response amplitudes were expected in case of independent processing of the sound envelope and the fine structure. However, cortical responses to the AM itself depend on the carrier frequency (Rees et al., 1986; Ross et al., 2000), and so to evaluate the contribution of possible confounds, the frequency characteristics of AM responses were assessed relative to the frequency characteristics of the ITD change responses.

The ITD stimuli were created by manipulating the phases of the AM in the left and right ear sounds. One further objective of the first experiment was to address whether the time courses of between-ear phase differences are represented as interhemispheric phase differences in the cortical responses. Comparing the frequency characteristics of the cortical phase representation and the ITD response could elucidate whether a phase computation at the cortical level could contribute to the envelope ITD processing.

Previous studies of fine-structure ITD found an asymmetry of larger responses to outward changes compared to inward changes (Ozmeral et al., 2016; Ross, 2008), which is consistent with a two-channel model of binaural processing (Magezi and Krumbholz, 2010). Another objective of the first experiment was to investigate possible differences between responses to inward and outward changes in the envelope ITD stimulus. Consistent findings for the envelope and fine-structure ITD would support common processing at the cortical level.

The aim of the second experiment was investigating how aging and concurrent masking sound affect envelope ITD processing, which is important for understanding the role of binaural hearing in SIN understanding. For example, when enhanced binaural cues are used for improving speech understanding, it would be important to know whether the binaural cues are still accessible in concurrent noise. The relation between binaural hearing and SIN understanding was established with a set of behavioural tests, including measuring hearing thresholds and temporal and spectral acuity in both age groups.

The general approach for the experimental studies was simultaneous recording of multiple types of cortical responses, which were auditory evoked onset responses (Näätänen and Picton, 1987), and change responses (Chait et al., 2005; McEvoy et al., 1990; Ross et al., 2007a), 40-Hz steady-state responses and 40-Hz phase resets (Ross, 2008; Vercammen et al., 2017), and cortical representations of the interaural phase disparities. According to the model of hierarchical processing of auditory information (Wessinger et al., 2001), the hypothesis is that some responses are related to processing the sensory input while others reflect the level of perception and beyond. The experimental condition of using an across-channel multi-talker babble masker was employed for differentiating between both levels of auditory processing. The general assumption is that the masking sound should not interfere with auditory processing of the sensory input in tonotopically organized channels. However, masking noise should interfere at a higher level of perception, where information is combined across frequency channels (Ross et al., 2012). Such a distinction between responses to the physical stimulus change and perception is essential for discussing the significance of the observed cortical responses.

2. Methods

2.1. Participants

In total 64 volunteers were recruited from the local community. Fourteen young adults (21–29 years, mean 24.2 years, eight female) participated in the first MEG experiment, whereas another ten (20–28 years, mean 22.2 years, six female) participated separately in behavioural tests. The second MEG experiment involved 19 young (18–30 years, mean 22.4 years, twelve female) and 21 older participants (63–77 years, mean 70.9 years, fourteen female), who also participated in a set of behavioural tests. All participants reported that they were healthy with no history of neurological, psychiatric or otological disorders. Hearing thresholds were tested with pure tone audiometry at the octave frequencies between 250 Hz and 8000 Hz using a modified Hughson-Westlake procedure. Exclusion criteria were hearing thresholds above 15 dB at more than one test frequency at or below 2000 Hz in young adults and 25 dB in older adults. Threshold differences between ears did not exceed 15 dB at more than one test frequency. None of the participants had experiences with psychoacoustic tests or MEG/EEG recordings. Participants provided written consent after they received information about the study, which was approved according to the Declaration of World Medical Association Declaration of Helsinki (2000) by the research ethics board at Baycrest Health Sciences. Participants received an honorarium for participation.

2.2. Behavioural tests

Before performing the first MEG experiment, frequency limits were established for fine-structure and envelope ITD discrimination using a three-up one-down two-alternatives forced-choice procedure (2AFC), implemented in Matlab with the Psychoacoustics toolbox (Soranzo and Grassi, 2014). All young and older participants in the second experiment also performed a set of psychoacoustic tests to understand the relation between the performance in detecting envelope ITD and hearing threshold, temporal and spectral acuity, and SIN performance. Moreover, spectral and temporal acuity were compared tested and compared with SIN understanding. Spectral acuity was tested with detection of a mistuned component in a complex sound composed from the eleven harmonics of a 220-Hz tone (Alain et al., 2012; Moore et al., 1986), which was presented at 80 dB sound-pressure level (SPL). The third harmonic (nominal 660 Hz) was modified in an adaptive procedure to have 1%–16% higher or lower frequency ($\Delta f = 6.6$ Hz–96 Hz). Participants indicated whether they perceived two sounds, which were the buzzing harmonic complex and an additional pure tone of the mistuned harmonic, or whether they heard a single buzzing sound only. Temporal acuity was tested with brief 1000-Hz tones composed of 20-ms leading and trailing markers and the gap duration ranging between 1 ms and 10 ms. Details about the stimuli have been reported (Ross et al., 2010;

Schneider and Hamstra, 1999). Tests of gap-detection and mistuned harmonics were implemented as adaptive two-alternatives forced-choice (2AFC) procedures using a one-up three-down strategy. Word understanding in noise was tested with the Quick-SIN test (Killion et al., 2004). The Quick-SIN test comprises short sentences containing five keywords each, binaurally presented with a four-talker babble noise at SNR of 25 dB–0 dB in 5-dB steps. For binaural hearing, we tested the upper-frequency limit for detecting interaural time differences in the envelope of 40-Hz amplitude-modulated sounds with stimuli closely related to the MEG paradigm. Pairs of stationary and moving sounds, 800 ms in duration each and 200 ms of silence between, were presented in random order. In a 2AFC procedure, participants indicated which sound moved between ears. Stationary sounds had a constant time delay of 2.0 ms between the envelopes of left and right ear sounds with a random selection of the leading ear. Moving sounds contained a single ITD change at the midpoint of the 800-ms stimulus, induced by switching the envelope phase difference between ears. To minimize spectral splatter, the envelope phase was smoothly shifted over a 50-ms interval. A −60 dB white noise floor was added to the stimuli. The experimental parameter for the 2AFC procedure was the carrier frequency beginning at 200 Hz. SIN loss was correlated with performance in binaural hearing, spectral and temporal acuity, as well as hearing thresholds, measured as pure tone average (PTA) across the test frequencies between 250 Hz and 8000 Hz. All behavioural tests were performed in a soundproof audiometric booth. Sound intensities were controlled with a clinical audiometer (GSI16, Grason Stadler, Eden Prairie, MN), using insert earphones (ER3A, Etymotic Research, Elk Grove Village, IL). The set of behavioural tests required about one hour. The thresholds for the 2AFC tests were defined by the mean across the final six consecutive reversals. The behavioural performance measures were analyzed using ANOVA and between-group t-tests with Welch correction for unequal variances. Significance was accepted at $\alpha = 0.05$.

2.3. Stimuli for the first MEG experiment

The sound stimuli were 40-Hz AM tones with a modulation depth of 100%, which had been shown to elicit strong auditory steady-state responses (Ross et al., 2000). An envelope ITD transition of 4 ms was achieved by delaying the envelope in one ear by 2 ms and advancing the envelope in the other ear by 2 ms. Zero phase difference in the stimulus carrier was preserved (Fig. 1). Transitions in the AM envelope were gradually introduced, always beginning at the minimum of the AM. The AM phase linearly accelerated or decelerated over the time course of one period of the 40-Hz AM, reaching the full ITD changes after 25 ms. Such smooth transitions minimized spectral splatter. The monaural envelope transition of 2 ms was below the threshold for detecting such change, which was found close to 3 ms behaviourally and as a modulation of the steady-state response (Ross and Pantev, 2004). Participants reported that they perceived the stimuli as originating from the center of the head and then changing into a spacious sound without clear lateralization. Other studies showed that similar stimuli could be lateralized toward the ear with the leading envelope (Bernstein and Trahiotis, 1985). However, we did not perform tests of lateralization. The experimental parameter was the carrier frequency, which was set to 250 Hz, 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz in the first experiment. Stimuli with different carrier frequencies were presented in separate blocks in counterbalanced order between participants. The stimulus timing was designed for eliciting separated onset responses and ITD change response, the first indicating sensation of the sound and the last detection of the ITD change (Ross et al., 2007a,b). The AM stimuli lasted for 4.0 s, and the ITD change occurred at 2.0 s (Fig. 1). Four stimulus types were designed. Stimuli in which the ITD changed from zero to 4 ms were termed outward ITD changes, and changing the ITD from 4 ms at the sound onset to zero was termed an inward change. Moreover, the leading envelope for inward and outward ITD changes was either in the left or the right ear. The different stimuli were presented in random order. The relatively long stimulus duration was chosen to reduce possible interactions between the sound onset response and the ITD change response. Stimuli were presented with the inter-onset interval uniformly randomized between 5.5 s and 6.5 s. For each carrier frequency, 120 stimuli, 30 of each type, were presented in a block of 12 min duration and repeated four times, requiring in total four one-hour sessions on subsequent days.

2.4. Stimuli for the second MEG experiment

The stimulus sequence was designed according to a previous study of ITD detection, employing an ongoing AM sound which contained multiple fast ITD changes intervened with short in-phase periods (Ross, 2008). The AM envelope was of the same phase in both ears at the beginning of the stimulus, and a first ITD change was introduced at 800 ms by advancing the envelope by 2 ms in the right ear and delaying it by 2 ms left. The 4-ms ITD interval ended at 1200 ms and was followed by a 400-ms interval of zero ITD. The next ITD change was introduced at 1600 ms now with the leading envelope in the left ear. In total 16 intervals with 4-ms ITD were included in a stimulus sequence of 13.6 s duration (Fig. 2A). Sequences were repeated 22 times with 16.0 s inter-onset interval within a block of 6 min duration. The stimulus carrier frequency was either 400 Hz, 800 Hz, 1200 Hz, 1600 Hz, or 2400 Hz and was held constant during a block.

The stimuli were embedded in two types of noise. One was a stationary broadband noise, which was used to mask possible spectral splatter outside the stimulus frequency, its overall SNR was 22.4 dB. The second noise was a multi-talker babble of four female French speakers, which was presented with 6 dB SNR. Both noise types were notch-filtered for maintaining 60 dB SNR within an octave band around the stimulus spectrum. The spectral densities of the noise types are illustrated with Fig. 2B and C, respectively. The multi-talker noise was used to investigate the effects of a concurrent temporally rich sound on the processing of envelope ITD. The hypothesis was that the notched babble masker would not interact with the stimulus and narrowly tonotopic organized responses related to sensory processing. It was assumed that masking did not affect processing in the auditory brainstem and the representation of the auditory input at the cortical level but affected higher-order auditory cortex responses. However, if brain responses related to perception act across channels, those responses would be affected by the babble masker. The ten stimulus conditions (five carrier frequencies, two noise types) were repeated twice within two recording sessions of about one-hour duration on separate days no more than a week apart.

Stimulus timing was controlled by Presentation software (Neurobehavioural Systems, Berkeley, CA). Sounds were presented through ER-3A audiometric sound transducers connected to the participant's ears via 2.5 m of plastic tubing and foam inserts. The time delay of 8 ms, caused by the sound travelling through the tubes, was considered during data analysis. Before each MEG recording, the individual sensation threshold at 1000 Hz was tested, and stimuli were presented at 60 dB above this threshold. Thus, the stimuli at different frequencies were presented at the same sound pressure level.

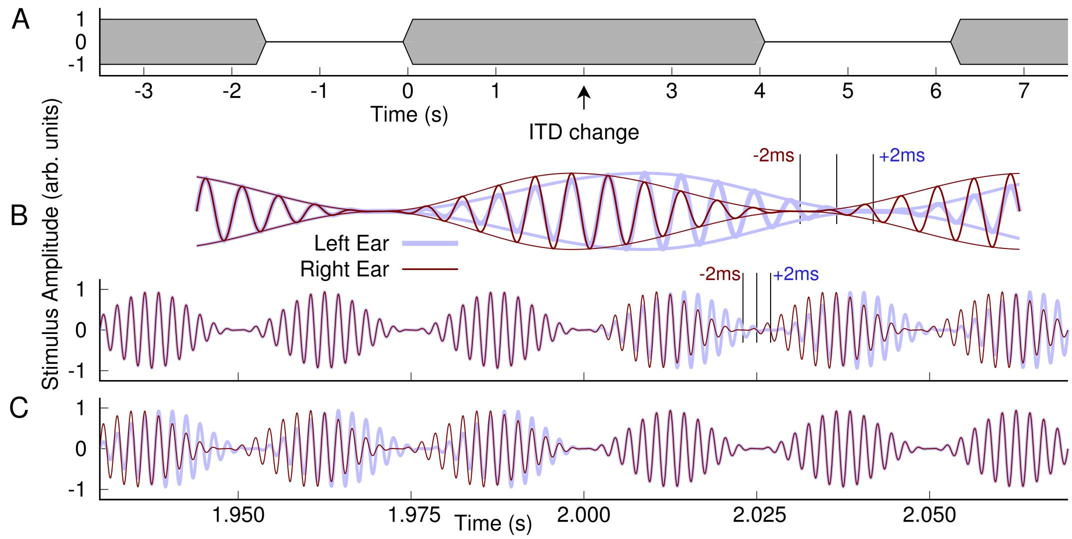

Fig. 1. Auditory stimuli for the first experiment. **A:** AM sounds of 4.0 s duration were presented with an inter-onset interval of 6.0 ± 0.5 s. The arrow indicates the ITD change at 2.0 s. **B:** Time course of an outward change on an enlarged time scale: The envelope of the left ear sound was delayed by 2 ms and the envelope in the right ear was advanced by 2 ms, resulting in an envelope ITD of 4 ms. No time difference occurred for the fine structure of the 500 Hz carrier signal. **C:** Time course of an inward change. The envelope ITD was 4.0 ms for the first 2.0 s; no difference occurred for the second half of the stimulus. Further stimulus conditions were an outward change with leading envelope left and an inward change from leading envelope left to zero ITD. The four stimulus types were presented in random order within an experimental block of constant carrier frequency.

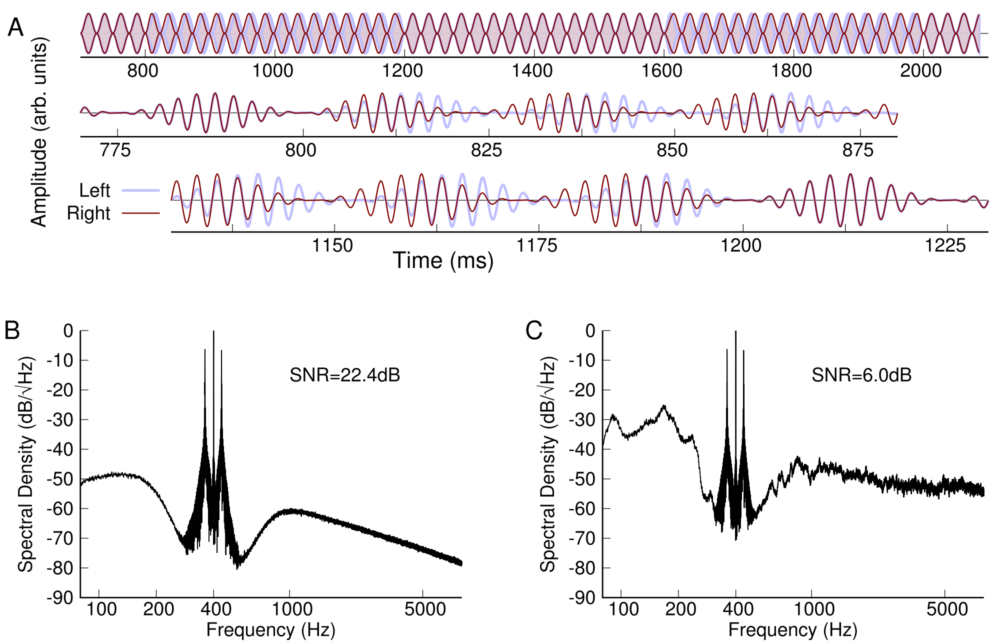

Fig. 2. Stimuli with alternating envelope ITD transitions for the second experiment. **A:** The first ITD change occurred at 800 ms and then every 400 ms thereafter. The right ear sound was leading between 800 ms and 1200 ms, followed by a 400-ms interval of zero ITD. The left ear sound was leading between 1600 ms and 2000 ms, again followed by a 400-ms interval of zero ITD. Alternating ITD intervals were continued for the total stimulus duration of 13.6 s containing eight intervals with right leading envelope, eight with left leading envelope, and 16 intervals with zero ITD. **B:** Spectral density of the 400-Hz stimulus embedded in white noise background containing an octave wide notch centred at the stimulus carrier. **C:** Spectral density of the stimulus and added multi-talker babble noise. Again, the noise was attenuated by an octave wide notch filter around the stimulus frequency of 400 Hz.

2.5. MEG data acquisition

The MEG acquisition was performed in a silent magnetically shielded room using a 151-channel first-order axial gradiometer type whole-head MEG system (Vrba and Robinson, 2001) (CTF-MEG, Port Coquitlam, BC, Canada). After online low-pass filtering at 300 Hz, the magnetic field data were sampled at 1250 Hz and stored continuously. Participants were seated comfortably in an upright position with the head resting inside the helmet-shaped MEG device. Participants kept their eyes open and focused their view on a fixation cross on the wall in front of the MEG seat. The head position was registered at the beginning and end of each recording block using three detection coils attached to the participant's nasion and the pre-auricular points. During each block, participants were instructed to maintain their head position best. A data block was rejected if the difference in head coil positions exceeded the threshold of ±4 mm in any direction. This procedure ensured that head movements did not affect the source localization accuracy.

2.6. Dipole modelling

Averaged auditory steady-state responses were calculated for dipole modelling. For this procedure, the continuous MEG signals were parsed into short epochs of 200-ms duration, beginning at each minimum of the stimulus AM. For artifact removal, a principal-component analysis was performed on each epoch. Components, exceeding the field strength of 1.0 pT in any channel were subtracted. Epochs containing eight periods of 40-Hz oscillations were averaged with partial overlap. Next, single dipoles in both hemispheres were fitted simultaneously to the 151-channel magnetic field distribution of the averaged 40-Hz response using the spatiotemporal fit as implemented in the *dfit* function of the CTF software. The data in the time interval between 50 ms and 150 ms were first modeled with a mirror-symmetric pair of dipoles in bilateral temporal areas. The resulting source coordinates were the initial points for fitting the dipole in one hemisphere while the coordinates in the other hemisphere were kept fixed. This last step was repeated, switching between hemispheres each time until the source coordinates showed no further variation. Dipole fits were accepted if the calculated field explained at least 90% of the variance of the measured magnetic field and if the standard deviation obtained from repeated measurements was less than 8 mm in any Cartesian coordinate. For each participant, multiple estimates of the dipole locations were obtained from repeated blocks under all experimental conditions in both experiments. Dipole coordinates, obtained with different stimulus frequencies, were compared to test for a tonotopical organization. Source coordinates and orientations were averaged across frequencies and repetitions to construct individual source models for each participant.

2.7. MEG data analysis

For the analysis of auditory cortex activity, the continuous MEG signals were parsed into stimulus-related epochs beginning 500 ms before stimulus onset and ending 500 ms after stimulus offset. Principal components exceeding 2.0 pT in any channel were subtracted for artifact removal. Source waveforms were calculated for every single trial based on the individual dipole model. This procedure of source space projection (Ross et al., 2000; Teale et al., 2013; Tesche et al., 1995) combined the 151-channel magnetic field data into two waveforms of cortical source strength measured in nano Ampere meter (nAm). The position of the MEG sensor relative to the participant's head may have changed between sessions and between participants. Such head moveeements would have caused spatial dispersion in group-averaged magnetic field data. However, the cortical source waveforms were not affected by the head position.

Four different evoked responses were analyzed in the cortical source activity. First, sequences of auditory evoked P1-N1-P2 responses were elicited by the sound onset and the ITD change. Second, the AM rhythm elicited 40-Hz oscillation. Third, the ITD change elicited a reset in the 40-Hz phase, and fourth, it was studied whether the interhemispheric phase difference in the 40-Hz oscillation would reflect the phase difference in the bilateral AM stimuli. All response types were analyzed with respect to the factors carrier frequency, masking, and age.

For analyzing the P1-N1-P2 responses, the time series of auditory cortex activity were parsed into stimulus-related epochs, containing 500 ms pre and 500 ms post-stimulus intervals. The epoch duration was 5.0 s for the first experiment and 14.6 s for the second. The time series were averaged across all trials of repeated experimental blocks separately for the different stimulus conditions. In the second experiment, further averaging was performed across repeated stimuli within a stimulus sequence, again for epochs including 500 ms pre and post stimulus intervals. Peak amplitudes of auditory evoked P1-N1-P2 responses were measured after 20-Hz low-pass filtering.

Time series of the 40-Hz responses were obtained by bandpass filtering the cortical source waveforms between 28 Hz and 56 Hz. The 40-Hz response reaches a constant amplitude and phase at about 250 ms after a change in the stimulus. The constant part of the 40-Hz response was termed the auditory steady-state response (ASSR). The ASSR amplitude was measured as the mean 40-Hz amplitude in the time interval between 250-ms after a stimulus change and the onset of the next stimulus change. Effects of the carrier frequency, noise, and the participant's age on the ASSR amplitude were analyzed.

The change in the envelope ITD was induced by delaying or advancing the AM envelope of the stimulus, which also can be described in terms of manipulating the phase of the AM sound. The cortical response to those stimulus changes was studied with the time courses of the phase of the 40-Hz responses. First, time courses of the magnitude of the phase, following the envelope ITD changes, would indicate a stimulus representation at the cortical level. Second, phase transients could serve as an indicator for cortical registration of ITD changes (Ross, 2008). Therefore, the temporal dynamics of phase changes $\Delta\varphi(t)$ were analyzed regarding the difference between the observed instantaneous phase $\varphi(t)$ of the 40 Hz oscillations and the phase $2\pi f_m t$ of the stimulus with the modulation frequency f_m. The amplitudes of the 40-Hz responses were obtained from discrete Fourier transform at 40 Hz by calculating the dot product between the response and a complex 40-Hz function. The time courses of the 40-Hz phase were obtained as the angle of the cross-frequency product between the 40-Hz response and a complex 40-Hz reference. Phase changes were expressed as a partial of the period of the 40-Hz oscillations (e.g. $\Delta\varphi = 90^{\circ}$ is related to a time delay of 6.25 ms).

3. Results

3.1. Behavioural tests

The group-mean psychometric function for fine structure ITD (Fig. 3A) showed that the 50% performance level was at 1450 Hz in group mean, with the range between 1300 Hz and 1560 Hz. Performance in the detection of an envelope ITD was more variable across participants as illustrated with the quartiles in the boxplots in Fig. 3B. In group mean, an envelope ITD was detected for a delay of about 1.5 ms at 1000 Hz, while a longer delay of more than 2.0 ms was required for detection at 250 Hz and 4000 Hz. Based on this result, the 4.0 ms ITD used in the MEG experiments was assumed as a suprathreshold stimulus at all test frequencies.

Group-mean hearing thresholds (Fig. 3C) were below 10 dB between 250 Hz and 8000 Hz for the young participants, while older adults showed elevated thresholds at higher frequencies, characteristic for their age (Cruickshanks et al., 1998). A mixed-effects ANOVA of the hearing thresholds revealed an effect of 'group' with elevated thresholds in older participants ($F(1,39) = 116.2$, $P < 0.0001$), an effect of 'frequency' with increase of thresholds at higher frequencies ($F(5,195) = 14.3$, $P < 0.0001$), and a 'group' × 'frequency' interaction ($F(5,195) = 31.1$, $P < 0.0001$) because high-frequency loss was observed in the older group only. No effect of 'side' was found ($F(1,39) = 0.2$). Thus, the audiograms were averaged across both ears (Fig. 3C).

The gap detection threshold, indicating the temporal acuity of hearing, was in mean close to 2.0 ms and was not different between age groups ($t(38) = 1.6$, $P > 0.05$). The threshold for detecting a mistuned harmonic, indicating spectral acuity, was slightly higher in older listeners ($t(27.3) = 2.20$, $P = 0.036$). However, the

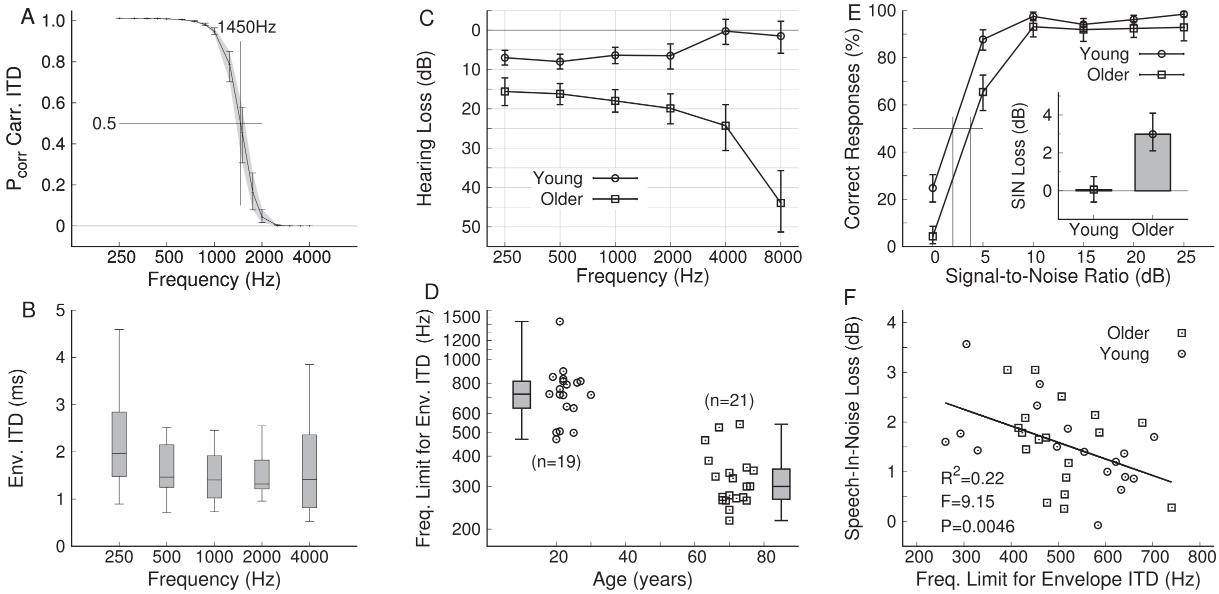

Fig. 3. Results of the behavioural tests. **A:** Fine structure ITD detection in young adults (n = 10): Probability of correctly discriminating a sound with fine structure ITD in a 2AFC procedure as a function of the carrier frequency. The error bars indicate the 95%-confidence limits for the mean at all test frequencies. **B:** Envelope ITD discrimination for the same 10 participants as in panel A: Box plots indicating the between-participant variation of the minimum detectable envelope difference for test frequencies between 250 Hz and 4000 Hz. **C:** Group mean audiograms for 19 young and 21 older participants, in the second experiment, averaged across ears. **D:** Behavioural frequency limit for using an envelope ITD cue for binaural hearing. **E:** Speech-in-noise (SIN) understanding using QuickSIN in 19 young and 21 older adults. **F:** Correlation between the performances in binaural hearing based on envelope ITD and SIN understanding.

distributions of individual results overlapped widely, and about half of the older participants performed as good as the young.

The QuickSIN test revealed that older listeners required 3 dB more SNR for speech understanding than young listeners ($t(34.8) = 4.75$, $P < 0.0001$). A closer look into the proportion of correct responses at the levels of the SNR (Fig. 3E) revealed that older participants missed some words already at high SNR, suggesting that factors like working memory and central auditory processing may have contributed to SIN understanding besides the physical interaction of speech and noise.

The young listeners discriminated envelope ITD of 4 ms in AM sound with carrier frequencies up to 742 Hz (95% CI = [656 Hz, 841 Hz]), while older adults could do this only at frequencies below 315 Hz (95% CI = [284 Hz, 351 Hz]). Individual frequency limits and box plots of the quartiles (Fig. 3D) demonstrate a clear separation between the ages. The group mean frequency limits were significantly different ($t(22.6) = 8.21$, $P < 0.0001$). Even after regressing out the effects of age on binaural hearing and the QuickSIN performance, the SIN loss was correlated with binaural hearing ($R^2 = 0.22$, $F(1,35) = 9.15$, $P = 0.0046$, Fig. 3F). However, no correlation was found between SIN loss and PTA thresholds ($R^2 = 0.07$, $F(1,37) = 2.87$, $P = 0.10$) and between binaural hearing and PTA threshold and temporal and spectral acuity ($F(1,37)<1.4$, $P>0.25$, for all).

3.2. MEG dipole locations

A MEG dipole approximation for the onset N1 response was successful for all individuals and all stimulus frequencies. The group-mean dipole coordinates in the MNI space, averaged across frequencies were −46.85 mm (left), −11.34 mm (parietal) and 5.14 mm (superior) for the left hemisphere and 50.89 mm, 10.10 mm, 5.82 mm right. The source coordinates coincided on a standardized atlas with Heschl's gyrus, located within the auditory cortex. The 95%-confidence limits for the mean coordinates were less than 4.0 mm in any direction. A left-right asymmetry, expressed by 1.24 mm more anterior source location in the right hemisphere, was consistent across participants ($t(13) = 2.55$, $P = 0.024$). High-frequency sources (4000 Hz) were located more medial and more superior than low-frequency sources (250 Hz). The extent of the tonotopic axis was 4.2 mm right ($F(4,52) = 3.99$, $P = 0.0067$) and 3.9 mm left ($F(4,52) = 3.96$, $P = 0.0070$).

3.3. First MEG experiment

Filtering the averaged auditory cortex responses with a 20-Hz low pass revealed the time series of the auditory evoked P1-N1-P2 response immediately following the stimulus onset, sustained negativity continuing for the duration of the stimulus presentation, a change response after the envelope ITD, and an off response. The overview of the grand averaged response waveforms in Fig. 4 illustrates the onset responses of similar size across stimulus frequencies, indicating the same sensation of the sounds, whereas the magnitudes of the change responses, indicating the initial registration of the ITD transition, decreased with increasing stimulus carrier frequency.

3.3.1. Auditory evoked onset responses

A repeated measures ANOVA for the N1 peak amplitude of the onset response with factors ‘frequency’ (five levels), ‘ITD’ (0, 4 ms), and ‘hemisphere’ (right, left), revealed main effects of ‘frequency’ ($F(4,52) = 5.68$, $P = 0.0007$) and ‘ITD’ ($F(1,13) = 16.4$, $P = 0.0014$). An effect of ‘hemisphere’ was not significant ($F(1,13) = 2.5$, $P = 0.14$, n.s.). Therefore, responses from both hemispheres had been averaged in Fig. 4. The N1 amplitude was larger when the onset of the stimulus contained a non-zero ITD (18.4 nAm) compared to stimuli with zero ITD (16.8 nAm) ($t(13) = 4.05$, $P = 0.0014$). The N1 amplitude increased from 17.2 nAm at 250 Hz to its maximum of 21.6 nAm at 1000 Hz and decreased toward higher frequencies, reaching the smallest value of 14.6 nAm at 4000 Hz (Fig. 5A).

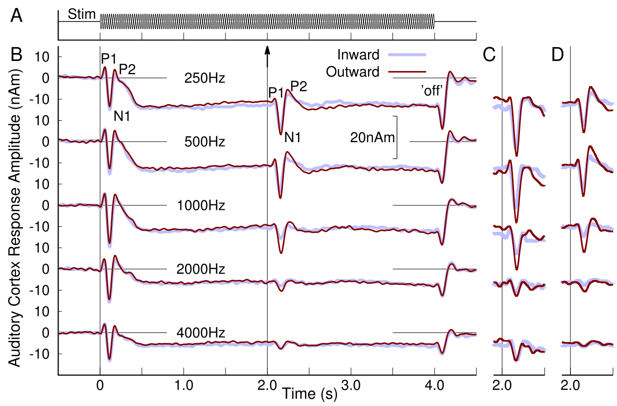

Fig. 4. Time series of auditory evoked responses in the first experiment averaged across left and right auditory cortices. **A:** Time series of the stimulus. **B:** Grand averaged (n = 14) time series, low-pass filtered at 20 Hz for the five stimulus frequencies between 250 Hz and 4000 Hz. **C:** ITD change responses in two participants who showed significant responses at 2000 Hz and 4000 Hz. **D:** Grand averaged (n = 12) ITD change responses excluding the participants shown in panel C.

3.3.2. ITD change responses

A repeated measures ANOVA for the change responses N1 peak amplitudes with the with factors 'frequency', 'hemisphere', and 'direction' of change (inward, outward) revealed main effects of 'frequency' ($F(4,52) = 37.5$, $P < 0.0001$) and 'direction' ($F(1,13) = 22.5$, $P = 0.0004$). The change response decreased with increasing frequency. The group mean amplitudes and significance levels of pairwise comparisons are illustrated in Fig. 5B. Outward changes elicited larger responses than inward changes ($t(13) = 4.80$, $P < 0.0001$). A 'frequency' × 'direction' interaction ($F(4,52) = 8.49$, $P < 0.0001$) was caused by different outward and inward changes at frequencies up to 1000 Hz but not at 2000 Hz and 4000 Hz.

Individual change responses were tested with a Rayleigh test, applied to a wavelet approximation of the change response, using a complex Morlet wavelet centred at 2100 ms and 6.0 Hz and half intensity bandwidth ±2.0 Hz (for details see: Ross et al., 2007a). For the outward change, significant responses at $P < 0.001$ were observed in all 14 participants at 250 Hz, 500 Hz, and 1000 Hz, and in three participants at 2000 Hz and two at 4000 Hz. For the inward change, individual responses were also significant for all participants at 250 Hz and 500 Hz, nine at 1000 Hz, two at 2000 Hz and 4000 Hz. A threshold for detection of interaural envelope disparity likely exists above 1000 Hz, while a few individuals showed a response at higher frequencies. Responses were consistently larger for outward than inward changes.

Change responses are shown separately in Fig. 4C for the two individuals whose responses were present beyond 2000 Hz. Notably, the change response at 4000 Hz did not exhibit the otherwise larger amplitude for outward changes compared to inward changes, which poses the question whether those individuals relied on other stimulus cues than the interaural time difference. Excluding the two individuals from the group-average emphasizes the disappearance of the change response at high stimulus carrier frequencies in the remaining twelve participants (Fig. 4D).

3.3.3. Amplitude of the 40-Hz ASSR

The 40-Hz response was separated from the simultaneously elicited low-frequency auditory evoked responses using a bandpass filter between 28 Hz and 56 Hz (Fig. 6). A transient gamma-band response characterized the time course of the 40-Hz response during the first 100 ms after stimulus onset. It was followed by a

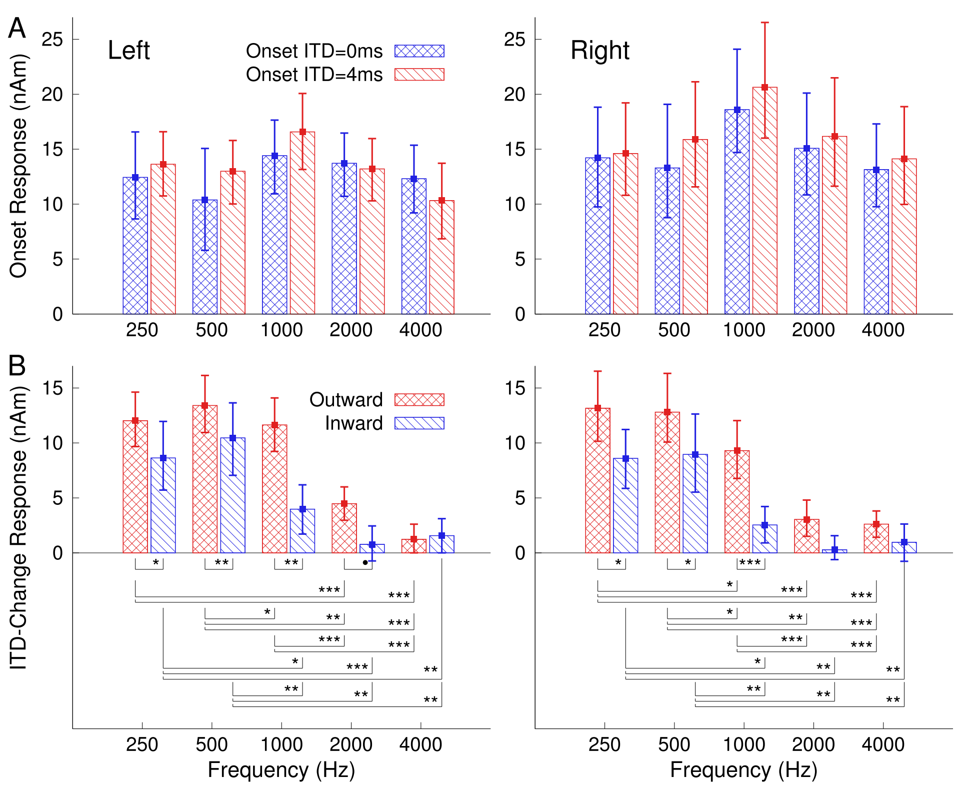

Fig. 5. Group mean amplitudes of **A:** N1 onset and **B:** ITD-change responses in the right and left hemispheres. Error bars indicate the 95%-confidence limits of the group means. Pairwise comparisons for change response showed larger responses to outward changes than inward changes at frequencies below or equal to 1000 Hz. N1 change responses were attenuated at higher frequencies while this was not the case for the N1 onset responses. (•: P < 0.05, *: P < 0.01, **: P < 0.001, ***: P < 0.0001).

build-up of the steady oscillation between 100 ms and 250 ms and almost the constant amplitude of the ASSR during the continuing stimulus. A dip in the constant amplitude became visible after the ITD change at 2.0 s (Fig. 6C), which was more pronounced at low than at higher frequencies.

A repeated measures ANOVA for the ASSR amplitude with the factors 'frequency' and 'hemisphere' revealed an effect of 'hemisphere' ($F(1,13) = 9.83$, $P = 0.008$) because of larger amplitudes in the right hemisphere than left ($t(69) = 6.33$, $P < 0.0001$) and an effect of 'frequency' ($F(4,52) = 32.7$, $P < 0.0001$). The ASSR amplitude was largest at 500 Hz and decreased to half of its size at 2000 Hz and 4000 Hz. The mean amplitudes and the 95%-confidence limits of the mean, as well as the results of pairwise comparisons, are illustrated in Fig. 6D. The transient gamma response after stimulus onset was less affected by variation in the carrier frequency ($F(4,52) = 2.94$, $P = 0.03$), its amplitudes were 1.4 nAm at 250 Hz, 2000 Hz and 4000 Hz and 1.8 nAm at 500 Hz and 1000 Hz and were not different between the stimulus conditions.

3.3.4. 40-Hz phase reset

The time course of the phase of the 40-Hz response to a 250-Hz stimulus with outward ITD change at 2.0 s is illustrated in Fig. 7A. The temporal dynamics of the phase included rapid phase transitions both after stimulus onset and after the ITD change and a sustained phase difference between hemispheres for the non-zero ITD interval.

The transient phase changes, which were termed phase resets, were studied with the time series of the 40-Hz phase, averaged across both hemispheres (Fig. 7B). The phase resets following the stimulus onsets were of almost equal size across frequencies and reached a value close to 6.0 ms, equivalent to a quarter period of 40-Hz oscillations. The phase reset following an ITD change was of similar size at 250 Hz and 500 Hz. However, the effect was smaller at higher frequencies. The time courses of phase changes in Fig. 7B suggest stronger phase resets for outward ITD changes compared to inward changes. Quantitative analysis using a repeated measures ANOVA with the factors 'hemisphere', 'frequency' and 'direction' of ITD change revealed no effect of 'hemisphere' ($F(1,13) = 3.06$, $P = 0.10$), which justified averaging across hemispheres for Fig. 7B. However, the ANOVA revealed effects of 'frequency' ($F(4,52) = 60.2$, $P < 0.0001$) and 'direction' ($F(1,13) = 95.2$, $P < 0.0001$). Group mean values and their 95%-confidence ranges are illustrated in Fig. 7C. The effects of phase reset were larger at low than high frequencies and larger for outward than inward ITD changes. An interaction between 'frequency' and 'direction' was significant ($F(4,52) = 6.19$, $P = 0.0004$) because outward changes were predominant over inward changes at 250 Hz ($t(13) = 6.32$, $P < 0.0001$), 500 Hz ($t(13) = 7.70$, $P < 0.0001$) and 1000 Hz ($t(13) = 5.76$, $P = 0.0001$), but not at 2000 Hz ($t(13) = 1.01$) and 4000 Hz ($t(13) = 1.21$).

3.3.5. Interhemispheric phase differences

Calculating the difference between the time courses of the 40-Hz phase in left and right auditory cortex (Fig. 7A) cancelled out the phase reset and revealed a time course of the sustained interhemispheric phase difference (Fig. 8A and B). The main finding was that the phase difference between stimuli in the left and right ears was represented as a sustained phase difference between the left and right auditory cortices. The magnitude of the interhemispheric phase difference reached about 2 ms and thus was smaller than the 4 ms ITD. In contrast to the phase reset, which was of a smaller magnitude at higher frequencies, the sustained phase differences were similar across carrier frequencies. When the stimulus phase was leading in the left ear, the 40-Hz phase was leading in the contralateral right auditory cortex and vice versa. The sustained phase changes were quantified as the mean phase in the non-zero ITD interval compared to the zero ITD time interval for the four stimulus conditions and all frequencies (Fig. 8C). Again, the figure illustrates that phase changes were consistent across frequencies. The magnitudes of phase differences between hemispheres were similar across stimulus conditions. However, how bilateral cortices contributed to the phase difference may have varied across stimulus conditions. For the outward ITD changes, a stimulus change from centred to left leading envelope resulted in a stronger phase change in the left hemisphere than right, and an ITD change toward right leading envelope resulted

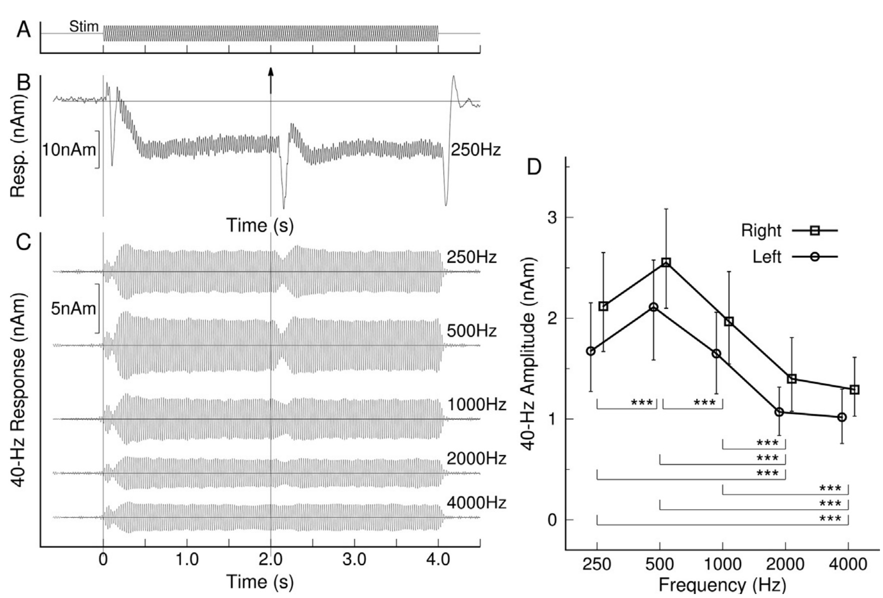

Fig. 6. Grand averaged ($n = 14$) time series and amplitudes of the 40-Hz responses. **A:** Stimulus with an ITD change at 2.0 s, indicated by the arrow. **B:** The time series of the 0–120 Hz wideband filtered response to a 250-Hz stimulus shows the overlay of simultaneously evoked slow auditory responses and the 40-Hz steady-state response. **C:** Bandpass filtering between 28 Hz and 56 Hz extracted the 40-Hz response, characterized by the transient gamma response in the 0–50 ms latency range, a built up of 40-Hz oscillations, and a brief dip in the amplitude following the ITD change stimulus. **D:** Group mean amplitude of the 40-Hz steady-state response in the right and left auditory cortices in relation to the stimulus carrier frequency. The error bars indicate the 95%-confidence limits and the asterisks the outcomes of pairwise comparisons (***: $P < 0.0001$).

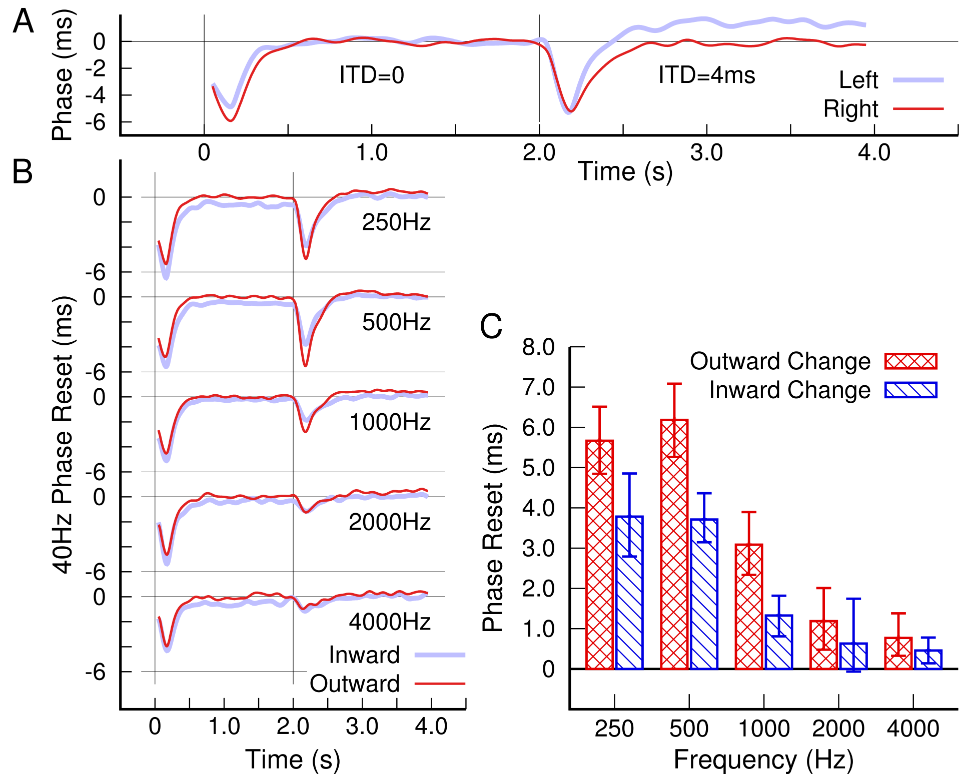

Fig. 7. Group mean (n = 14) time courses of 40-Hz phase resets after stimulus onset at time zero and after the ITD change at 2 s. **A:** The phase response to a 250-Hz stimulus with ITD change toward leading sound envelope in the left ear illustrates two main effects, phase resets after the stimulus onset and the ITD change, and a sustained phase difference between hemispheres during the envelope ITD interval. **B:** The mean of 40-Hz phase in left and right auditory cortices shows phase resets after stimulus onset and the ITD change of similar size for the 250 Hz and 500 Hz stimuli, while the size of the change response declines with higher frequencies. Outward changes elicited larger phase resets than inward changes. **C:** Group means of the magnitude of the phase reset following an ITD change for the different stimulus conditions. Error bars indicate the 95%-confidence limits for the mean.

in the strongest phase change in the right auditory cortex. For inward ITD changes, a change from leading envelope in the left ear toward a centred stimulus resulted in a stronger phase change in the right hemisphere than left and vice versa. The stimulus change from left leading to centred sound could be interpreted as a change toward more right lateralization and stronger phase change in the right hemisphere. Common to all stimulus frequencies, sustained phase changes were most substantial in the hemisphere contralateral to the ear with the leading envelope.

3.4. Second MEG experiment

3.4.1. Auditory evoked responses

Fig. 9 summarizes the waveforms of grand averaged evoked responses for the young and older age groups. The stimulus onset elicited P1-N1-P2 responses of similar sizes for all frequencies and both age groups. The P2 and a sustained wave of the onset response were larger with the babble noise because of the masker onset coincided with the stimulus onset. Grand averages across all frequencies are shown in Fig. 9A for the young and Fig. 9B for the older participants. The first ITD-change response, which was elicited by an outward change at 800 ms latency, was indicated by upward pointing arrows in Fig. 9. Similar responses occurred for 16 repeated stimuli in the sequence and were averaged for Fig. 9C and D, in which time zero referred to the onset of outward ITD changes. The ITD change responses were substantially smaller than the onset response, which was considered by adjusting the amplitude scales in Fig. 9C and D. Responses to inward ITD changes, indicated by downward arrows in Fig. 9, were identified only at 400 Hz in the low noise condition. Outward ITD change responses in the low noise condition were largest at 400 Hz for both groups. Responses declined with increasing frequency in both age groups. While in the young group, the 800-Hz response was of similar size as at 400 Hz, it was strongly attenuated in the older. Babble noise attenuated the ITD responses, which were clearly expressed at 400 Hz only.

Objective detection of individual responses to outward ITD changes, using phase statistics on wavelet coefficients, succeeded in all 19 young participants at 400 Hz, in 18 at 800 Hz, 14 at 1200 Hz, five at 1600 Hz and three at 2400 Hz showing a steep decline above 1200 Hz. With babble noise, the number of individual responses was reduced to 16 at 400 Hz, five at 800 Hz and a single participant at 1200 Hz. The same signal statistics found significant responses in 20 out of 21 older participants at 400 Hz, in 12 at 800 Hz, two at 1200 Hz, and single cases at 1600 Hz and 2400 Hz, showing a steep decline in the number of individual responses above 800 Hz. In the presence of babble noise, only six older participants showed a significant response at 400 Hz and three at 800 Hz.

A mixed design ANOVA analyzed group differences in ITD change N1 responses with the between-group factor ‘age’ and within group factors ‘frequency’ and ‘masking’. The ANOVA revealed main effects of ‘frequency’ ($F(4,152) = 42.6$, $P < 0.0001$) and of ‘masking’ ($F(1,38) = 75.9$, $P < 0.0001$). Responses were smaller at high compared to low frequencies. Also, responses were smaller with the babble noise compared to the white noise. Only a tendency was found for an effect of ‘group’ ($F(1,38) = 3.76$, $P = 0.06$). A two-way interaction was found between ‘frequency’ and ‘masking’ ($F(4,152) = 13.0$, $P < 0.0001$) and a three-way interaction between ‘group’, ’frequency’, and ‘masking’ ($F(4,152) = 5.86$, $P = 0.0002$). Two-sample t-tests revealed that responses at 400 Hz were not different between groups with the low-level white noise

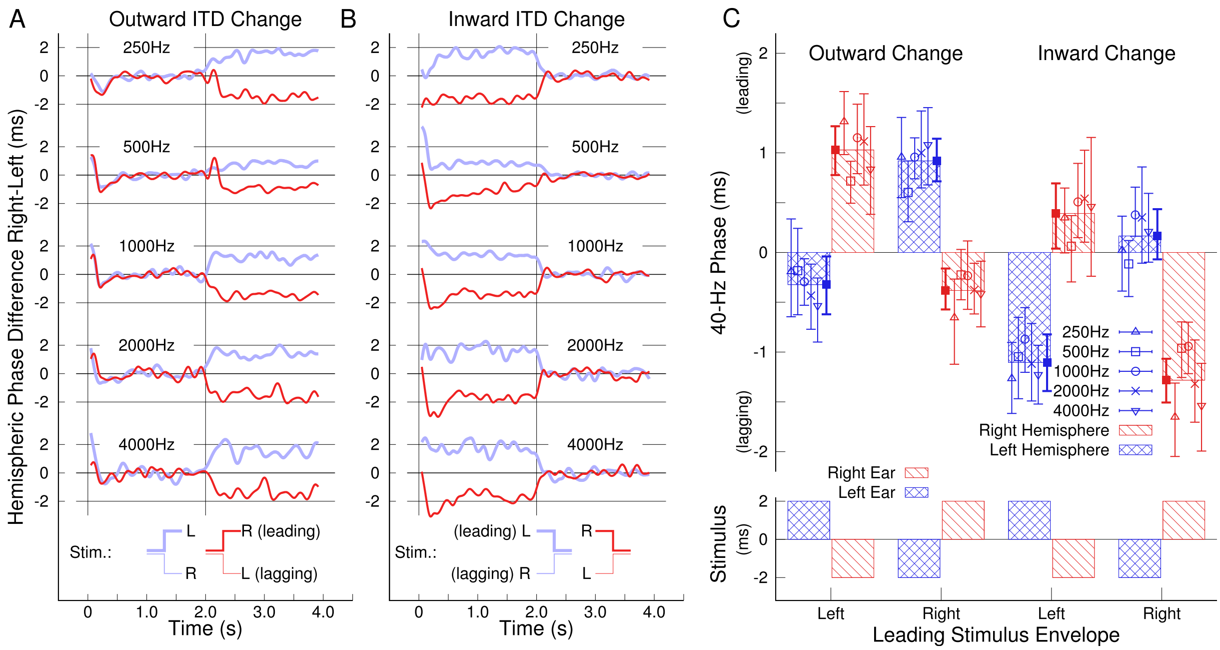

Fig. 8. Sustained interhemispheric phase differences. **A:** Positive values indicate leading phase right, negative values indicate a leading phase left. An outward ITD change with leading phase in the left ear resulted in a leading phase in the contralateral right hemispheric response (light blue lines). Vice versa, the left auditory cortex response was leading when the right ear stimulus was leading (dark red lines). **B:** Inward changes from leading phase in the left ear (blue) and the right ear (red). The ITD of 4.0 ms in the stimulus envelope was represented by an interhemispheric phase difference in the brain responses on the order of 2 ms at all carrier frequencies. **C:** The 40-Hz phase in the left and right hemispheres, calculated as the mean over the ITD time interval and compared to the zero-ITD interval, showed asymmetric contributions to the inter-hemispheric phase difference. For outward changes, a contralateral leading phase was predominant, while for inward changes the ipsilateral lagging phase was largest. The boxes and thick line error bars indicate the means across frequencies and their 95%-confidence ranges. The thin line error bars indicate the 95%-confidence ranges for individual frequencies. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

condition (t(36.7) = 0.5, P = 0.62, n.s.). However, when the babble noise masker was present, the response in the older group was smaller than in young adults (t(29.3) = 2.49, P = 0.019). ITD change responses were smaller in older compared to young listeners even in the low-noise condition at 800 Hz (t(35.3) = 3.86, P = 0.0005) and 1200 Hz (t(29.0) = 2.90, P = 0.0071). Babble noise attenuated the responses at all frequencies in the young group and between 400 Hz and 1600 Hz in the older group (Fig. 10).

3.4.2. Amplitude of the 40-Hz ASSR

Amplitudes of the 40-Hz ASSR were measured as peak spectral amplitudes across the whole stimulus sequence. The ASSR amplitude declined by about 30% when the carrier frequency increased from 800 Hz to 2400 Hz in both groups, while the overall level depended on hemispheres and masking (Fig. 11). A mixed design repeated measures ANOVA revealed an effect of the between-group factor ‘age’ (F(1,38) = 4.40, P = 0.043), with a larger grand mean amplitude of 1.55 nAm in older listeners compared to 1.05 nAm in the young (t(26.7) = 2.27, P = 0.03). The ANOVA revealed main effects of ‘masking’ (F(1,38) = 86.1, P < 0001) because of smaller 40-Hz amplitudes with noise, of ‘hemisphere’ (F(1,38) = 60.3, P < 0.0001) because of larger responses right than left, and of ‘frequency’ (F(4,152) = 28.4, P < 0.0001) because of an amplitude decline with increasing frequency. A ‘hemisphere’ × ‘masking’ interaction was significant (F(1,38) = 29.2, P < 0.0001) because of a more considerable effect of masking in the right hemisphere compared to left. The latter was tested by comparing the laterality index, which was calculated as LI=(R-L)/(R + L), as LI = 0.107 with masking and LI = 0.152 without (t(39) = 3.80, P = 0.0005).

3.4.3. 40-Hz phase reset

The time courses of the 40-Hz phase were analyzed with respect to phase resets elicited by the ITD changes and hemispheric phase differences, representing the stimulus phase at the cortical level. The phase resets were analyzed by averaging the phase responses across hemispheres, thus cancelling the effects of the sustained interhemispheric difference. Fig. 12A and B provide overviews about the temporal dynamics of the 40-Hz phase in young and older adults. Phase reset occurred after outward ITD changes, reaching their maximum magnitude at about 200 ms latencies. The peak values decreased with increasing frequency. A phase reset, following an inward change, was much smaller than for an outward change and was observed only at 400 Hz in the young group. Presenting concurrent babble noise attenuated the magnitude of the phase reset.

Group mean magnitudes of phase resets, elicited by outward ITD changes, the 95%-confidence intervals of the mean, and the outcomes of pairwise comparisons, using bootstrap resampling, are shown in Fig. 12C. The magnitude of the phase reset decreased with increasing frequency and was smaller at 800 Hz compared to 400 Hz in both age groups and noise conditions. Responses at 1200 Hz were smaller than at 800 Hz in the young group. Pairwise comparisons revealed a reduced response magnitude under the babble noise condition at all test frequencies between 400 Hz and 1600 Hz in both age groups. The babble masker abolished the response above 800 Hz, while significant phase resets were elicited up to 1600 Hz under the low noise condition in both age groups. Differences between the age groups became evident during the transition toward higher frequencies. The phase reset was smaller in older adults compared to young at 800 Hz in the low noise condition and already at 400 Hz with the babble masker.

3.4.4. Interhemispheric phase differences

Calculating the difference between the 40-Hz phase in the right

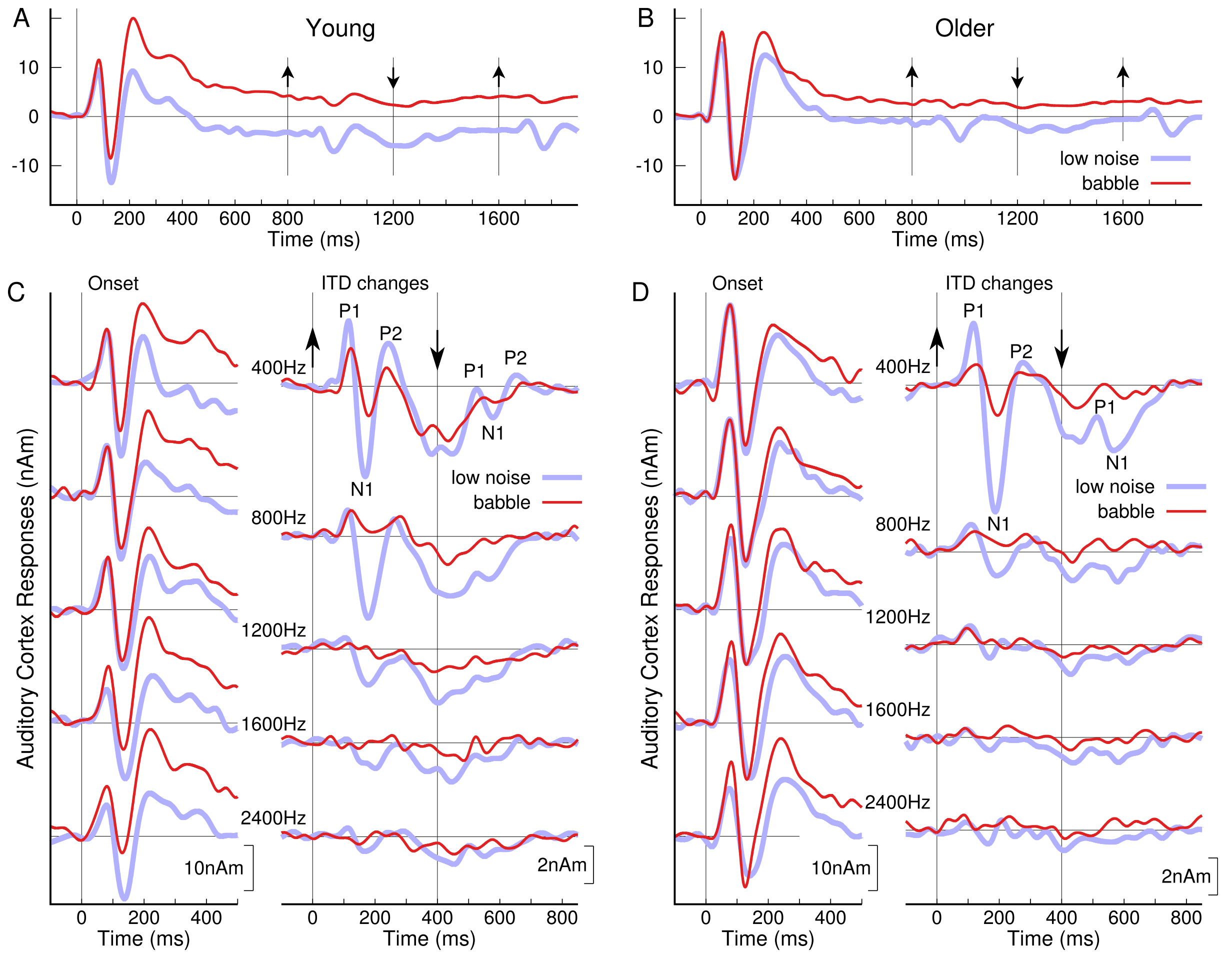

Fig. 9. Time series of 20-Hz low-pass filtered auditory evoked responses in the second experiment averaged across left and right hemispheres in young and older listeners at low-level white noise or higher level multi-talker babble noise. **A:** Grand averaged responses in the young adults show P1-N1-P2 onset responses, change responses to the outward ITD transitions at 800 ms and 1600 ms, and smaller ITD responses after the inward change at 400 ms. Onset responses were of similar magnitude with both types of noise, while the ITD change responses were attenuated with the babble noise. **B:** Grand averaged responses for older participants. **C:** Onset and ITD change responses for the five stimulus frequencies in the young group. ITD responses were averaged across repeated stimuli within a sequence irrespective of whether the stimulus changed toward the left or right leading envelope. Time zero corresponds to outward changes. Inward changes occurred at 400 ms as indicated by arrows. **D:** Onset and change responses in the older group.

and left auditory cortices cancelled out the transient phase resets, which were of similar magnitudes left and right, and resulted in time courses of the interhemispheric phase differences (Fig. 13A and B). The stimulus ITD of 4 ms was represented as a 2-ms difference between the right and left cortical responses, with no significant variations across stimulus frequencies, noise conditions, and age. Bar graphs of the mean phase in the left and right auditory cortices (Fig. 13C) show that the response contralateral to the ear with the leading stimulus phase contributed predominantly to the interhemispheric phase difference.

4. Discussion

This study is the first report of cortical auditory evoked responses, and 40-Hz phase resets, elicited by transient changes in the envelope ITD of AM sound. The evoked ITD change responses and 40-Hz phase resets were largest for low-frequency sounds and were strongly attenuated for higher frequencies. The upper-frequency limit was reduced in older listeners compared to the young. In contrast, auditory evoked onset responses and amplitudes of the 40-Hz ASSR were less affected by the sound frequency and age. Outward ITD changes elicited larger responses than inward ITD changes, similar as previously observed for the fine structure ITD. Sustained phase differences in the AM stimulus envelopes were represented as interhemispheric phase differences with high acuity regardless of the stimulus frequency and age. A multi-talker masking noise, sparing the frequency band of the AM stimulus, attenuated the ITD change response and the 40-Hz phase resets. However, it had a lesser effect on the ASSR amplitude and did not affect the cortical representation of the sustained phase differences between the right and left ear.

4.1. Behavioural performances

Older adults in this study showed typical age-related hearing loss compared to young, specially at high frequencies. Moreover, older listeners required a larger SNR for SIN understanding. SIN understanding and hearing thresholds were not correlated with one other, although hearing loss has been found previously as the leading cause for SIN deficits (Humes, 1996; Van Rooij and Plomp, 1990). No effect of age was found for temporal acuity, measured with gap detection. Spectral acuity, measured with the mistuned-harmonics paradigm, was slightly lower in older listeners. Binaural hearing was not correlated with the hearing threshold, which is consistent with findings that detection of fine structure ITD at low frequencies was not affected by high-frequency hearing loss (Moore et al., 2012).

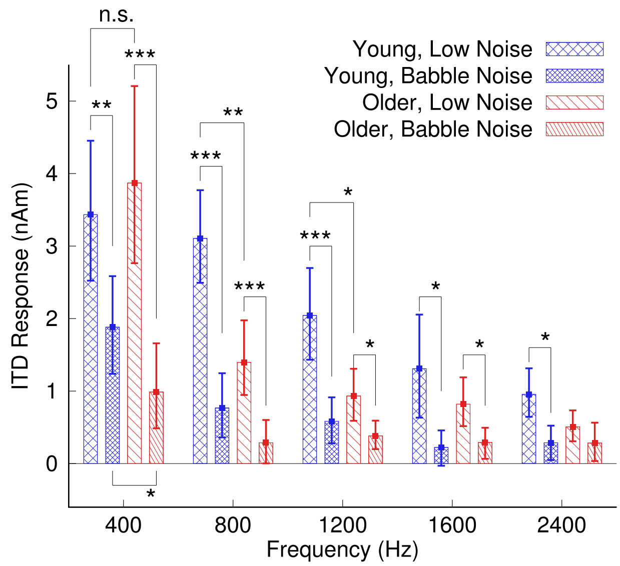

Fig. 10. Group mean amplitudes of the N1 change responses to outward ITD transitions for the five stimulus frequencies, two types of masking, and two age groups. Error bars denote the confidence ranges of the group means. (n.s.: not significant, *: P < 0.01, **: P < 0.001, ***: P < 0.0001).

However, the frequency limit for envelope ITD detection declined with age similarly as observed for the fine structure ITD (Grose and Mamo, 2010). Performance in binaural hearing was strongly affected by aging, and most importantly, SIN loss was correlated with binaural hearing, even after regressing out the effect of age, but SIN loss was not correlated with spectral and temporal acuity. Thus, performance in binaural hearing based on envelope ITD may predict SIN understanding better than measures of spectral and temporal acuity. One reason may be that envelope cues become more important for speech understanding in noise than in quiet (Qi et al., 2017). Moreover, recent studies showed that training envelope ITD cues improved SIN understanding in children (Lotfi et al., 2016) and older adults (Delphi et al., 2017), supporting the significance of binaural hearing based on envelope cues for SIN understanding.

4.2. Brain responses indicating stimulus sensation

This study employed simultaneous recording of multiple types of brain responses, which could be used as control conditions to rule out possible confounds. Sound onset responses indicated that participants could hear the stimuli, 40-Hz ASSR indicated processing of the stimulus AM, and an interhemispheric phase difference showed the representation of the stimulus ITD at the cortical level. We discuss first the effects of the stimulus frequency, aging and masking on the stimulus representation.

4.2.1. Sound onset responses

Clear N1 onset responses, indicating the sensation of the stimulus, were elicited under all stimulus conditions in all participants. The N1 in the first experiment was slightly larger at 1000 Hz than at higher and lower frequencies. One explanation is that the sound intensity was held constant for all frequencies. Highest sensitivity at 1000 Hz led to largest responses at this frequency. No effects of the carrier frequency, age, and masking were found for the onset response in the second experiment. The results corroborate the literature showing consistent N1 amplitudes across the lifespan (Picton et al., 1984; Tlumak et al., 2015). The frequency characteristic of the onset N1was identical with the findings from a similar study of fine structure ITD (Ross et al., 2007a). The tonotopic organization of the N1 generator (Pantev et al., 1988) could explain that the notched noise did not attenuate the N1 onset response.

4.2.2. Amplitudes of the 40-Hz ASSR

The 40-Hz AM of the stimulus sounds conveyed the ITD information. Effects of the carrier frequency and age on the size of the 40-Hz ASSR could have been limiting factors for the ITD change related 40-Hz phase reset. The ASSR amplitude in the first experiment was largest at 500 Hz, slightly smaller at 250 Hz, and decreased with increasing frequency. Consistently, the ASSR amplitudes in the second experiment were of the same scale, showed the maximum at 800 Hz, and declined with increasing frequency. In both experiments, the smallest amplitude was not below 50% of the maximum. Previous findings of similar frequency characteristics of the 40-Hz ASSR (Pantev et al., 1996; Ross et al., 2000) had been related to properties of the auditory periphery such as innervation

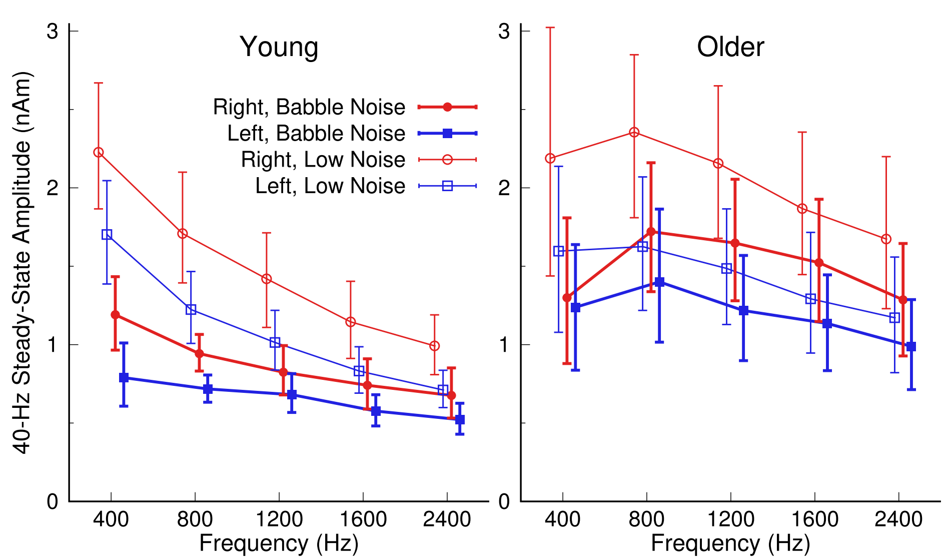

Fig. 11. Amplitudes of the 40-Hz steady-state response as a function of the stimulus frequency for left and right auditory cortex responses, low-level broadband noise and babble noise, and both groups of young and older participants. The error bars denote the 95%-confidence ranges of the group means.

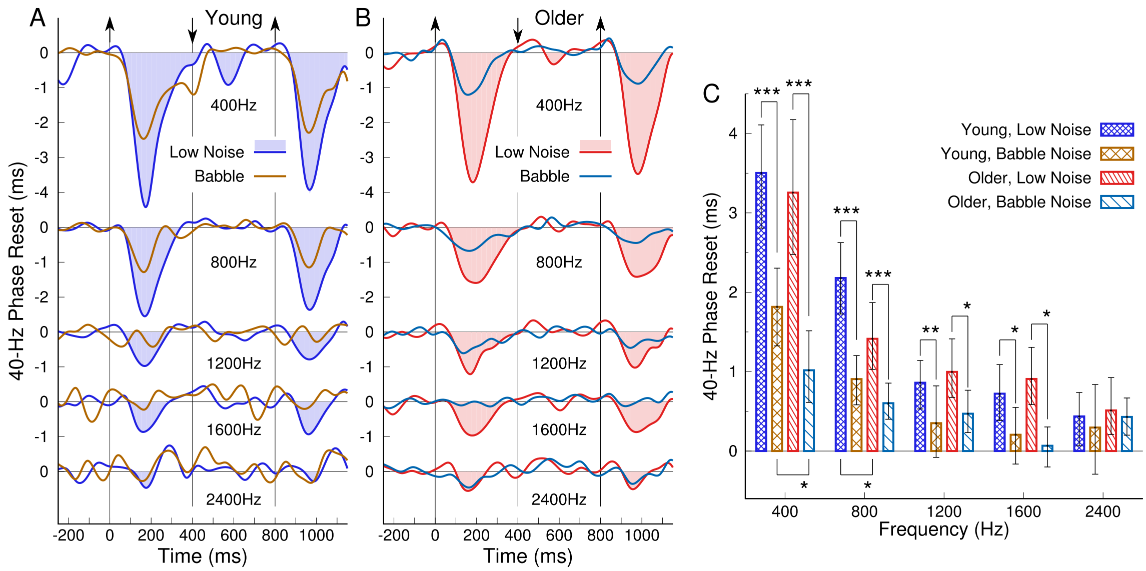

Fig. 12. 40-Hz phase resets in the second experiment. The magnitude of phase changes was measured in ms as partials of the 40 Hz period. Negative values indicate a leading phase. Time zero relates to the onset of outward ITD changes. **A:** Time courses of phase reset were obtained by averaging the phase responses across left and right auditory cortex for both types of masking sound in young participants **B:** in older participants. **C:** Group mean magnitudes of phase resets elicited by outward ITD changes at the five stimulus frequencies, two types of masking, and both age groups. The error bars denote the confidence ranges of the group means. (*: P < 0.01, **: P < 0.001, ***: P < 0.0001).

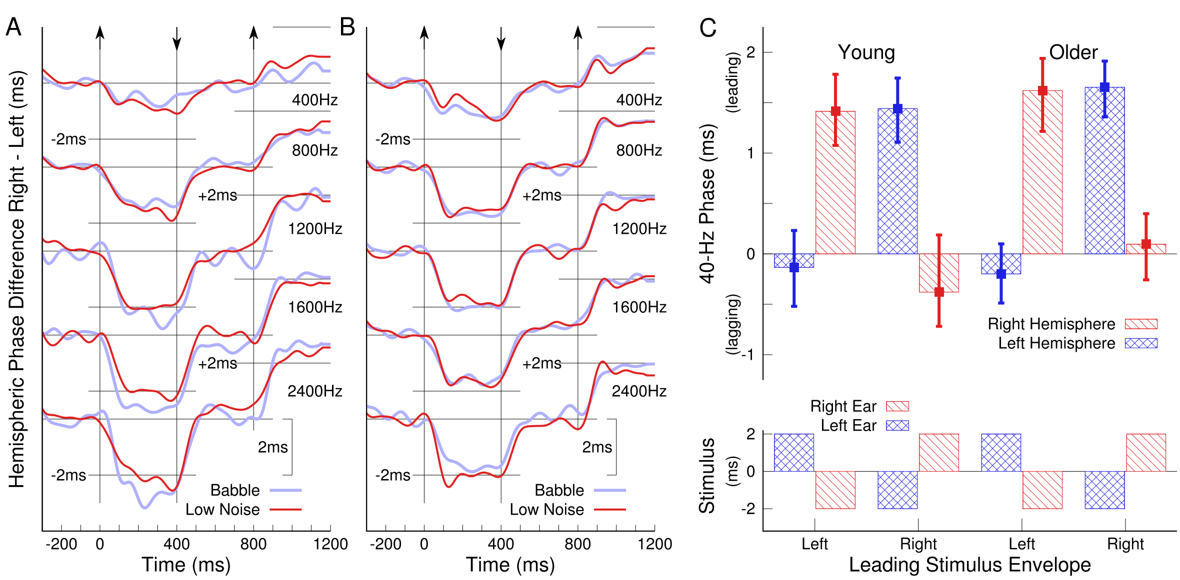

Fig. 13. Interhemispheric phase differences. **A:** The time courses show a leading phase in the left hemisphere (negative values) for outward ITD changes with leading phase in the right ear at time zero and leading phase right (positive) when the left ear phase was leading after 800 ms. **B:** Interhemispheric phase relation in older listeners. The factors masking and age had little effects on the phase representation. **C:** Group mean 40-Hz phase in the right and left hemispheres show an asymmetric contribution to the interhemispheric phase difference: The largest phase response occurred contralateral to the ear with leading ITD phase.

of a more substantial number of hair cells in the cochlea at low frequencies compared to higher frequencies (Galambos et al., 1981). Moreover, perceived loudness rather than stimulus intensity may determine the amplitude (Otsuka et al., 2016). The ASSR amplitude was close to its maximum value between 500 Hz and 1000 Hz, which is the frequency range within the ITD characteristics showed the steepest decline. Unlikely, the small changes in the ASSR amplitude itself caused the decline of the ITD responses toward higher frequencies.

4.2.3. 40-Hz ASSR in older listeners

The 40-Hz ASSR amplitudes were larger in older listeners compared to young listeners, suggesting no aging-related decline of the cortical representation of the sound envelope itself. This finding corroborates previous reports that aging did not reduce the amplitude of the auditory 40-Hz response (Johnson et al., 1988; Tlumak et al., 2015). EEG studies found that the amplitudes of middle latency responses, closely related to the transient 40-Hz responses, increased with aging (Amenedo and Díaz, 1998; Azumi et al., 1995; Chambers and Griffiths, 1991; Woods and Clayworth, 1986). Changes in the concentration of neurotransmitters may underlay the increase in the 40-Hz amplitude in older age (Ahveninen et al., 2002; Jääskeläinen et al., 1999). Larger 40-Hz ASSR in Alzheimer's Disease patients (Osipova et al., 2006; van Deursen et al., 2011) had been linked to changes in the efficacy of GABAergic inhibitory interneurons, involved in the generation of gamma oscillations. While further work is required for interpreting the functional significance of the 40-Hz increase, there was no indication that temporal processing at the scale of the 40-Hz AM was affected by age.

4.2.4. Representation of the stimulus ITD in interhemispheric phase differences

The envelope ITD was represented at the cortical level as a sustained interhemispheric phase difference in the 40-Hz ASSR. The phase difference can be explained by the asymmetries of the auditory pathways. If each auditory cortex had received symmetric input from both ears, the ITD would have been cancelled out. However, contralateral projections are stronger because of a higher number of fibres in contralateral connections (Jäncke et al., 2002; Rosenzweig, 1951). Thus, the predominant representation of the contralateral input outbalances the phase in the cortical response to the phase in the contralateral ear. Moreover, contralateral projections are faster than ipsilateral (Loveless et al., 1994), causing shorter latency for the auditory N1 response (Pantev et al., 1998) and the 40-Hz ASSR (Ross et al., 2005). The shorter latency in the stronger contralateral pathway resulted in the dominant representation of the leading envelope as observed consistently in both experiments. The smaller phase difference between auditory cortices compared to the stimulus ITD can be explained by the effect of combining bilateral stimuli along the auditory pathways and partially cancelling out the ITD. The interhemispheric phase difference was independent of the stimulus frequency even though the 40-Hz amplitude declined with increasing frequency. The time courses of the phase were most clearly expressed at highest frequencies in both experiments because the low-frequency responses were affected by concurrent phase resets, which were absent at highest stimulus frequencies. Interhemispheric phase differences of the 40-Hz ASSR have not been reported before, and it is not clear whether the precise phase representation has a functional significance.

In summary, the multiple MEG measures demonstrated that the stimulus AM and its envelope ITD was represented with high acuity at the cortical level. However, provided the different frequency characteristics for ITD detection and the phase representation, no evidence is given that the interhemispheric phase difference at the auditory cortex is used as a cue for binaural hearing.

4.3. Frequency characteristic of ITD responses

The ITD change N1 responses were substantially attenuated at higher frequencies and practically absent at highest test frequencies, which was in contrast to the small variations in the onset N1 across stimulus frequencies, The ITD change response declined steeply between 1000 Hz and 2000 Hz. The second experiment corroborated this frequency characteristic, which was similar as observed for fine structure ITD (Ross et al., 2007b). The frequency characteristics for the envelope ITD suggests that envelope ITD is processed in frequency selective channels rather than ITD processing based on envelope information independent of the carrier.

4.4. 40-Hz phase reset, elicited by ITD change

Phase resets indicated the envelope ITD changes. The magnitude of the phase reset was consistent across frequencies for the sound onset, but for the ITD changes, they showed a steep decline with increasing frequency. In a previous study, detection of 40-Hz phase resets was a more reliable indicator for fine structure ITD changes than the evoked response (Ross, 2008). A similar advantage of the phase reset was not evident in this study. The reason was that two different phase effects occurred concurrently, a transient phase reset and cortical representation of the stimulus phase changes, while the latter effect was stronger than anticipated. Especially, when the magnitude of the phase reset was small, close to the detection threshold, it was not always successful, disentangling the phase effects.

So far ITD changes have been considered mainly for 40-Hz AM stimuli. Some observed properties could have been specific to 40-Hz brain responses. However a recent study by Vercammen et al. (2017) extended the experimental findings to a wider range of modulation rates at 20 Hz, 40 Hz, and 80 Hz and replicated several response characteristics like the asymmetry of inward and outward changes, indicating that the findings are likely valid for an extensive frequency range, covering beta and gamma bands.

4.5. Hemispheric symmetry in the ITD responses

Auditory evoked ITD changes, 40-Hz phase resets, and the sound onset responses were of symmetric size in the left and right auditory cortex. One exception was the 40-Hz ASSR, which was larger in the right hemisphere, as reported before (Ross et al., 2005). The right-left difference can be explained by the asymmetry of the human auditory cortex (Shaw et al., 2013), not specific to sound localization. However other studies reported lateralization of sound localization-related responses. Larger activity contralateral to the sound lateralization was found in the fMRI bold signal (Von Kriegstein et al., 2008). Another MEG study with free-field stimulation showed that the N1 onset responses to sound from a midline speaker was slightly larger in the right hemisphere when the sound was preceded by a right side adapter sound compared to an adapter sound at the left side (Salminen et al., 2010). However, the stimuli in the current study were not perceived as strongly lateralized, which could have been the reason for the absence of response lateralization.

4.6. Asymmetry between outward and inward ITD changes

Evoked responses and 40-Hz phase reset to outward changes were stronger than to inward changes. The asymmetry between outward and inward changes was even stronger in the second experiment with faster stimulus repetition rate, in which responses to inward changes were practically absent. The findings correspond to the previous reports about fine structure ITD responses using long (Ross et al., 2007b) and short inter-stimulus intervals (Ross, 2008). The asymmetry of larger outward than inward responses had been interpreted as evidence for representation of ITD in two broadly tuned channels (Magezi and Krumbholz, 2010). The novel finding here is that the response asymmetry has been shown for envelope ITD also.

An alternative explanation could be that the inward change response is an off response. Off responses to ITD changes have been shown in the auditory cortex of ferrets (Hartley et al., 2011). The auditory off response is commonly smaller than the onset response because the number of auditory off-neurons is about 30% of on-neurons (Xu et al., 2014). This can be seen in Fig. 4: the size of the N1 off response is about one-third of the N1 onset response. However, outward and inward change responses were of more similar size. The more substantial contrast between outward and inward change responses became evident with a shorter inter-stimulus interval in the second study. This indicates that the adaptation properties of both responses might be different. In the second experiment, intervals with zero-ITD occurred in the stimulus sequence twice as frequent as intervals with either left or right leading ITD, which could have caused stronger adaptation for the inward responses.

The similarity between properties of cortical responses to fine structure ITD and envelope ITD supports the concept that different cues for sound localization merge at cortical level into a common code independently of the different sub-cortical processing of fine structure or envelope cues. A common coding schema at the cortical level could explain a recent report of the interaction of envelope ITD and fine-structure ITD although both ITD cues occurred at different time scales (Moore et al., 2018).

4.7. The effect of masking on the different ITD responses

The across-channel multi-talker noise strongly attenuated the ITD change responses and the 40-Hz phase reset, however, had a lesser effect on the 40-Hz ASSR. Previous studies showed that contralateral masking, another type of across-channel masking, attenuated the amplitudes of 40-Hz ASSR (Galambos and Makeig, 1992a; Galambos and Makeig, 1992b; Maki et al., 2009). However, unlike ipsilateral noise, which abolished the ASSR completely, contralateral noise reduced the amplitudes by no more than half of its value in quiet. Those findings are in line with our recent work, suggesting that at least two components of 40-Hz ASSR exist. The first, related to the sensory input, is processed within tonotopic channels and was not affected by contralateral noise. The second, generated in higher order thalamocortical circuits, was attenuated by contralateral noise (Ross and Fujioka, 2016; Ross et al., 2012). Contralateral masking is one example of across channel making, and similar effects were assumed for the notch-filtered babble noise in the current study. Under the assumption, that the babble noise interacted with auditory processing at a level of perception rather than with early sensory responses, the ITD change response and the 40-Hz phase reset can be interpreted as brain responses at or beyond the level of perception. This again is consistent with the interpretation that the ITD change response and the 40-Hz phase reset relate to a cortical representation of the outcome of prior ITD processing at the sub-cortical level.

4.8. Effects of age on ITD processing

Consistent 40-Hz ASSR in young and older participants suggested that temporal processing in the 40-Hz range was preserved in older age. However, the N1 ITD response as well the 40-Hz phase reset were smaller in older listeners at 800 Hz compared to young listeners, while they were of the same size at 400 Hz in both age groups. Moreover, masking attenuated the ITD response more in older than in young listeners. A common explanation for the effect of age on ITD processing is that the temporal acuity for processing the fine structure of the sound declines along the auditory pathway (Frisina, 2001). A previous study, showing a similar age-related decline in the fine structure ITD response (Ozmeral et al., 2016) reported also reduced hemispheric laterality of responses, which was not observed in this study.

Could the observed age-related decline in hearing explain the effects on ITD processing? To answer this question, multiple outcome measures were used in the current study, which enabled differentiating between hearing the stimulus details and perceiving the ITD changes. In addition to the ITD change responses, the onset responses at the various carrier frequencies were analyzed, as well as the ASSR and the cortical representation of the AM phase. First, the preserved onset responses showed, that older listeners could hear the sounds. Second, they processed the 40-Hz amplitude modulation as reflected in the ASSR amplitudes. Third, consistent phase responses across the age groups suggested that the acuity in the phase processing was not affected by age. In summary, the brain responses showed that the sound envelope was represented with high acuity in older listeners, and the hypothesis that age-related hearing loss could explain declined binaural processing was not supported. Finally, the observations from the brain responses are consistent with the reported behavioural performances.

Older listeners were more vulnerable to the multi-talker masking, which could be related to their reduced ability to inhibit irrelevant information (Hwang et al., 2017). Moreover, spectral acuity could have been reduced, resulting in wider frequency channels and therefore stronger interference across frequencies. The steep decline of ITD responses toward higher frequencies, even stronger expressed in older listeners, was very similar as reported for fine structure ITD. Thus it can be concluded that envelope ITD processing at the sub-cortical level requires neural synchrony at the carrier frequency as it does for fine structure ITD, although both ITD cues are probably processed in different neural structures.

Considering both the aging-related changes in subcortical auditory processing and central auditory processing at the cortical level seems essential for the intervention of restoring or improving binaural hearing. Specifically, high-level noise may interact with the cortical processing of binaural cues, and the listener may not be able accessing the binaural cues for perception. Thus, restoring and improving binaural hearing at low or moderate noise levels may not provide the same benefits at higher noise levels. For example, enhancing envelope ITD cues for cochlear implant users resulted in lower thresholds for ITD detection, but did not improve speech intelligibility in reverberation (Monaghan and Seeber, 2016). Experimental paradigms like the one used in the study, observing multiple types of cortical responses and employing masking approaches for the distinction between sensory representation and perception may help further studies of brain function in complex listening situations.

5. Conclusion

This study is the first comprehensive report of human cortical responses to ITD changes in the envelope of AM sound. The comparison between onset responses and ITD change responses supported that the observed effects of the stimulus frequency, masking, and age were specific to the ITD change responses and were not confounded by changes in the representation of the sensory input. Several characteristics of the envelope ITD responses were strikingly consistent with previously reported fine-structure ITD responses. The steep frequency characteristic indicates that subcortical processing of the envelope ITD requires phase locking to the stimulus fine structure. Thus envelope ITD detection seems to involve a holistic mechanism applied to the complete acoustic signal and is not performed after envelope extraction. The asymmetry between cortical responses to inward and outward ITD changes was similar to previous findings for fine-structure ITD, which indicates that envelope and fine-structure ITD find a common representation at the cortical level.

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.heares.2018.09.001.

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