Multiple Auditory Steady State Responses (80–101 Hz): Effects of Ear, Gender, Handedness, Intensity and Modulation Rate

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Objective: To evaluate how the amplitudes and latencies of auditory steady state responses (ASSRs) to multiple stimuli presented at rates between 80 and 101 Hz vary with the ear of stimulation, the handedness or gender of a subject, and the rate and intensity of the stimuli.

Design: ASSRs were recorded in a group of 56 young adults (27 females, 13 left handed) using several stimulus conditions. In the two main conditions, four sinusoidally amplitude-modulated tones (each uniquely modulated using rates between 80 and 105 Hz) with carrier frequencies of 500, 1000, 2000, and 4000 Hz, were presented concurrently to each ear (eight total). In the first condition the modulation rates for the left ear were slower than those for the right and in the second condition this relationship was reversed. Other conditions evaluated the responses to single stimuli, to multiple stimuli presented in one ear only and to multiple stimuli presented dichotically (four in each ear) with rates that decreased rather than increased with increasing carrier frequency. Stimuli were presented at an intensity of 73 dB SPL except in two conditions wherein the intensity was 53 dB SPL.

Results: At 73 dB SPL, multiple-stimulus ASSRs were significantly reduced (monotic or dichotic) compared with single-stimulus ASSRs, especially at 1000 and 2000 Hz. There were significant differences between monotic and dichotic stimulation. When the stimuli were presented dichotically, the amplitude of the response varied with the relative rates of modulation for the stimuli presented in each ear. ASSRs were larger in the ear with the higher rate when the carrier frequencies were 500 and 1000 Hz and when the modulation rates were <90 Hz. There were no consistent effects of gender or ear of stimulation. There were also no significant effects of handedness.

Conclusions: Presenting multiple stimuli at 73 dB SPL in the same ear decreases the amplitude of the ASSR compared with when the stimuli are presented singly. This is caused by the masking effect of low on higher carrier frequencies and some other inhibitory effect of high on lower frequencies. Dichotic stimulation can increase the amplitude of the response to stimuli modulated more rapidly (and concomitantly decrease the responses to the stimuli modulated more slowly). This effect occurs only for carrier frequencies <2000 Hz and for modulation frequencies <90 Hz. Dichotic stimulation also causes a small but highly significant decrease in the latency of the response compared with monotic stimulation.

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INTRODUCTION

Recent studies have suggested that innate differences between the right and left ears might possibly contribute to hemispheric asymmetries in auditory processing. Many reports have documented differences between auditory processing in the hemispheres of adults (Zatorre & Belin, 2001). Neonates show left-right ear differences in their otoacoustic emissions and auditory brain stem responses (ABRs) (Sininger & Cone-Wesson, 2004, 2006). Because of the preferential connectivity of each ear to the contralateral cortex, these early ear-related asymmetries in auditory processing could drive the development of hemispheric asymmetries.

In a recent article studying normal adult subjects (Picton, et al., 2007), we found a significant ear-related difference in the amplitude of the auditory steady state responses (ASSR). When eight stimuli were presented simultaneously (four in each ear), the responses to stimuli in the right ear were larger than the responses to stimuli in the left ear. The ear differences were larger at low compared with high carrier frequencies and were larger at higher intensities (Fig. 1, left).

We had not noticed any ear-related differences in previous studies using normally hearing subjects. A reexamination of data from an earlier study (Picton, et al., 2005) showed a nonsignificant left-sided (rather than right-sided) amplitude predominance (Fig. 1, right). The two studies differed in many ways: (i) the dichotic stimuli were presented using intensity sweeps in the 2007 study and at discrete intensity levels in the 2005 study, (ii) the modulation rates for the same carrier frequency were higher in the right ear than the left in the 2007 study and vice versa for the 2005 study, and (iii) there were relatively more female subjects in the 2007 study (11 of 13 in the normal dichotic part of the study) compared with the 2005 study (5 of 10).

To determine whether these paradigm differences or subject gender contributed to the discrepancy in ear asymmetry, we recorded ASSRs from 56 subjects with approximately equal numbers of men and women using counter-balanced stimulus conditions wherein the modulation rates were higher in either the left ear or the right ear. We also investigated conditions designed to evaluate other factors that might have contributed to the asymmetry, particularly the use of single or multiple stimuli. Finally, we evaluated the handedness of our subjects, and made a particular effort to recruit a sufficient number of left-handed subjects to allow this analysis.

METHODS

Subjects

Fifty-six subjects (age 18–34 years, mean 25) participated in these experiments. Each subject provided informed consent. Twenty-nine of the subjects were male (age 19–34 yr, mean 26) and 27 were female (age 18–34, mean 24). We particularly recruited 13 (6 female) left-handed subjects. Handedness was evaluated using the Edinburgh Handedness Inventory (Oldfield, 1971). The means and standard deviations for the laterality quotient (which varies between −100 for left-handed subjects and +100 for right-handed subjects) were 78 ± 18 for the right handed subjects and −61 ± 22 for the left-handed

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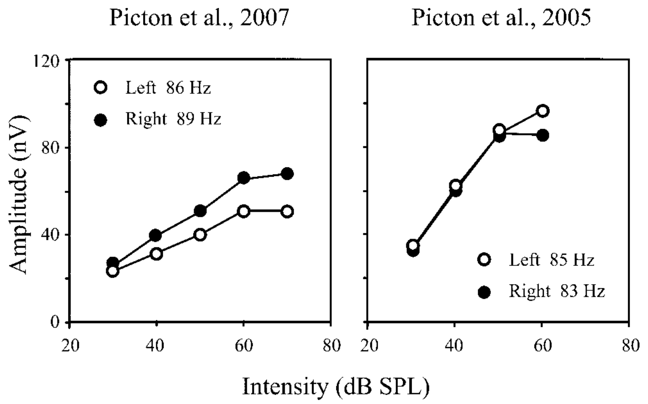

Fig. 1. Previously recorded data. The left graph shows the amplitudes of the 1000-Hz ASSRs recorded in a study using sweeps of intensity (Picton, et al., 2007). The right-ear responses are larger than the left-ear responses. The right graph shows the amplitudes from an earlier study recording responses at discrete intensities. There were no significant ear-related differences. If anything, the responses were larger in the left ear.

subjects. All subjects were tested using pure-tone audiometry in each ear at octave frequencies from 250 to 8000 Hz. All thresholds were 20 dB HL or better.

Stimuli

The stimuli were sinusoidally amplitude-modulated tones with a modulation depth of 100%. The different experimental conditions are shown in Table 1 with the modulation frequencies rounded to the closest whole number. The actual frequencies were calculated so that an integer number of cycles fit exactly into a recording epoch of 1.024 sec. For example, the lowest modulation frequency presented as 80 Hz in the table was actually 80.078 Hz (John & Picton, 2000a).

Stimuli were created and presented using a MASTER research system (John & Picton, 2000a). The stimuli underwent digital-to-analog conversion at a rate of 32 kHz (for each ear).

TABLE 2. Stimulus intensities (dB SPL)

	Frequency (Hz)			
Stimulus source	500	1000	2000	4000
MASTER stimuli left ear	72.1 ± 0.1	74.9 ± 0.1	73.8 ± 0.0	73.9 ± 0.4
MASTER stimuli right ear	71.1 ± 0.1	74.1 ± 0.2	72.9 ± 0.1	74.0 ± 0.4
Audiometer left 70 dB HL	76.1 ± 0.0	70.9 ± 0.1	73.5 ± 0.1	79.7 ± 0.1
Audiometer right 70 dB HL	76.4 ± 0.0	71.2 ± 0.2	73.0 ± 0.0	79.0 ± 0.4

Means and standard deviations of stimulus intensities from three separate calibration sessions.

The intensity of the stimuli was adjusted to a nominal intensity of 73 dB SPL using a Grason Stadler Model 16 Audiometer and presented to the subjects through Etymotic Model 3A insert earphones.

The individual carrier frequencies were calibrated using a Larson-Davis System 824 sound level meter with a 2-cc coupler and a linear weighting at the beginning, middle, and end of the study. As shown in Table 2, there were slight variations across the different carrier frequencies (up to 3 dB) and between the earphones used for the two ears (up to 1 dB). There were also slight variations across the three different calibration sessions but these did not exceed 1 dB. These differences were too small to cause significant effects on the ASSRs. The audiometer used to assess pure tone thresholds was also calibrated. As shown in Table 2, there was no more than a 1 dB difference between the ears (for each carrier frequency) and all stimuli were within 1 dB of the International Standards Organization (ISO) standard levels for Etymotic insert earphones (thresholds of 5.5, 0.0, 3.5, and 5.5 dB SPL for 500, 1000, 2000, and 4000 Hz, respectively, ISO 389-2, 1994), with the exception of the 4000-Hz stimuli, which were 4 dB higher than the standard (in both ears). Before analysis, the

TABLE 1. Stimulus conditions: modulation frequencies (Hz)

			Left ear carrier frequency (Hz)				Right ear carrier frequency (Hz)			
	Condition	N (F)*	500	1000	2000	4000	500	1000	2000	4000
1	Ascending left slower	56 (27)	80	86	92	98	83	89	95	101
2	Ascending right slower	56 (27)	83	89	95	101	80	86	92	98
3	Monotic left	30 (17)	80	86	92	98				
4	Monotic right	30 (17)					83	89	95	101
5a	Single	28 (16)	80							
5b		30 (17)		86						
5c		28 (16)			92					
5d		28 (16)				98				
5e		14 (6)					83			
5f		30 (17)						89		
5g		14 (6)							95	
5h		14 (6)								101
6	Single stimulus both ears	30 (17)		86				89		
7	Descending left slower	42 (21)	98	92	86	80	101	95	89	83
8	Descending right slower	42 (21)	101	95	89	83	98	92	86	80
9	Ascending left slower 53 dB	16 (8)	80	86	92	98	83	89	95	101
10	Ascending right slower 53 dB	16 (8)	83	89	95	101	80	86	92	98

** N is the number of subjects examined in that condition. Values within the brackets are the numbers of female subjects in each condition. All conditions were run at 73 dB SPL except the last two.*

behavioral thresholds measured in our subjects were compensated to ISO standards according to these calibrations.

Recordings

ASSRs were recorded from an electrode placed at the vertex, using a reference on the midposterior neck and an electrode placed on the left clavicle as ground. Subjects slept or drowsed in a reclining chair, located within a darkened sound-attenuated chamber during the recordings. The EEG was amplified by a factor of 10,000 using a Grass LP511 amplifier with a filter band pass of 30 to 300 Hz. The signal was further amplified by a factor of 5 on the MASTER input board (yielding a cumulative amplification of 50,000), and analog-to-digital converted at a rate of 1000 Hz. Individual data epochs of 1024 points each (1.024 sec) were rejected if they contained any value which exceeded ±80 μV. Sixteen individuals' data epochs were collected and linked together into sweeps lasting 16.384 sec. As each sweep was completed it was combined with a running-average sweep using weighted averaging based on the energy in the EEG between 70 and 110 Hz (John, et al., 2001). The averaged sweep was analyzed using a fast Fourier transform. The amplitude of the steady state response to a given carrier frequency was measured at the frequency of modulation for that carrier in the resulting amplitude spectrum. This amplitude was compared with the amplitudes in adjacent regions of the spectrum (60 frequency bins below and 60 frequency bins above the response frequency, i.e., between −3.7 and +3.7 Hz) using an F-ratio with 2 and 240 degrees of freedom (dfs) (Picton, et al., 2003). A response was judged as significantly different from residual EEG noise at a criterion of $p < 0.05$. The onset phase of the response was determined from the fast Fourier transform coefficients. This was converted into a latency in milliseconds (L) using the formula

$$L = 1000 \times (720 - \varphi)/(360 \times f_m)$$

where φ is the onset phase in degrees and f_m is the modulation frequency. This formula is based on the idea that one full cycle of the stimulus occurs before the cycle wherein the phase is measured (John & Picton, 2000b). For each condition of our experiments, two replications of 20 sweeps were collected. These were combined to give a final average recording based on 40 sweeps, or ~11 min of data (more than sufficient to obtain highly significant responses at the intensity levels used).

Experimental Conditions

The first two stimulus conditions shown in the Table 1 were tested in all 56 subjects. These conditions assessed whether the relative modulation rate in each ear may affect the responses. In these experimental conditions, four stimuli were presented to each ear. The modulation frequencies ascended with increasing carrier frequency. In the first condition the modulation frequencies for carriers presented in the left ear were slower than for the corresponding carriers in the right ear, and in the second condition this relationship was reversed. The main hypothesis was that the stimuli with faster rates would evoke larger responses.

Several subordinate conditions were derived from the first stimulus condition, each involving only some of the subjects (see column N in Table 1). Two conditions (3 and 4) evaluated responses to monotic stimuli. The rationale for these recordings was to see the effects of multiple stimulation with stimuli at four different carrier frequencies without stimuli in the other ear. The original hypothesis for this study was that there would be significant effects of carrier frequency with the higher frequencies being reduced in size because of the presumed upward spread of masking from the lower frequency stimuli.

Eight additional conditions (5a–h) measured the responses to each of the eight stimuli presented in the first condition when they were presented singly and provided data to compare "dichotic," "monotic," and "single" presentation modes. Our hypothesis was that at the intensity of 73 dB SPL the single stimulus mode would give larger amplitudes than either multiple stimulation mode (cf. John, et al., 1998). For the 1000-Hz carrier frequency we also presented a single stimulus to each ear using the modulation frequencies of the first condition (condition 6). This allowed us to compare single responses to the left ear alone (condition 5b) with the responses to the right ear alone (condition 5f) and with both ears (condition 6).

A pair of stimulus conditions (7 and 8) used the same modulation frequencies as in the first two conditions with the modulation frequencies descending rather than ascending with increasing carrier frequency. These conditions were set up once it became apparent that the first two conditions were showing interaction effects only for the 500 and 1000 Hz stimuli. However, these lower carrier frequencies were also associated with lower modulation frequencies. Conditions 7 and 8 were designed to disentangle this confound.

The final two conditions replicated the first two conditions except that the stimuli were presented at 53 dB rather than 73 dB SPL. These conditions were set up once it was realized that at 73 dB the amplitude varied with carrier frequency quite differently than what one might have expected from studies using lower intensity stimuli.

Analysis

An analysis of variance (ANOVA) was used to evaluate the data from the first two conditions (56 subjects) by comparing two groups (male/female) over three repeated measures (stimulus ear, carrier frequency, and relative rate). A second ANOVA evaluated these measures as a function of handedness rather than gender (two separate ANOVAs rather than one involving both handedness and gender were reported to make things simpler). Group and repeated-measures ANOVAs were also used for the single versus dichotic 1000 Hz comparisons (conditions 5b, 5f, and 6) wherein there were data for 30 subjects, and for the descending modulation frequencies (conditions 7 and 8) with 42 subjects. For the other analyses, based on smaller numbers of subjects, we did not consider the group effects. The repeated-measure factors in the ANOVAs varied with the conditions and are more easily followed when described with the results. Geisser-Greenhouse corrections were used to counter any inhomogeneity of variance for the repeated measures. Results were accepted as significant at $p < 0.05$. Post hoc pairwise comparisons were only assessed for significance if the main or interaction effects on the experimental ANOVA were initially significant.

Box plots were used to evaluate group effects (Tukey, 1977). These were constructed using programs adapted from those of Cleveland (1993) as instantiated in the Data Visualization Toolbox for MATLAB (www.datatool.com).

RESULTS

Behavioral Thresholds

Measured thresholds were adjusted by the average audiometer calibrations before evaluation. The right ear thresholds were slightly (1.5 dB) but significantly lower than those in the left ear ($F = 8.00$, df 1,54; $p < 0.01$). The average thresholds and standard errors were 6.7 ± 0.5 dB HL for the right ear and 8.2 ± 0.6 dB HL for the left ear. There was also a significant effect of carrier frequency ($F = 5.15$, df 3,162; $p = 0.005$), with the thresholds decreasing with increasing carrier frequency. In addition, female subjects showed slightly (2.2 dB) lower thresholds than male subjects ($F = 5.97$, df 1,54; $p < 0.05$). The average thresholds and standard errors were 6.4 ± 0.6 dB HL for females and 8.6 ± 0.6 dB HL for males. Interactions between gender and ear and between gender and frequency were not significant. Handedness did not significantly affect thresholds and did not interact with either ear or frequency.

Ear and Relative Rate

For the main experimental paradigm where the relative rates between the two ears were switched (first two conditions of Table 1), an ANOVA assessed the following repeated-measure factors: condition (modulation rate left ear higher or right ear higher), carrier frequency, and ear. The amplitude results were complex and showed a highly significant condition by frequency by ear interaction ($F = 40.6$; df 3,162; $p < 0.001$), a significant condition by ear interaction ($F = 108.9$; df 1,54; $p < 0.001$), and a significant main effect of frequency ($F = 12.5$; df 3,162; $p < 0.001$). The results are shown in Figure 2. The amplitudes were larger in the ear with the higher modulation frequency (condition by ear interaction) but only for the 500 and 1000 Hz stimuli (condition by ear by frequency interaction). In addition, the responses were smaller at frequencies 1000 and 2000 Hz than at the other frequencies (main effect of frequency)—the 500-Hz response being larger than both the 1000 and 2000 Hz responses and the 4000-Hz response being larger than the 2000-Hz response. The latency analysis showed a strong frequency effect ($F = 666.4$; df 3,162; $p < 0.001$), with the latency being longer for lower carrier frequencies. In addition, there were significant condition by frequency by ear ($F = 31.5$; df 3,162; $p < 0.001$) and condition by ear ($F = 12.8$, df 1,54; $p < 0.01$) effects, the latencies changing with ear and condition at 500 Hz but not at the other frequencies.

The female subjects showed responses that were on an average slightly larger (by 11%) and slightly earlier (by 0.1 msec) than the responses of the male subjects. However, the ANOVAs showed no significant main effects of gender for either amplitude or latency, and no interactions with gender on the other analyses. There were no significant effects of handedness or interactions of the other factors with handedness and the means were virtually identical for the right- and left-handed groups.

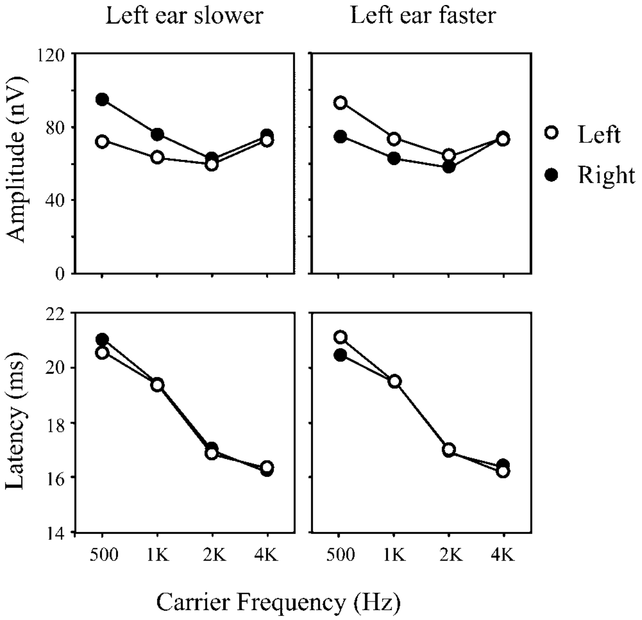

Fig. 2. Effect of modulation frequencies and relative rates between the ears. Amplitudes and latencies for the ASSRs recorded to multiple stimuli presented at the modulation frequencies described in the first two conditions of Table 1. The responses at 500 and 1000 Hz were larger in the right ear in the first condition when the modulation frequencies were faster in the right ear (left graphs) and in the left ear in the second condition when the modulation frequencies were faster in the left ear (right graphs).

Multiple Stimulation (Dichotic and Monotic Conditions)

In 14 subjects, we recorded responses to single stimuli (in eight different conditions 5a–h), and to eight simultaneous dichotic stimuli (four in each ear, condition 1). The modulation frequencies were the same as those in the first condition with left-ear stimuli again having slower modulation frequencies than right-ear stimuli. An ANOVA of the amplitude data showed significant main effects of single/multiple condition ($F = 4.8$; df 1,13; $p < 0.05$) and frequency ($F = 3.8$; df 3,39; $p < 0.05$), with significant interactions between condition and ear ($F = 6.1$; df 1,13; $p < 0.05$), and between condition and frequency ($F = 7.9$; df 3,39; $p < 0.005$). The results are shown in the left half of Figure 3. The amplitude was smaller for the

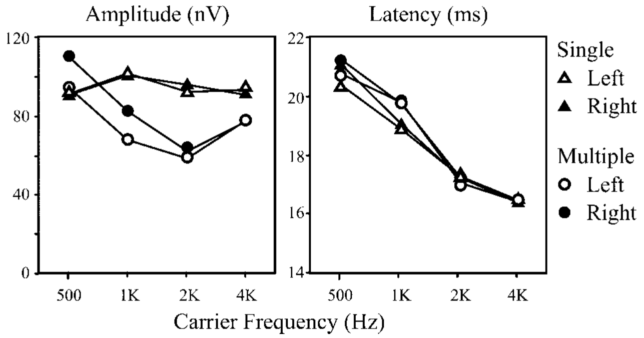

Fig. 3. Single and multiple stimuli. These results compare the effects of presenting multiple stimuli simultaneously (four in each ear) to presenting the stimuli singly. The amplitude is decreased for frequencies 1000 and 2000 Hz. The latency shows complicated interactions with an increase in latency at 1000 Hz when the stimuli are presented simultaneously.

1000 and 2000 Hz responses in the multiple (dichotic) condition (main effect of frequency), and the amplitudes at 500 and 1000 Hz were larger in the right ear in the dichotic condition (condition by frequency effect). A supplementary ANOVA was carried out to assess only the data in the single conditions (5a–h) and showed no significant effects of ear ($F = 0.001$) or frequency ($F = 0.68$) and no interaction ($F = 0.30$). The latency ANOVA (condition, frequency, ear) showed a significant main effect of frequency ($F = 146.1$; df 3,39; $p < 0.001$) and significant interactions between frequency and ear ($F = 9.0$; df 3,39; $p < 0.001$) and frequency and condition ($F = 5.0$; df 3,39; $p < 0.05$). The latency was later for lower frequency stimuli and was later for the dichotic condition at 1000 Hz.

The effects of presenting multiple stimuli to one ear (monotic: conditions 3 and 4) or both (dochotic: condition 1) ears were examined in 30 subjects. The amplitudes showed interactions among all factors (ear by condition by frequency: $F = 4.7$; df 3,87; $p < 0.01$). A supplementary ANOVA that was performed using only the monotic data showed a significant effect of frequency (with 1000 and 2000 Hz being smaller) but no significant effect of ear or interaction. Thus, the ear by condition effect occurred only when the stimuli were dichotic. This interaction was caused by the responses being bigger in the right ear but only at frequencies 500 and 1000 Hz and only in the dichotic condition. In the dichotic condition, this was caused by both a reduction in the left ear and an enhancement in the right ear compared with when the stimuli were presented monotically. Compared with monotic presentation, dichotic presentation will produce slightly larger responses (at 500 and 1000 Hz) in the ear with the relatively higher modulation rates, and slightly smaller responses in the ear with the relatively lower modulation rates. These results are illustrated in Figure 4.

The latency analysis showed highly significant main effects of frequency ($F = 488.6$; df 3,87; $p < 0.001$) and condition ($F = 10.4$; df 1,29; $p < 0.001$). As clearly demonstrated on the right of Figure 4, the latency decreased significantly as the carrier frequency became higher. The latency was on an average 0.31 msec shorter in the dichotic condition compared with the monotic condition. The latter effect was quite consistent, occurring in about three quarters of the subjects for both the right ear and the left ear stimuli. The right side of Figure 5 shows the distributions of the monotic-dichotic difference for the 30 subjects, combined across the different frequencies.

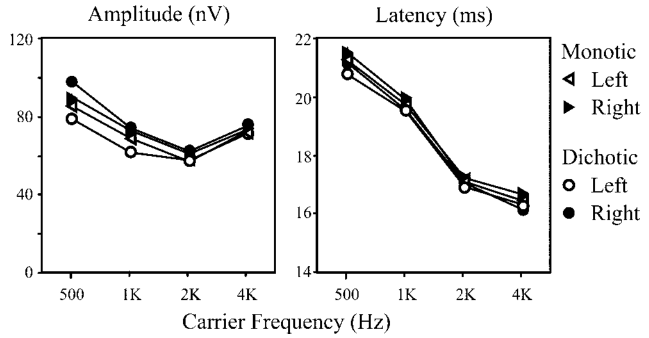

Fig. 4. Monotic vs. dichotic stimulation. The response amplitudes were not different between the ears when the stimuli were presented monotically. However, when presented dichotically the responses became larger in the right ear and smaller in the left ear at carrier frequencies 500 and 1000 Hz. The latencies showed a small decrease in the dichotic conditions.

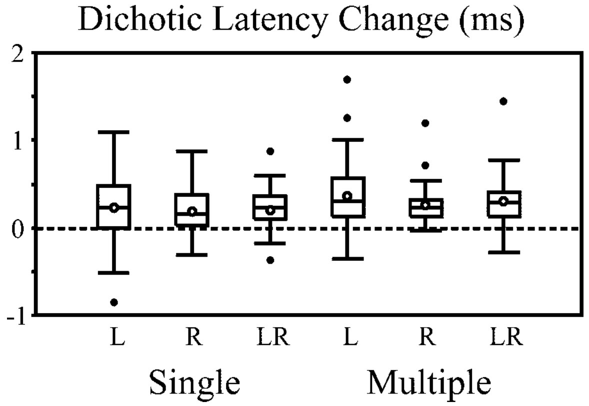

Fig. 5. Dichotic latency changes. This figure shows the distributions of the latency difference between the monotic condition and the dichotic condition. The latency is generally shorter in the dichotic condition. The data on the left are for the "single" stimulus conditions (1000 Hz)—conditions 5b and 5f vs. condition 6. Data are shown for the left ear stimuli (L), the right ear stimuli (R), and both combined (LR). The data on the right are for the conditions with four stimuli in each ear ("multiple")—conditions 3 and 4 vs. condition 1. For these plots the data have been averaged across the different carrier frequencies.

Single 1000-Hz Stimulus to One or Both Ears

To look at the effects of dichotic stimulation independently of the effects of multiple stimuli within one ear, we evaluated in 30 subjects the responses to 1000-Hz stimuli presented singly to the left ear (modulated at 86 Hz, condition 5b) or right ear (modulated at 89 Hz, condition 5f) or to both ears simultaneously (condition 6). The ANOVAs considered group factors of either gender or handedness and repeated-measure factors of ear and condition. The response was slightly but significantly larger ($F = 10.8$; df 1,28; $p < 0.005$) and earlier ($F = 11.1$; df 1,28; $p < 0.005$) in the dichotic condition than in the single condition, with no significant interactions between ear and condition. The responses in the dichotic condition were on average 8% larger than during the monotic condition. The monotic-dichotic latency difference was on an average 0.21 msec (left side of Fig. 5). In addition, there was a significant effect of gender on the latency ($F = 7.2$; df 1,28; $p < 0.005$), the responses of female subjects occurring 0.89 msec earlier than the male subjects. The female subjects had responses that were on an average 14% larger than the responses of the male subjects, but this difference did not reach significance ($F = 3.0$; df 1,28; $0.05 < p < 0.10$). These results are illustrated in Figure 6.

Modulation Frequencies and Carrier Frequencies

The ear by condition interactions for the response amplitude in the first two stimulus conditions were only seen for the stimuli with lower carrier frequencies (500 and 1000 Hz). Because this might have been related to the concomitant lower modulation frequencies for these stimuli, we evaluated the effects on the response amplitudes of using lower modulation frequencies with higher carrier frequencies. To explore this issue we reversed the order of the modulation frequencies in the first two conditions to give conditions 7 and 8 in Table 1. Forty-two subjects who participated in conditions 1 and 2 were also evaluated in conditions 7 and 8. Because the initial ANOVA evaluating all these data showed complex three- and

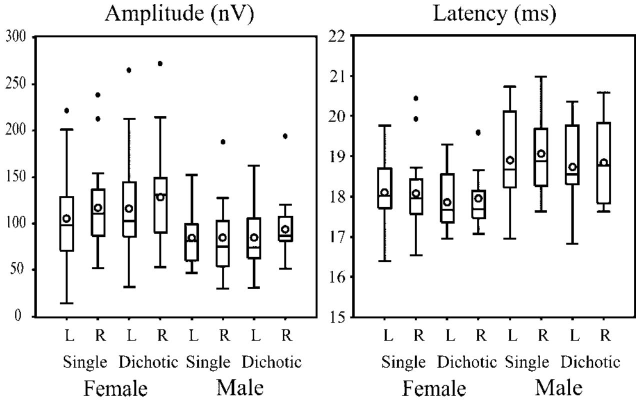

Fig. 6. Possible gender differences. Responses to 1000-Hz stimuli, presented singly or dichotically to the left ear (L) or to the right ear (R) in 30 subjects. The amplitude differences between female and male subjects were not significant (left). Despite the large intersubject variance, there were nevertheless significant female-male differences in latency (right) in this particular set of subjects. The smaller repeated-measures effects of dichotic vs. single were significant for both amplitude and latency.

four-way interactions, we performed post hoc ANOVAs for each of the two "directions" (ascending or descending modulation frequencies). The data in the initial two conditions for these 42 subjects (top graphs of Fig. 7) were essentially the same as in all 56 (top graphs of Fig. 2), showing the same ear by condition by frequency interaction ($F = 30.8$; df 3,120; $p < 0.001$), condition by ear ($F = 96.00$; df 1,40; $p < 0.001$), and frequency ($F = 5.50$; df 3,120; $p < 0.01$), effects. For conditions 7 and 8, there was a significant main effect of ear ($F = 4.57$; df 1,40; $p < 0.05$), with the stimuli in the right ear evoking larger responses. There was also a significant effect of frequency ($F = 4.03$; df 3,120; $p < 0.05$), with the response at 2000 Hz being smaller than the others (though the post hoc effects were borderline). For these "descending" conditions, there were no significant condition by ear by frequency or condition by ear interactions. The results are illustrated in the bottom graphs of Figure 7.

There were no significant effects of gender on the responses although the means for the descending conditions showed that the female responses were on average 0.31 msec earlier. The amplitudes were essentially the same for the male and female subjects.

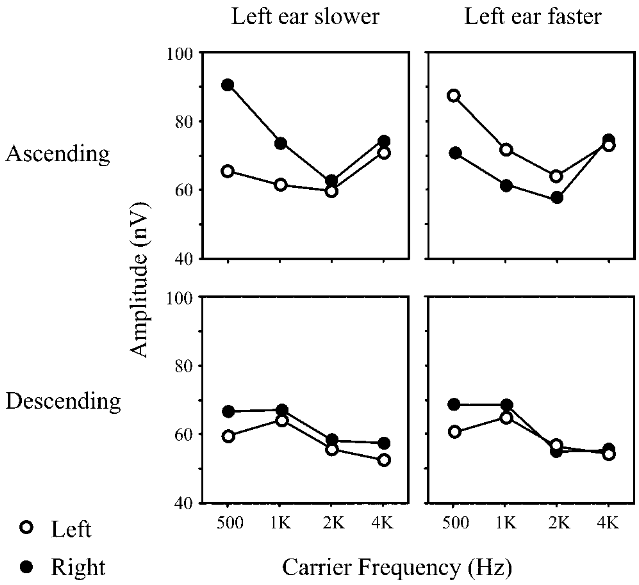

Fig. 7. Ascending and descending modulation frequencies. The upper graphs represent the ASSR amplitudes for 42 subjects in the first two conditions in Table 1. The pattern is similar to that in Fig. 2 (based on all 56 subjects). The lower graphs show the amplitudes when the modulation frequencies were reversed—as detailed in the last two conditions in Table 1.

Effects of Intensity

Sixteen subjects were evaluated using stimuli presented at 53 dB rather than 73 dB SPL. The average results are shown in Figure 8. The amplitudes at 73 dB replicated those seen in the larger groups of subjects. The pattern at 53 dB was strikingly different. There were significant frequency ($F = 5.11$; df 3,42; $p < 0.05$) and condition by frequency by ear ($F = 7.17$; df 3,42; $p < 0.01$) effects but the pattern of the effects was different from that underlying the similar effects at 73 dB. At the lower intensity the largest responses were for the 1000 and 2000 Hz stimuli rather than for the 500 Hz stimulus at the higher intensity. The latencies were on average 0.7 msec later at the lower intensities and showed similar condition by ear by frequency effects at both intensities (involving mainly the latency at 500 Hz, as in the larger group results shown in the lower part of Fig. 2). In 14 of the 16 subjects, we also recorded responses to single 1000 Hz stimuli at 53 dB SPL. These single-stimulus responses had essentially the same amplitude (average 55 nV) as the 1000 Hz responses in the multiple-stimulus recordings (average 57 nV) at this lower intensity.

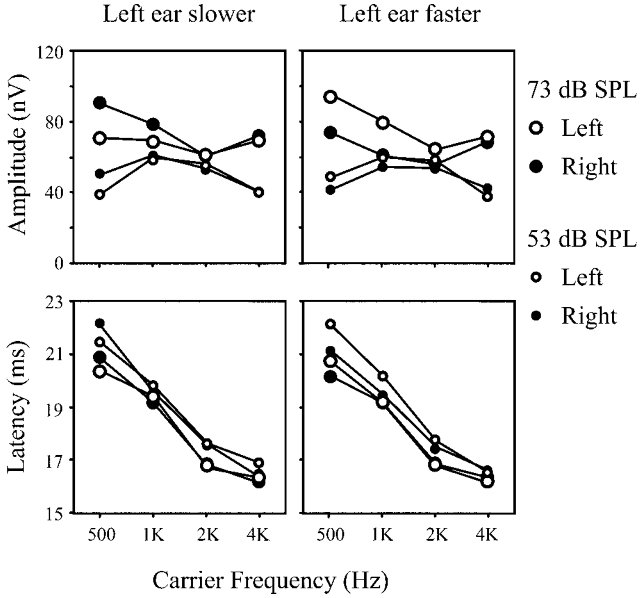

Fig. 8. Effects of intensity. The upper graphs represent the ASSR amplitudes for 16 subjects in the first two conditions and last two conditions in Table 1. The pattern at high intensity is similar to that in Figure 2 (based on all 56 subjects). At the lower intensity the interactions between condition and frequency and ear are similar but the overall frequency effect is different, with the 1000 and 2000 Hz tones being larger. The lower graphs show the latencies. The basic pattern is the same as that in the lower part of Figure 2, with the latencies being longer at the lower intensity.

DISCUSSION

Behavioral Thresholds

The behavioral thresholds showed small but significant differences between left and right ears and between male and female subjects. These differences need to be considered in relation to the ASSR findings. The tendency for the ASSR to be slightly larger in female subjects might, for example, be related to the lower thresholds in the female subjects. However, the ASSR data are variable and we were unable to find either significant gender differences in the ASSRs or correlations between ASSR measurements and behavioral thresholds.

Our subjects showed slightly better (1.5 dB lower) behavioral thresholds in the right ear compared with the left. After testing the first 20 subjects of this study, we wondered whether this asymmetry might have been related to our sequence of assessing the thresholds in the left ear and then in the right ear (cf. Thornton, et al., 2003). However, this difference remained even when we reversed the sequence for the next subjects. Our results confirm previously reported ear asymmetries in pure-tone thresholds. Kannan and Lipscomb (1974) found a significant asymmetry (with the right ear having lower thresholds) in their review of several large audiometric studies, but the asymmetry was mainly in male subjects. Chung et al. (1983) found that thresholds in the right ear were about 1 dB lower (better) than in the left ear in both male and female subjects in a group of over 50,000 subjects screened for possible noise-induced hearing loss. Subjects who had used guns were excluded from the study to rule out the possibility of any shooting-related noise-induced hearing asymmetry (cf. Job, et al., 1998).

Our female subjects showed thresholds (combined across ears) that were slightly (2.2 dB) lower than in the male subjects. In our group of subjects, this difference did not vary with ear or frequency. Other investigators have reported gender-related threshold differences in young adults. Corso (1963) found that thresholds in young subjects (18–40 yr) were consistently lower in female subjects than in male subjects by about 1 dB. Royster et al. (1980) found young (20–40 years) adult female thresholds between 500 and 2000 Hz to be about 1 dB lower than male thresholds, with the difference being greater at higher frequency and greater for older subjects. Dreisbach et al. (2007) found a similar frequency by gender effect. Cooper (1994) found gender-related differences but only at higher frequencies and only in white subjects. Kurakata et al. (2006), however, found a mean male-female difference of <0.5 dB between 500 and 4000 Hz in young subjects (15–29 yr).

The small decrease in thresholds with increasing frequency may have been caused by the levels of background acoustic noise in the sound-attenuated room, which were within the recommended levels but slightly greater at the lower frequencies.

Ear-Related ASSR Asymmetries

Despite the behavioral threshold asymmetry, we had difficulty demonstrating consistent ear-related asymmetry in the ASSR measures that could not be attributed to the confounding effect of differences in modulation rate between the ears. Within one subgroup of our subjects (those evaluated in conditions 7 and 8) the responses were significantly larger in the right ear. However, there was no overall ear-effect in the conditions in which all 56 subjects participated. Clearly, the relative rate between the ears—whether the left ear stimuli have faster or slower rates (as we shall discuss later)—is the main contributor to the asymmetries that we found in the sweep study of 2007. However, an underlying small ear asymmetry might explain why the data from the 2005 study (which had faster left ear rates) did not show any significant asymmetry—the relative rate effect may have been countered by a small right ear effect in this small group of subjects.

Gender-Related ASSR Effects

The ASSRs tended to be earlier in latency and larger in amplitude for female than for male subjects. However, in only one statistical examination (the latencies in conditions 5 and 6) did these gender differences reach significance. Nevertheless, they are consistent with previous findings of earlier ASSR latencies in female subjects (0.78 msec in John & Picton, 2000b). At modulation rates of 80 to 105 Hz, the ASSRs are largely generated in the brain stem (Herdman, et al., 2002). Our small gender-related latency differences for the ASSR fit with the literature for the transient brain stem responses. The ABR to clicks has consistently shown gender-related changes, being larger (Kjaer, 1979; Michalewski, et al., 1980) and earlier (Beagley & Sheldrake, 1978; Don, et al., 1993; McClelland & McCrae, 1979) in female subjects. These differences may be present in the newborn period (Sininger, et al., 1998), and they become more apparent during childhood (O'Donovan, et al., 1980; Thivierge & Côté, 1990). The size of the head (Trune, et al., 1988) and the length of the cochlear partition (Bowman, et al., 2000; Don, et al., 1993) are major determining factors, but temperature and hormones also contribute (recently reviewed by Hall, 2006).

A smaller head size has several effects. A decreased length of the auditory pathway will decrease the latency and increase the synchronization of the fiber discharges. Increased synchronization increases the compound potential formed by the summation of individual fiber discharges. Other effects are a decreased distance between brain stem and scalp and decreased thickness of the skull, both of which facilitate the spread of the electrical field from brain stem generator to scalp electrode.

Gender effects on the ASSRs may occur and be similar to those found for the ABR. However, the standard errors of our measurements of latency were 0.1 to 0.2 msec. A larger sample size would therefore be necessary to demonstrate conclusively and consistently gender-related differences of a few tenths of a millisecond that might be predicted on the basis of the ABR (where the typical wave V latency difference is 0.2 msec). Similar problems exist for the amplitude comparisons.

Effects of Multiple Stimuli

The stimulus-related effects recorded in our experiments were complicated and involved significant interactions between stimulus parameters. To understand the effects, we shall consider them in terms of what happens when one goes from single stimuli to multiple stimuli presented monotically and then to multiple stimuli presented dichotically.

Amplitude • Single stimuli presented alone show responses that do not vary significantly in their amplitude across carrier frequencies and that are virtually identical in the two ears. When multiple stimuli are presented either monotically or dichotically at 73 dB SPL, the amplitude is decreased at 1000 and 2000 Hz relative to what is obtained with single presentation (Fig. 3). Previous results have shown little effect of multiple-stimulus presentation compared with single-stimulus presentation at lower intensities (e.g., 60 dB SPL in Lins & Picton, 1995). John et al. (1998) showed that the responses became smaller with multiple stimulation when the intensity of the stimuli was 75 dB SPL but not 60 dB SPL. Previous results with multiple stimulation at lower intensities (Fig. 2 of Herdman & Stapells, 2001; Fig. 2 of John, et al., 2002; Table 3 of Luts, et al., 2006) have shown that the responses were either approximately equal across carrier frequencies or larger at the midfrequencies. Responses recorded in the final two conditions (Fig. 8) show that at 53 dB the response is indeed larger for carrier frequencies of 1000 and 2000 Hz. This is quite different from the responses at 73 dB, which were larger at 500 and 4000 Hz.

The effects of one stimulus on the response to another stimulus of different frequency are complex (Durlach, 2006). Although one stimulus may sometimes enhance or sensitize the response to another (Galambos, et al., 1972), most stimulus interactions are inhibitory. These effects are usually considered under the rubric of "masking," a term with many meanings: in psychophysics it typically refers to the elevation of threshold, but it may also refer to changes in how well a stimulus is discriminated or recognized; in physiology, masking refers to the decrease in amplitude or rate of a response (Delgutte, 1990). Masking is most commonly related to the excitation-pattern of a stimulus on the basilar membrane and pure-tone masking has its main effect on stimuli of higher frequency (Wegel & Lane, 1924). However, physiological studies have also demonstrated a phenomenon called "suppression" (Arthur, et al. 1971), which occurs in the cochlea at the level of the hair cells (Keefe, et al., 2008), and which adds to the effects of excitation-pattern masking (Gifford & Bacon, 2000). Unlike excitation-pattern masking, suppression is bidirectional in terms of frequency, and at lower intensities a response is more inhibited by suppressor tones of higher than lower frequency. Lateral inhibitory circuits in the central nervous system likely serve to sharpen the frequency specificity of the response (Houtgast, 1972; Moore & Glasberg, 1982). These central masking effects often also go under the name of "suppression." One differentiating feature is that central suppression is delayed whereas cochlear suppression is exactly simultaneous with the suppressing stimulus.

The U-shaped curve we obtained in the present study at the 73 dB SPL intensity—with the amplitudes lowest at frequencies 1000 and 2000 Hz (Fig. 2)—is likely due to two different processes, both of which become more apparent at higher intensities. One is the masking effect of low-frequency stimuli on higher frequency stimuli caused by the asymmetry of the traveling wave activation pattern. This explains why the 500-Hz response is larger than the responses to higher frequencies in the multiple-stimulus conditions. However, it does not explain the relative sparing of the 4000-Hz response. There is, therefore, an extra inhibitory effect of high-frequency stimuli on lower frequency stimuli (cf. John, et al. 1998, Ross, et al. 2003). This may be related to suppression, but whether such suppression is cochlear or central remains unresolved. Because peripheral suppression is most prominent at frequency differences between probe and suppressor of less than an octave (Keefe, et al., 2008), our effects are most likely central in origin.

Presenting multiple stimuli simultaneously at high intensity decreases the responses to stimuli with higher carrier frequencies compared with when they are presented singly. This effect is largest at 1000 and 2000 Hz (Fig. 3). This can be mainly related to the tone-on-tone masking. Again, the effects are less than what might be expected at 4 kHz. This might be related to an additional inhibitory effect of high-frequency stimuli on the responses to stimuli to stimuli of lower frequency.

When multiple stimuli are presented monotically the responses show the same pattern regardless of the ear to which they are presented (the triangular responses in Fig. 4). However, when they are presented dichotically, the responses at 500 and 1000 Hz become larger than their contra-lateral counterparts in the ear where the modulation frequency is higher. This effect explains the different asymmetries that have been reported in previous articles. In the Picton et al., 2007 article where the modulation frequencies were slower in the left ear the responses were larger in the right ear, and in the Picton et al., 2005 article where the modulation frequencies were higher in the left ear, there was a tendency for the responses to be larger in the left ear at higher intensities. The fact that the latter asymmetry was not as striking as the former might suggest some underlying tendency for there to be a larger response in the right ear (as discussed above).

The effect of the relative rates of modulation did not occur when the modulation frequencies were set up so that the higher carrier frequencies were associated with lower modulation frequencies (bottom of Fig. 8). The effect, therefore, depends on two factors: the carrier frequency being $<$2000 Hz and the modulation frequency $<$90 Hz.

The effect of dichotic stimulation differed between conditions wherein there were four stimuli or one stimulus in each ear. With four stimuli in each ear we found a combination of slight enhancement (at 500 Hz) and attenuation (at the higher frequencies). With the single stimulus conditions (Fig. 6) we showed a small but significant increase in amplitude with dichotic stimulation. There is likely a small enhancement of the response when the other ear is stimulated with the same carrier frequency but this is overwhelmed by the interfrequency masking and suppression effects when multiple stimuli are presented to both ears.

Latency • The latency increases with decreasing carrier frequency, in keeping with the latencies of the traveling wave in the cochlea. The calculation of latency from phase according to the suggestions of John and Picton (2000b) remained consistent across the variety of modulation frequencies used in our present experiments. One might have expected the 500-Hz responses to be a little later when comparing the present latencies to those of John and Picton (2000b). The shorter latency in the current recordings might have been due to some basal shift in the locus of maximal activation for this low-frequency stimulus because its intensity was higher than in the previous paper (73 versus 60 dB SPL).

As we changed from a single stimulus to multiple stimuli, the latency showed complicated changes, with the main change being an increase in latency at 1000 Hz. When comparing the monotic multiple stimuli to dichotic multiple stimuli, the latency decreased when the stimuli were presented dichotically (Fig. 5). This facilitatory effect was similar to that observed when single stimuli were presented dichotically (Fig. 6, right). This result replicates the findings in the sweep study (Picton, et al., 2007), although the differences in the present study (0.31 msec in the comparison of the multiple stimulus conditions and 0.21 msec in the comparison of the single stimulus conditions, averaging to 0.26 msec) were less than in the 2007 study (around 1.2 msec at high intensities). It is not clear what this dichotic difference represents. The envelope-following response might be facilitated and its latency thus decreased by concomitant input to the other ear. Further studies would be needed to see whether this contralateral input needs to be modulated or needs to be at the same frequency. The effects of intensity also need considering. Herdman and Stapells (2001, their Fig. 2) found a small decrease in phase delay with dichotic stimulation as opposed to monotic stimulation for frequencies 1, 2, and 4 kHz (but not at 500 Hz) at 60 and 30 dB SPL but these differences were not significant. Another possibility is that the latency difference might represent a separate binaural response that adds to the monaural response to change the phase (and hence the measured latency) of the summed response. A positive monotic-dichotic latency difference occurred in about three quarters of the subjects (Fig. 5). It remains to be determined whether some variant of this measurement might be reliable enough to provide evidence for normal binaural integration.

Processes underlying relative rate effects • The binaural interactions between stimuli with the same carrier frequency but envelopes of different frequency point to several different processes in the early auditory analysis of multiple stimuli. Such interactions require that part of the recorded ASSR be generated by neurons responding to stimuli from either ear (Yin, 2002). These binaural neurons can only contribute a small amount to the response because the response to binaural stimulation is approximately equal to the sum of the monaural responses (Lins, et al., 1995). The formation of steady state responses requires phase locking of responses to the modulation frequency. Binaural neurons generating ASSRs are therefore likely most sensitive to carrier frequencies of 1500 Hz or below. Binaural localization based on phase/time only occurs at these lower frequencies (Stevens, 1936). The inputs to these neurons would mainly come at the rate of modulation of the amplitude modulated tones presented to each ear. The effects could be either facilitatory (e.g., the latency shortening as noted in stimulus Fig. 5, or the enhanced amplitude in the dichotic single stimulus conditions) or inhibitory. The input with the faster rate could come to dominate the overall output of a group of such binaural neurons, because there might be greater overall inhibition of the input from the ear with the slower rate than vice versa. Furthermore, their responses may more easily synchronize to the faster frequency. Responses of binaural neurons are probably maximally elicited by the peak amplitude of the modulated tones. If the stimulus peaks from one ear are occurring more frequently than the other, there are a few times when the peaks of the more slowly modulated stimulus are separated by two peak responses to the faster stimulus in the other ear rather than just one. This may cause the neuron to be better synchronized to the fast stimulus.

Clinical Implications

One of the prominent findings in the present study is the large intersubject variability of the responses (Fig. 6). This implies that the time for demonstrating responses will vary greatly from one subject to another, even at moderate to high intensities. The nature of this variability and its relation to such things as head size, skull thickness, and electrode location (with respect to the orientation of the dipole sources) need further evaluation. Possible small ear- and gender-related differences in the ASSR are obscured by the overall intersubject variance. The largest amplitude effects noted in this study concerned the relative rates of modulation between the two ears. If one ear is a priori suspected of having hearing loss, during dichotic ASSR testing that ear might perhaps be evaluated with higher modulation frequencies than used for corresponding carrier frequencies in the other ear. Conversely, audiologists should not conclude that amplitude asymmetries at high intensity are necessarily related to threshold asymmetries in hearing-impaired subjects or to earphone-asymmetries in normal subjects. The monotic-dichotic latency difference might become a useful measurement of binaural interaction and central auditory processing. However, further study would be required to determine stimulus conditions wherein such an effect could be reliably demonstrated in all subjects. The fact that the responses to high frequencies are relatively small at high intensities when using multiple stimuli simultaneously suggests some caution when assessing elevated high-frequency thresholds. Sometimes these might be elevated by the multiple stimulus technique (Picton, et al., 1998) and sometimes not (Herdman, et al., 2003). Interfrequency inhibitory effects at high intensity might also be used to study central interactions, but again the reliability of these effects needs further evaluation.

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