

# Hemispheric asymmetry of auditory steady-state responses to monaural and diotic stimulation<sup>1</sup>

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## Abstract

Amplitude modulations in the speech envelope are crucial elements for speech perception. These modulations comprise the processing rate at which syllabic (~3-7 Hz) and phonemic transitions occur in speech. Theories about speech perception hypothesize that each hemisphere in the auditory cortex is specialized in analyzing modulations at different timescales, and that phonemic-rate modulations of the speech envelope lateralize to the left hemisphere whereas right lateralization occurs for slow, syllabic-rate modulations.

In the present study, neural processing of phonemic- and syllabic-rate modulations was investigated with auditory steady-state responses (ASSRs). ASSRs to speech-weighted noise stimuli, amplitude modulated at 4, 20 and 80 Hz were recorded in 30 normal-hearing adults. The 80 Hz ASSR is primarily generated by the brainstem, whereas 20 and 4 Hz ASSRs are mainly cortically evoked and relate to speech perception. Stimuli were presented diotically (same signal to both ears) and monaurally (one signal to the left or right ear). For 80 Hz, diotic ASSRs were larger than monaural responses. This binaural advantage decreased with decreasing modulation frequency. For 20 Hz, diotic ASSRs were equal to monaural responses while for 4 Hz diotic responses were smaller than monaural responses. Comparison of left and right ear stimulation demonstrated that with decreasing modulation rate a gradual change from ipsilateral to right lateralization occurred. Together these results (1) suggest that ASSR enhancement to binaural stimulation decreases in the ascending auditory system and (2) indicate that right lateralization is more prominent for low-frequency ASSRs. These findings may have important consequences for electrode placement in clinical settings, as well as for the understanding of low-frequency ASSR generation.

## Introduction

Spoken language consists of a continuous stream of acoustic information. Temporal envelope information plays an important role for accurate speech intelligibility (Shannon et al. 1995). The temporal envelope of speech contains multiple rates of amplitude modulations (AMs), ranging between 2-50 Hz (Drullman et al. 1994; Rosen 1992). Particularly, modulations near 4 and 20 Hz are important because they fall within the rate of syllabic (~3-7 Hz) and phonemic (~12-50 Hz) transitions in speech (Poeppel 2003).

The ability of the brain to detect these modulations can be assessed by auditory steady-state responses (ASSRs). ASSRs are oscillatory potentials that synchronize to the rate of a rhythmic auditory signal (Picton et al. 2003). It is assumed that ASSRs are generated by neuronal ensembles at the brainstem, subcortical and cortical level (e.g. Herdman et al. 2002). Studies have however shown that the dominant ASSR generator is determined by the modulation rate. That is, 80 Hz ASSRs are thought to be predominantly generated by brainstem sources, whereas low-frequency ASSRs (such as 4 and 20 Hz) are dominated by cortical sources (e.g. Herdman et al. 2002; Lehongre et al. 2011; Millman et al. 2010). This idea is supported by studies in animals (e.g. Frisina et al. 1990; Joris et al. 2004) and in humans (e.g. Giraud et al. 2000) showing that cortical neurons are more specialized than brainstem neurons to follow slow modulations.

In literature, most ASSR studies focused on the 80 and 40 Hz frequency regions. Yet, ASSRs to lower modulation frequencies may be more closely related to speech processing and may thus provide important higher-level information about speech perception and central auditory functioning (Alaerts et al. 2009; Poelmans et al. 2012). Anatomical models predict that in the cortex, auditory information is transmitted to the hemisphere contralateral to stimulus presentation (Bailey 2010). However, theories about speech perception assume that the left and right hemisphere also have a functional preference to process certain modulation rates (Goswami 2011; Poeppel et al. 2008). Whereas the right hemisphere is thought to preferentially process syllabic-rate modulations (Abrams et al. 2008; Hämäläinen et al. 2012; Millman et al. 2010), a bilateral (Hämäläinen et al. 2012; Herdman et al. 2003) or left hemispheric (Belin et al. 1998; Jamison et al. 2006; Johnsrude et al. 1997) preference for phonemic-rate modulations is assumed. Results of prior studies on hemispheric asymmetry of ASSRs have been inconclusive (Hämäläinen et al. 2012; Herdman et al. 2002; Ross et al. 2005; Schoonhoven et al. 2003; Yamasaki et al. 2005), and may be influenced by the nature of the stimulus (e.g. noise, pure tones), presentation parameters (e.g. monaural left/right ear,

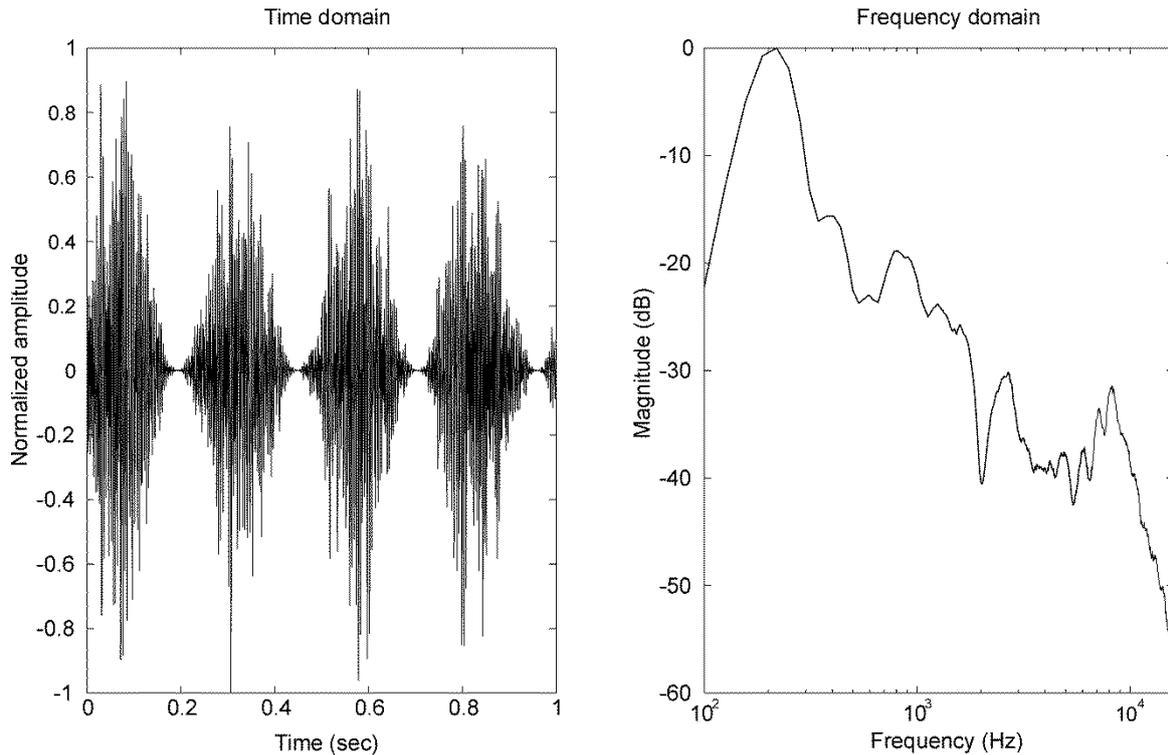
binaural or dichotic presentation), recording technique (EEG, MEG), and data analysis technique (scalp versus source analysis).

The present study aimed to systematically examine the topography (response-strengths and response asymmetry) of phonemic- (20 Hz) and syllabic-rate (4 Hz) ASSRs. As a control condition, 80 Hz ASSRs were included for two reasons. First, this modulation frequency is thought to be generated in the brainstem and therefore less affected by functional laterality. Second, this modulation frequency is generally assessed in clinical measurements of hearing thresholds and may therefore provide important information to optimize recordings. In a within-subject design, we assessed the influence of monaural (one signal to the left or right ear) versus diotic (same signal to both ears) auditory input. Additionally, response asymmetry along the auditory pathway was investigated.

## **Methods**

***Participants.*** Thirty adults participated (mean age: 22 years 3 months, SD: 2 years 1 month; 21 female participants) in the present study. All participants were native Dutch speakers, without a history of brain damage, language problems, psychiatric symptoms, visual problems or hearing loss. They were right-handed, assessed by the Edinburgh Handedness Inventory (Oldfield 1971), and were required to have normal audiometric pure-tone hearing thresholds (i.e., 25 dB HL or less for all octave frequencies from 0.25-8.0 kHz) at both ears.

***Stimulus parameters.*** Continuous amplitude modulated speech-weighted noise stimuli were created. The noise carriers were derived from the speech-weighted masking noise of the “Leuven Intelligibility Sentence Test” (LIST) (van Wieringen & Wouters 2008). This noise represents the long-term average speech spectrum of 730 sentences of a female speaker (Figure 1, right panel). Noises were 100% amplitude modulated at modulation frequencies near 4, 20 and 80 Hz. These modulation frequencies were adjusted to ensure an integer number of modulation cycles occurred within each data block of 1.024 s (i.e. epoch) (John & Picton 2000b), resulting in exact modulation frequencies of 3.91 Hz, 19.53 Hz and 80.08 Hz respectively. For simplicity, these modulation frequencies will be further referred to as the rounded frequencies: 4, 20 and 80 Hz respectively. Stimuli were generated in Matlab R14 (The MathWorks Inc. 2005). A time and frequency domain representation of the 4 Hz AM stimulus is given in Figure 1.



**Figure 1** The time (left panel) and frequency (right panel) domain representation of the 4 Hz amplitude modulated speech-weighted noise stimulus.

**Experimental protocol.** Stimuli were presented with Etymotic Research ER-3A insert earphones at 70 dB SPL, in three ways: (1) monaurally to the left ear (LE), (2) monaurally to the right ear (RE), and (3) bilaterally, diotic to both ears (BE). The EEG was recorded in a double-walled and soundproof booth with a Faraday cage. Participants were asked to lie down on a bed and to watch a soundless movie to stay alert. Two ASSR recordings were carried out for each stimulus within the same session.

**ASSR recording parameters.** The continuous EEG was recorded by 10 surface Ag/AgCl electrodes on the scalp, placed in accordance with the international 10-20 system for electrode placement (Malmivuo & Plonsey 1995). EEG was recorded from two central electrodes, Oz and Fpz, three left hemispheric electrodes, P3, F3 and M1 (left mastoid) and three corresponding right hemispheric electrodes, P4, F4 and M2 (right mastoid). The reference electrode was placed at Cz and the ground electrode at the right clavicle. Inter-electrode impedances were kept below 5 kOhm at 30 Hz. The electrodes were connected to a low-noise Jaeger-Toennies multichannel amplifier. Each EEG channel was amplified with a gain of

50000 and band-pass filtered between 0.2 Hz and 100 Hz (6 dB/octave), 2 Hz and 100 Hz (6 dB/octave) and 20 Hz and 300 Hz (6 dB/octave), for the 4 Hz, 20 Hz and 80 Hz modulation frequencies respectively. The amplified EEG signals were recorded and stimuli were presented by a RME Hammerfall DSP Multiface multichannel soundcard in combination with the experimental Setup ORL for Multichannel ASSR (SOMA) (Van Dun et al. 2008) at a sampling rate of 32 kHz and downsampled to 1 kHz. The continuous EEG was recorded in epochs. Each epoch consisted of 1024 samples (corresponding to 1.024 seconds). Sixteen successive artifact-free epochs were linked into a sweep (corresponding to 16.384 seconds). Online artifact rejection was set to 100  $\mu$ V, to exclude muscle artifacts. For each stimulus, 18 sweeps were recorded.

**ASSR data analysis.** Data analyses were performed by means of MATLAB R14 (The MathWorks Inc. 2005). Ten percent of the recorded epochs, i.e., those with the largest noise values, in each recording were rejected to exclude artifacts. Sweeps were reconstructed by linking 16 consecutive low-noise epochs. For each recording, the remaining 16 sweeps of EEG were weighted-averaged in the time domain and transformed into the frequency domain using a Fast Fourier Transform (FFT). Subsequently, the signal-to-noise ratio (SNR) of the response was calculated by the log-transformation of the ratio between the power spectral density of the response-frequency bin (S) and the power spectral density averaged over 40 adjacent frequency bins on each side of the response-frequency bin (corresponding to approximately 2.44 Hz to the left and right side of the modulation frequency) (N). The response amplitude is defined as the difference between the square root of S and the square root of N.

Because the EEG noise level at the ASSR modulation frequency changes over time, the present study evaluated ASSRs based on their SNRs. A response was considered significant when the *F*-ratio statistic showed a significant difference ( $p < 0.05$ ) between the response-power and the mean noise-power (John & Picton 2000a), corresponding to a response-SNR of 4.85 dB. In the analyses, the baseline level of the response-SNRs was placed at 0 dB because this indicates that the response plus the noise has the same power as the noise estimate based on the adjacent off-frequency bins. Negative response-SNRs were then transformed to the baseline level of 0 dB.

For the three modulation frequencies, the highest response-SNRs were found at mastoid (M1 and M2), parietal (P3 and P4) and occipital (Oz) electrodes, whereas the smallest responses were recorded at frontal electrodes (F3, F4, and Fpz). These frontal

electrodes were less sensitive to record significant responses as evidenced by the higher number of participants with nonsignificant responses (Table 1) and were excluded for further analyses. Additionally, the midline occipital electrode (Oz) was excluded, to allow the comparison of right and left hemispheric responses. Response-SNRs of parietal and mastoid electrodes over the same hemisphere were averaged into a measure for right hemispheric (P4 and M2) and a measure for left hemispheric (P3 and M1) processing.

**Table 1** Percentage of participants with non-significant responses for frontal, mastoid and parietal electrodes for modulation frequencies of 80 Hz, 20 Hz and 4 Hz and for diotic (BE), left ear (LE) and right ear (RE) stimulation.

Percentage non-significant responses (%)									
	80 Hz			20 Hz			4 Hz		
	parietal	mastoid	frontal	parietal	mastoid	frontal	parietal	mastoid	frontal
<b>BE</b>	2	0	11	9	5	11	21	17	32
<b>LE</b>	11	5	16	7	3	21	17	10	30
<b>RE</b>	9	3	28	4	3	22	7	5	19
<b>Mean</b>	<b>7</b>	<b>3</b>	<b>18</b>	<b>7</b>	<b>4</b>	<b>18</b>	<b>15</b>	<b>11</b>	<b>27</b>

Furthermore, individual laterality indices (LI) were calculated. The LI was based on the Root-Mean-Square average of response amplitudes of electrodes over the right (*R*: P4 and M2) and the left hemisphere (*L*: P3 and M1). The LI was then calculated as the difference between *R* and *L* normalized by the sum of *R* and *L*, corresponding to the following formula:

$$LI = (R - L) / (R + L)$$

Thus, the LI was +1 for a response completely asymmetrical to the right hemisphere, zero for a symmetrical response, and -1 for a response completely asymmetrical to the left hemisphere. For the calculation of these indices, negative ratios between response-amplitudes and the average noise-amplitudes were converted to zero, indicating that signal and noise were equally high.

**Statistical analyses.** Statistical analyses were performed with SPSS 16 (SPSS Inc. 2008). For each stimulus, a test and retest were recorded. Test-retest differences in response-SNR were investigated separately for each modulation frequency by a RM-ANOVA with the factors test

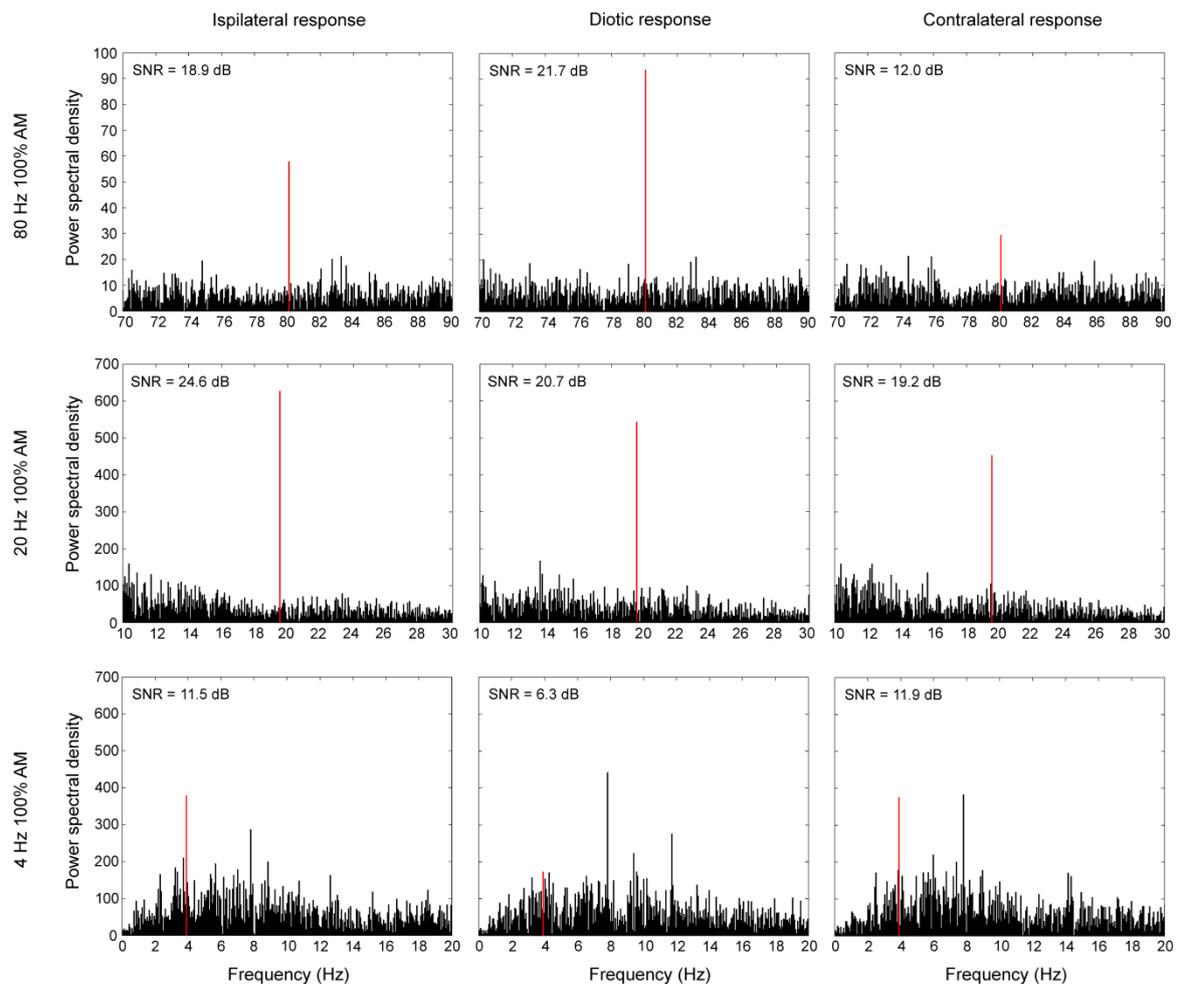
(test, retest), stimulation (BE, LE, RE) and electrode (all eight electrodes) as within-subject factors. Results showed no main effect of test or any interaction with this factor for any of the tested modulation frequencies (all  $F < 2.15$ ,  $p > 0.127$ ). Because there were no significant differences in response-SNR between the test and retest, both recordings were linked together and FFT statistics were carried out over the linked data, i.e., after 32 sweeps. This prolonged duration resulted in better averaging of the data and higher response-SNRs.

Normality of the response-SNRs and LIs was tested by a Kolmogorov-Smirnov test separately for all stimulations, modulation frequencies and electrodes. The significance level was set at  $p < 0.01$ , to adjust for multiple comparisons. All response-SNRs and LIs were normally distributed according to this criterion.

Response-SNRs were analyzed by a series of repeated measures analyses of variance (RM-ANOVA). Reported p-values of the RM-ANOVA were Greenhouse-Geisser corrected and post hoc analyses were Bonferroni corrected for multiple comparisons. LIs were analyzed with a one-sample  $t$ -test to test whether lateralization was significantly different from zero. All statistical analyses were two-tailed ( $\alpha = 0.05$ ).

## Results

**Response-strength.** As an example, the EEG frequency spectrum of one representative participant, recorded over the electrode at the left mastoid (M1) is shown in Figure 2. This plot shows the EEG frequency spectrum to ipsilateral left ear stimulation (left panel), to diotic stimulation (middle plot), and to contralateral right ear stimulation for the 80 Hz (upper row), 20 Hz (middle row) and 4 Hz (bottom row) modulation frequencies.



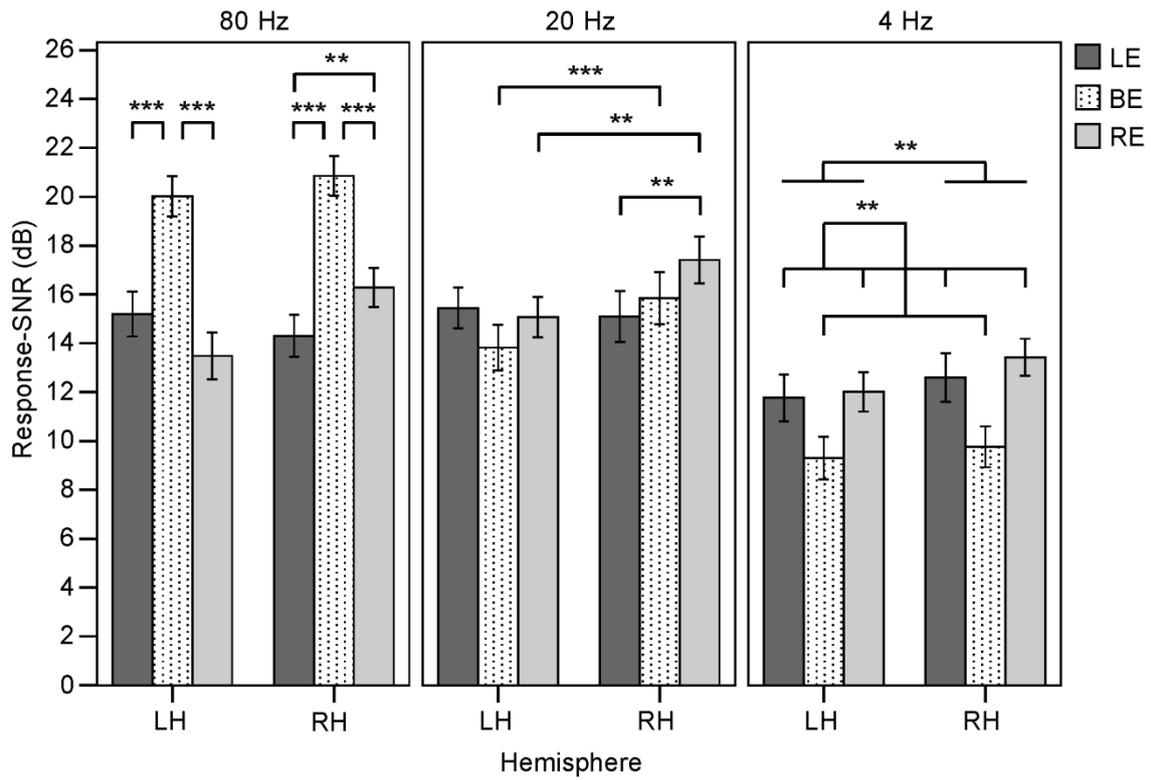
**Figure 2** The EEG frequency spectrum of one representative participant recorded over an electrode at the left mastoid (M1), in response to the 80 Hz (upper row), 20 Hz (middle row) and 4 Hz (bottom row) AM stimuli. The power spectral density of response (red) and noise (black) is plotted over a range of frequencies. Left panels: ASSRs recorded in response to ipsilateral left ear stimulation. Middle panels: ASSRs to diotic stimulation. Right panels: ASSRs to contralateral right ear stimulation.

Group data are shown in Figure 3. To examine the influence of stimulation side on the response-strength of ASSRs, a RM-ANOVA with the factors stimulation (BE, LE, RE) and hemisphere (left hemisphere (LH), right hemisphere (RH)) as within-subject factors was tested separately for each modulation frequency.

For 80 Hz, a main effect of Stimulation [ $F(2,58) = 85.18, p < 0.001$ ] and a Stimulation x Hemisphere interaction [ $F(2,58) = 15.00, p < 0.001$ ] was found. For both hemispheres, BE elicited larger responses than LE and RE [all mean differences  $\geq 4.6$  dB, all  $t(29) \geq 4.57, p \leq 0.001$ ]. Additionally in the RH, ipsilateral RE elicited larger responses than LE [mean difference: 2.0 dB, SE: 0.6 dB,  $t(29) = 3.34, p = 0.007$ ]. Although ipsilateral responses also seem larger than contralateral responses for LH electrodes, this difference was not significant [mean difference: -1.7 dB, SE: 0.8 dB,  $t(29) = -2.23, p = 0.100$ ].

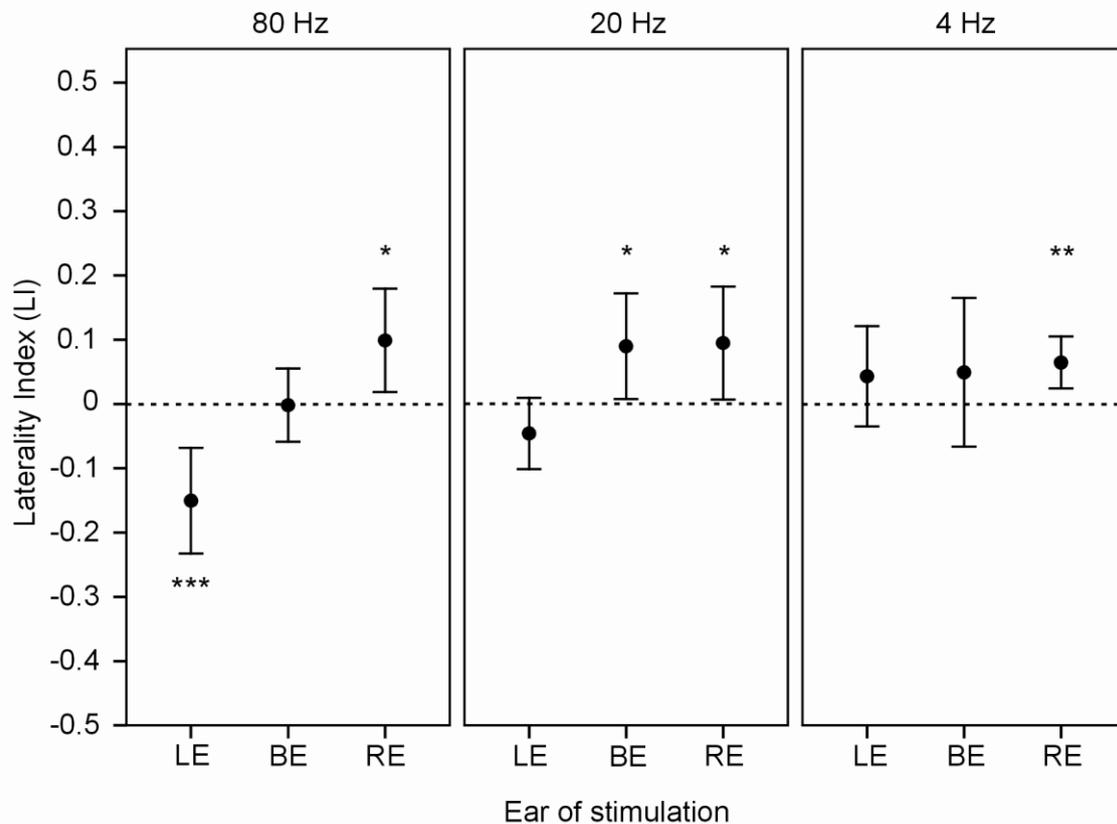
For 20 Hz, a main effect of Hemisphere [ $F(2,58) = 8.47, p = 0.007$ ] and a Stimulation x Hemisphere interaction [ $F(2,58) = 13.09, p < 0.001$ ] was found. At RH electrodes, responses to RE were larger than responses to LE [mean difference: 2.3 dB, SE: 0.6 dB,  $t(29) = 3.70, p = 0.003$ ]. This difference was not observed at LH electrodes [mean difference: -0.4 dB, SE: 0.5 dB,  $t(29) = -0.73, p = 1.000$ ]. Additionally, this interaction revealed that responses were larger in the RH compared to the LH for BE [mean difference: 2.0 dB, SE: 0.5 dB,  $t(29) = 4.10, p < 0.001$ ] and RE [mean difference: 2.3 dB, SE: 0.7 dB,  $t(29) = 3.44, p = 0.002$ ] but not for LE [mean difference: -0.3 dB, SE: 0.5 dB,  $t(29) = -0.67, p = 0.509$ ]. Moreover, the difference between LE and RE was characterized by increased RH activation for RE compared to LE [mean difference: 2.3 dB, SE: 0.6 dB,  $t(29) = 3.70, p = 0.003$ ].

Finally for 4 Hz, significant main effects of Stimulation [ $F(2,58) = 8.09, p = 0.002$ ], and Hemisphere [ $F(2,58) = 11.69, p = 0.002$ ] were found. Overall, BE elicited smaller responses compared to monaural LE [mean difference: -2.7 dB, SE: 1.0 dB,  $t(29) = -2.62, p = 0.042$ ] and RE [mean difference: -3.2 dB, SE: 0.9 dB,  $t(29) = -3.57, p = 0.004$ ]. In contrast, LE and RE did not differ from each other [mean difference: 0.5 dB, SE: 0.6 dB,  $t(29) = 0.93, p = 1.000$ ]. Additionally, RH responses were larger than LH responses [mean difference: 0.9 dB, SE: 0.3 dB].



**Figure 3** Average response-strengths for left ear (LE: left, dark grey bars), diotic (BE: middle, dotted bars) and right ear (RE: right, light grey bars) stimulation, for 80 Hz AM, 20 Hz AM and 4 Hz AM. Bars represent the average response-SNRs for left (LH) and right hemisphere (RH) electrodes. Error bars indicate  $\pm 1$  SE \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

**Laterality.** Hemispheric asymmetry of the ASSRs was investigated with laterality indices, shown in Figure 4. Individual LIs were evaluated separately for each modulation frequency and stimulus presentation manner.



**Figure 4** Mean laterality indices (LI) for 80 Hz, 20 Hz and 4 Hz AM, for left ear (LE), diotic (BE) and right ear (RE) stimulation. Error bars represent the 95% confidence interval of the mean \* $p \leq 0.05$ , \*\* $p \leq 0.01$ , \*\*\* $p \leq 0.001$

A significant ipsilateral asymmetry was found for 80 Hz ASSRs. LE led to clear leftward asymmetry [LI = -0.15,  $t(29) = -3.738$ ,  $p = 0.001$ ], whereas RE led to rightward asymmetry [LI = 0.10,  $t(29) = 2.518$ ,  $p = 0.018$ ]. Responses were symmetrical for BE [LI = -0.002,  $t(29) = -0.060$ ,  $p = 0.953$ ]. For 20 Hz ASSRs, asymmetry to the right hemisphere was found for RE [LI = 0.10,  $t(29) = 2.211$ ,  $p = 0.035$ ] and BE [LI = 0.09,  $t(29) = 2.243$ ,  $p = 0.033$ ]. For LE, the absolute LI was substantially negative, however, this apparent asymmetry to the left hemisphere did not reach significance [LI = -0.05,  $t(29) = -1.686$ ,  $p = 0.102$ ]. For 4 Hz ASSRs, RE led to right hemispheric asymmetry [LI = 0.06,  $t(29) = 3.271$ ,  $p = 0.003$ ], whereas no significant asymmetry was found for LE [LI = 0.04,  $t(29) = 1.138$ ,  $p = 0.265$ ]. Symmetrical responses were also found for BE [LI = 0.05,  $t(29) = 0.871$ ,  $p = 0.391$ ].

These results were confirmed by an individual subject analysis. Analogous to Abrams et al. (2008), participants were categorized as having left ( $LI < 0$ ) or right ( $LI > 0$ ) asymmetric ASSRs. Table 2 shows the number of participants demonstrating left- or right ASSR asymmetry for the three modulation frequencies and stimulus presentation sides. A binomial test confirmed the ipsilateral, left asymmetry to LE for 80 Hz. Left asymmetry was present in 83% of participants [ $z = 3.65, p < 0.001$ ]. Also for 20 Hz, right hemispheric asymmetry was confirmed by asymmetry observed in 80% [ $z = 3.29, p = 0.001$ ] and 90% [ $z = 4.38, p < 0.001$ ] of participants for BE and RE respectively. Finally, for 4 Hz the significant right asymmetry to RE was confirmed by asymmetry observed in 70% [ $z = 2.19, p = 0.043$ ] of participants. However, even though right asymmetry to LE was not significant, right asymmetry was observed in 70% [ $z = 2.19, p = 0.043$ ] of participants.

**Table 2** Number of participants ( $N = 30$ ) demonstrating left (LH) or right (RH) ASSR asymmetry to left ear (LE), diotic (BE) and right ear (RE) stimulation and for 80 Hz, 20 Hz and 4 Hz AM.

		<b>LH</b>	<b>RH</b>
<b>LE</b>	80 Hz	25 (83%)	5 (17%)
	20 Hz	19 (63%)	11 (37%)
	4 Hz	9 (30%)	21 (70%)
<b>BE</b>	80 Hz	18 (60%)	12 (40%)
	20 Hz	6 (20%)	24 (80%)
	4 Hz	15 (50%)	15 (50%)
<b>RE</b>	80 Hz	10 (33%)	20 (67%)
	20 Hz	3 (10%)	27 (90%)
	4 Hz	9 (30%)	21 (70%)

## Discussion

In auditory neuroscience, studies vary in the way stimuli are presented to the participants. Given the complexity of excitatory, inhibitory and interhemispheric connections in the auditory pathway (e.g. Bailey 2010), the stimulus presentation manner may influence the way neural responses are recorded. The present study investigated ASSRs to AM stimuli presented diotically or monaurally to the left or right ear to examine whether stimulus presentation manner has an impact on the response-strength and asymmetry of scalp-recorded ASSRs. Results revealed two main findings. First, at the brainstem level, diotic ASSRs were larger than monaural responses and this binaural advantage decreased with decreasing modulation frequency. Second, comparison of left and right ear stimulation demonstrated that with decreasing modulation rate a gradual change from ipsilateral to right lateralization occurred.

Given that ASSRs to low modulation frequencies are generated at higher levels of the auditory system (Herdman et al. 2002; Picton 2011), the present results suggest that different physiological mechanisms operate on diotic information along the ascending auditory pathway. That is, whereas diotic 80 Hz responses were up to 6.6 dB larger than monaural responses, diotic ASSRs were equal to monaural responses for 20 Hz, while diotic responses were even up to 3.2 dB smaller than monaural responses for 4 Hz ASSRs. Even though this effect was never explored for 20 or 4 Hz ASSRs, a similar trend of a decreasing binaural advantage with decreasing modulation frequency can be found in ASSR studies at 80 and 40 Hz. Moreover, previous ASSR studies reported enhanced binaural compared to monaural ASSRs at 80 Hz (Lins & Picton 1995) and only slightly higher binaural than monaural responses at 40 Hz (Picton et al. 2003). This finding may be explained based on the physiological properties of the underlying neural generators. It was shown that 80 Hz ASSRs can be generated by two dipolar brainstem sources (a left and a right lateralized source at the brainstem level), and that in case of monaural stimulation, the ipsilateral source is responsible for the 80 Hz ASSR generation (Herdman et al. 2002). This implies that, in case of diotic stimulation, 80 Hz responses are larger than monaural responses because of the summed activity of both active sources.

Cortical 40 Hz sources are thought to be characterized by a tangential and radial orientation in the supratemporal plane (Herdman et al. 2002; Poulsen et al. 2007; Spencer 2009). At this level, the distance between sources is larger, resulting in a smaller superposition of two active sources in case of diotic stimulation and a stronger influence of the geometry of electrodes and sources, the relative strength of each source and the orientation

and timing of these sources on scalp-recorded responses. Nonetheless, based on the present findings that diotic 4 Hz responses were even smaller than monaural responses, it seems unlikely that the source configuration alone can explain the observed scalp topography.

The observed differences between diotic and monaural responses may (in part) also reside in the functional characteristics of the auditory system. In this context, the present results may suggest that diotic information is encoded hierarchically along the ascending auditory pathway. It is possible that in the auditory periphery excitatory processes underlie enhanced binaural responses whereas inhibitory influences operate at higher levels of the auditory system. This may in turn relate to perceptual processes such as binaural integration (Gelfand 2001), i.e. the integration of input from the left and right ears into a binaural construct. It is known that binaural integration takes place in the auditory brainstem and that at higher levels of the auditory system, binaural processing continues on an integrated construct (Colburn et al. 2006). If after binaural integration differences between left and right ear inputs disappear and binaural processing continues on an integrated construct (Picton 2011), then at the cortical level differences between monaural and diotic ASSRs may decrease as well.

Alternatively, if 80 Hz ASSRs are sensitive to binaural integration, they may be valuable to evaluate related binaural perceptual processes. For instance, 80 Hz ASSRs have previously been shown to be responsive to binaural cues related to sound localization (i.e. interaural time/loudness differences) (Zhang & Boettcher 2008). The difference between diotic and monaural 80 Hz ASSRs in the present study may then reflect encoding differences between sound sources. Similarly, diotic stimulus presentation is also known to result in binaural summation, the percept of greater loudness to binaural compared to monaural stimulation at the same supra-threshold SPL. Given that ASSR amplitudes increase with increasing stimulus intensity (Picton et al. 2003), it seems that binaural summation can be measured with 80 Hz ASSRs and not with 20 and 4 Hz ASSRs.

Nonetheless, 80 Hz ASSRs do not reflect all binaural processes. Binaural masking level differences, reflecting the benefit from using both ears instead of one when detecting signals in noise, were only found for cortically-evoked, 7 Hz ASSRs (Wong & Stapells 2004) and not for 80 Hz (Wong & Stapells 2004), or even 40 Hz (Ishida & Stapells 2009) ASSRs. Similarly, the addition of contralateral noise to a monaural stimulus did not affect the amplitude of 80 Hz ASSRs whereas 40 Hz ASSR amplitudes were suppressed with the addition of contralateral noise, suggesting stronger binaural interaction for 40 Hz than for 80

Hz (Maki et al. 2009). Future studies will have to elucidate the exact role of binaural processing on ASSRs.

The second important finding of this study resides in the comparison of both monaural conditions, revealing a gradual change from ipsilateral to rightward asymmetry when lowering the modulation frequency from 80 Hz to 20 Hz to 4 Hz. While 80 Hz ASSRs were significantly higher in the hemisphere ipsilateral to the stimulus presentation, 20 Hz ASSRs only demonstrated a significant ipsilateral asymmetry to right ear stimulation, with the majority of participants (63%) also demonstrating ipsilateral asymmetry to left ear stimulation. Comparable to 20 and 80 Hz ASSRs, 4 Hz ASSRs demonstrated ipsilateral asymmetry to right ear stimulation. Additionally, although statistical analyses failed to reveal significant right asymmetry to left ear stimulation, individual laterality analyses demonstrated right asymmetry in 70% of participants, suggesting that contralateral, right asymmetry to left ear stimulation is small but present in the majority of individuals.

As suggested earlier, scalp-recorded response asymmetry may be influenced by the source configuration of underlying sources. Based on findings that the afferent auditory system crosses over to the contralateral side in the superior olivary complex (Bailey 2010) and that 80 Hz ASSRs are generated in the brainstem (Herdman et al. 2002; Kuwada et al. 1986; Picton et al. 2003), the present 80 Hz results suggest that the dominant neural generators of this ASSR are located earlier in the auditory pathway than the contralateral crossover. In case of monaural stimulus presentation, the ipsilateral ASSR source is then more strongly activated than the contralateral source (Herdman et al. 2002), resulting in stronger ipsilateral scalp recorded responses. This is consistent with previous ASSR studies reporting smaller or even absent 80 Hz ASSRs contralateral to the stimulus (Poelmans et al. 2012; Small & Stapells 2008; van der Reijden et al. 2005).

At higher levels of the auditory system, response asymmetry is more complex. Taking into account the anatomical crossover to the contralateral side (Bailey 2010) and the bihemispheric interactions via the corpus callosum (Bamiou et al. 2007), response asymmetry may result of anatomical as well as functional preferences in the auditory system. Anatomically, response asymmetry of 4 Hz and 20 Hz ASSRs might result from an asymmetrical location of left and right hemispheric sources. Ross et al. (2005) suggested that the dominant cortical ASSR source underlying the 40 Hz responses is located more anterior in the right hemisphere than in the left hemisphere. Assuming that this asymmetry also applies for 4 Hz and 20 Hz ASSRs, the use of a small electrode array in the present study may have led to an asymmetrical recording of underlying sources. However, given that the present

results were based on mastoid and parietal electrodes, one may expect that the source activity of the more distant source (i.e. the anterior right hemispheric source) is less well recorded and that the observed right asymmetry is rather an underestimation of the true underlying asymmetry.

Functionally, it has been suggested that both hemispheres differ in their sensitivity to follow certain modulation rates (Goswami 2011; Pöppel 2003; 2008), with a right hemispheric preference for processing syllabic-rate modulations (~3-7 Hz) (Abrams et al. 2008; Hämäläinen et al. 2012; Millman et al. 2010) and a bilateral (Hämäläinen et al. 2012; Herdman et al. 2003) or left hemispheric (Belin et al. 1998; Jamison et al. 2006; Johnsrude et al. 1997) preference for phonemic-rate modulations (~12-50 Hz). Based on the monaural stimulus presentation conditions in the present study, the 4 Hz results support the idea of right lateralization of slow, syllabic-rate modulations. Similarly, the present 20 Hz results suggest ipsilateral sensitivity to phonemic-rate modulations. However, the hypothesized asymmetry could not be found in all conditions, probably because scalp-recorded ASSRs reflect a combination of anatomical and functional characteristics of the auditory system. Nonetheless, mapping the underlying topography of these responses may be interesting to evaluate sensitivity to important modulation frequencies in the speech envelope, specifically in clinical populations with monaural hearing aids, deviant hemispheric asymmetries or interhemispheric transfer dysfunction.

The present study was the first to investigate systematically far-field ASSR asymmetry for 20 and 4 Hz ASSRs by comparing different stimulation sides. Only two previous studies investigated ASSR asymmetry with a similar paradigm (Ross et al. 2005; Yamasaki et al. 2005). Both studies only focused on 40 Hz ASSRs, representing the higher end of phonemic-rate modulations, and results were rather contradictory. Whereas Ross et al. (2005) demonstrated right asymmetry of 40 Hz ASSRs, Yamasaki et al. (2005) suggested a left hemispheric specialization for this modulation rate. With different experimental paradigms, evidence was found for a right hemispheric preference for processing syllabic-rate modulations (Abrams et al. 2008; Hämäläinen et al. 2012), and a bilateral activation for processing phonemic-rate modulations (Hämäläinen et al. 2012). Possible factors contributing to these contradicting results are differences in recording techniques (MEG: Ross et al. 2005; EEG: Yamasaki et al. 2005), or stimulus factors such as duration (longer stimuli: Abrams et al. 2008; Hämäläinen et al. 2012; Ross et al. 2005; short stimuli: Yamasaki et al. 2005) or complexity (real speech: Abrams et al. 2008; modulated noise: Hämäläinen et al. 2012; modulated pure tones: Ross et al. 2005; Yamasaki et al. 2005). Future studies assessing

asymmetry and comparing binaural to monaural responses with high-density EEG recordings should be undertaken to analyze the complete scalp topography as well as the underlying activity of equivalent electric dipolar sources inside the brain.

In sum, the present results demonstrate that scalp-recorded responses are recorded asymmetrically depending on which ear is stimulated and that this effect differs for syllabic- and phonemic-rate modulations. These findings have important consequences for electrode placement in clinical settings, as well as for the understanding of low-frequency ASSR generation. In a clinical context, these findings reveal that (1) in case of monaural stimulation the most optimal electrode placement to record the frequently used 80 Hz response is ipsilateral to the stimulated ear, and that (2) low-frequency ASSRs (4 Hz and 20 Hz) are optimally recorded at electrodes placed over the right hemisphere and to right ear stimulation. Experimentally, the present study demonstrates that (1) the highest 80 Hz ASSRs are recorded to diotic stimulation, whereas monaural stimulation seems more optimally to record 4 Hz ASSRs, and that (2) monaural stimulus presentation can induce response asymmetry recorded at far-field electrodes. Therefore, stimulus presentation manner is an important factor to take into account when comparing absolute ASSR amplitudes or SNRs and for interpreting far-field response asymmetry.

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