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Air-Conduction Auditory Steady-State Response: Comparison of Interchannel Recording Using Two Modulation Frequencies

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Wafaa A. Kaf*
Ali A. Danesh†

Abstract

Background: Two-channel auditory steady-state response (ASSR) recording at high and low MF (modulation frequency) most likely provides an insight about the response amplitude and latency from different directions at the brainstem level and at the thalamus or cortical level. Little is known about the combined relationship between MF (39 and 79 Hz) and electrode montages (ipsilateral and contralateral) to single AM (amplitude modulation) tones on the ASSR amplitude and latency.

Purpose: To determine if ipsilateral versus contralateral response asymmetries are present at the brainstem level (79 Hz ASSR) and at the thalamus or cortical levels (39 Hz ASSR).

Research Design: Descriptive and inferential statistics for interchannel ipsilateral and contralateral ASSR amplitude and latency to 79 and 39 Hz.

Study Sample: Twenty-five normal-hearing, right-handed young female adults participated in the study. All participants were right-handed, and their age ranged between 18 to 28 years (mean 24.5 ± 1.6 years).

Data Collection and Analysis: Ipsilateral and contralateral ASSR to 39 and 79 Hz MF and 100% AM stimuli were recorded at 500, 2000, and 4000 Hz carrier frequencies at 65 dB SPL. The ASSR amplitudes and phases were determined for each MF across Fc (carrier frequency) for the two channels to the test (right) ear. ASSR amplitude and latency between recording montages for each MF and across carrier frequency were compared by computing two-way repeated measures ANOVA.

Results: The mean ipsilateral ASSR amplitudes to 39 Hz across frequency were slightly larger (228.6 ± 61.6 μV) than the contralateral response amplitude (223.2 ± 78 μV) while the mean ipsilateral 79 Hz amplitudes were smaller (127.3 ± 114.8) compared to contralateral 79 Hz amplitude (154.6 ± 112.7 μV). For latency response, the mean ipsilateral/contralateral latency difference, on average, was 1 msec or less for both MFs. Results, in normal female adults, indicated no significant interchannel ASSR asymmetries for amplitude and latency ($p > 0.05$) at the brainstem (79 Hz ASSR) and at the thalamus or cortical levels (39 Hz ASSR).

Conclusions: Interchannel ipsilateral and contralateral ASSR amplitude and latency to 79 and 39 Hz are not significantly different in normal, young female adults. Two-channel recording of ASSR to different MFs may be of clinical value in otoneurologic assessment.

Key Words: Air conduction, auditory cortex, auditory evoked potentials, auditory steady-state response, brainstem, contralateral recording, generator sites, ipsilateral recording, modulation frequency, recording montage, stimulus rate, thalamus

Abbreviations: 3-CLT = three-channel Lissajous trajectory; ABR = auditory brainstem response; AEP = auditory evoked potentials; AM = amplitude modulation; AMLR = auditory middle-latency response; ASSR = auditory steady-state response; Fc = carrier frequency; FFT = fast Fourier transform; MEG = magnetoencephalographic; MF = modulation frequency (envelop of a modulated tone); SNR = signal-to-noise ratio

*Communications Sciences and Disorders, Missouri State University, Springfield, Missouri; †Department of Communication Sciences and Disorders, Florida Atlantic University, Boca Raton, Florida

Wafaa A. Kaf, Communication Sciences and Disorders, Missouri State University, Springfield, MO 65897; Phone: 417-836-4456; Fax: 417-836-4242; E-mail: wafaakaf@missouristate.edu

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Sumario

Antecedentes: El registro de respuestas auditivas de estado estable (ASSR) en dos canales, tanto en alta como en baja MF (frecuencia modulada), posiblemente aporta una apreciación sobre la amplitud y latencia de la respuesta proveniente de diferentes direcciones, tanto a nivel de tallo cerebral y tálamo, como a nivel cortical. Se sabe poco sobre el efecto de la relación combinada entre MF (39 y 79 Hz) y los montajes de electrodos (ipsilateral y contralateral) en relación con tonos sencillos de AM (amplitud modulada) sobre la amplitud y la latencia de las ASSR.

Propósito: Determinar si existe asimetría en las respuestas ipsilaterales vs. contralaterales a nivel del tallo cerebral (79 Hz ASSR) y a nivel talámico y cortical (39 Hz ASSR).

Diseño de la investigación: Estadísticas descriptivas y por inferencia para latencia y amplitud de ASSR intercanal ipsilateral y contralateral a 79 y 39 Hz.

Muestra del Estudio: Veinticinco mujeres adultas jóvenes, diestras y normoyentes participaron del estudio. Todas las participantes eran diestras y sus edades variaron entre 18 y 28 años (media de 24.5 ± 1.6 años).

Recolección y Análisis de los Datos: Se registraron estímulos ipsilaterales y contralaterales de ASSR a 39 y 79 Hz de MF y 100% de AM, en frecuencias portadoras de 500, 2000 y 4000 Hz, a 65 dB SPL. Se determinaron las amplitudes y fases de las ASSR para cada MF en todas la Fc (frecuencia portadora) en los dos canales del oído de prueba (derecho). Se compararon las latencias y amplitudes de las ASSR entre los montajes de registro de cada MF y en todas las frecuencias portadoras, por medio del cómputo de un ANOVA de medidas repetidas de dos vías.

Resultados: Las amplitudes ipsilaterales medias de las ASSR a 39 Hz en todas las frecuencias fueron levemente mayores (228.6 ± 61.6 μV) que las amplitudes de las respuestas contralaterales (223.2 ± 78 μV), mientras que las amplitudes ipsilaterales medias a 79 Hz fueron menores (127.3 ± 114.8 μV) comparadas con la amplitud contralateral a 79 Hz (154.6 ± 112.7 μV). Para las latencias de las respuestas, la diferencia ipsilateral/contralateral media de latencia, en promedio, fue 1 mseg o menos para ambos MF. Los resultados, en mujeres adultas normales, no mostraron asimetrías intercana significativas en las ASSR, para amplitud o latencia ($p > 0.05$) a nivel de tallo cerebral (79 Hz ASSR) y a nivel del tálamo y la corteza cerebral (39 Hz ASSR).

Conclusiones: Las latencias y amplitudes intercanal, ipsilaterales y contralaterales para las ASSR a 79 y 39 Hz, no fueron significativamente diferentes en mujeres adultas, jóvenes, normales. Los registros de dos canales para ASSR a diferentes MF pueden tener valor clínico evaluaciones otoneurológicas.

Palabras Clave: Conducción aérea, corteza auditiva, potenciales evocados auditivos, respuestas auditivas de estado estable, tallo cerebral, registros contralaterales, sitios generadores, registros ipsilaterales, modulación de la frecuencia, montaje de registro, tasa de estimulación, tálamo

Abreviaturas: 3-CLT = Trayectoria de Lissajous de tres canales; ABR = Respuesta auditiva del tallo cerebral; AEP = potencial evocado auditivo; AM = modulación de la amplitud; AMLR = respuesta auditiva de latencia media; ASSR = respuesta auditiva de estado estable; Fc = frecuencia portadora; FFT = transformación rápida de Fourier; MEG = magnetoencefalográfico; MF = frecuencia modulada (envolvente de un tono modulado); SNR = tasa señal-ruido

Human auditory steady-state response (ASSR) can be recorded using modulation frequencies (MFs) (i.e., envelop of a modulated tone or stimulus rates) between 4 and 450 Hz (Rickards and Clark, 1984). The ASSR amplitude shows significant enhancement at rates near 40 Hz (Galambos et al, 1981) and 80 Hz (Cohen et al, 1991; Lins et al, 1995). ASSR responses near 80 Hz are believed to be generated mainly in the brainstem, whereas responses near 40 Hz have dual generator sources in the brainstem and in the auditory cortex in humans (Herdman et al, 2002) and in guinea pigs (Yoshida et al, 1984). There is supporting evidence suggesting that the 80 and 40 Hz ASSR responses largely arise from the same neurons that generate transient auditory evoked potentials (AEPs). For example, it has been reported that 80 Hz responses represent the superimposition of individual transient auditory brainstem responses (ABR), while the 40 Hz responses represent the superimposition of individual transient auditory middle-latency responses (AMLR) (Galambos et al, 1981; Hari et al, 1989; Gutschalk et al, 1999; Pethe et al, 2001; Herdman et al, 2002; Kuwada et al, 2002).

Given this relationship between 80 Hz ASSR and ABR, and between 40 Hz ASSR and AMLR, the reported findings on the effect of stimulus rate and electrode montage on the ABR and AMLR can be used to provide predictions of the ipsilateral/contralateral ASSR amplitude and latency. Several ABR reports showed either a slight increase in wave V amplitude with increasing stimulus rate up to 50/sec (Jewett and Williston, 1971) or no significant change in amplitude with stimulus rate up to 80/sec (Don et al, 1977; Picton et al, 1981). Increased stimulus rate has been used clinically to save testing time during hearing threshold estimation by recording ABR wave V amplitude, and to stress the brainstem for otoneurologic assessment by analyzing wave V latency (Jacobson et al, 1987; Schwartz and Schwartz, 1991). Several human and animal studies have shown that AMLR increases in amplitude with reducing stimulus rate less than 10/sec (Picton et al, 1974; Buchwald et al, 1981; McGee et al, 1983; Knight et al, 1985; Erwin and Bauchwald, 1986; Jerger et al, 1987).

Although not studied extensively, the effect of MF on the ASSR also shows a general trend of increasing response amplitude and latency with decreasing MF, with some amplitude enhancement around 40 Hz (Galambos et al, 1981; Rickards and Clark, 1984; Stapells et al, 1984; Suzuki and Kobayashi, 1984; John and Picton, 2000). More specifically, the 40 Hz response is much larger for lower carrier frequencies (Galambos et al, 1981; Ross et al, 2003) while the 80 Hz response is larger for the middle carrier frequencies (John, Dimitrijevic, et al, 2002; John, Purcell, et al, 2002), although it can be recorded at extended high frequencies above 8 kHz (Tlumak et al, 2007).

In addition to the effect of stimulus rate/MF, recording montage is known to affect recording of AEPs. Multichannel magnetoencephalographic (MEG) recordings, multichannel recording using independent component analysis, brain mapping, and three-channel Lissajous trajectory (3-CLT) have been reported to improve identification and confirmation of response waveform, amplitude, and latency for transient AEPs (Hashimoto et al, 1981; Pratt et al, 1983, 1995; Hall et al, 1984; Sininger and Don, 1989; Durrant et al, 1994; Van Dun et al, 2007). Compared to two-channel recording (ipsilateral: vertex to the mastoid of stimulated ear; contralateral: vertex to the contralateral mastoid), the multichannel MEG, brain mapping, and 3-CLT recordings provide real time analysis of the magnitudes and latencies with more comprehensive descriptions of the surface-recorded electrical activity of the auditory system (Scherg, 1984; Pratt et al, 1985, 1986; Martin et al, 1986; Gardi et al, 1987). However, two-channel recording is more appealing clinically because it is less complex, and with well-established normative data, and it provides additional and confirmatory diagnosis in less test time.

Several studies that have compared ipsilateral and contralateral air-conduction ABR and AMLR have reported few differences between recording channels in humans and animals (Gross et al, 1967; Edwards et al, 1985; Hatanaka et al, 1988; Stapells and Mosseri, 1991; Pratt et al, 1995; Tucker and Ruth, 1996). For example, contralateral ABR recording improved distinction of wave IV and V complex, and it prolonged wave V latency of 0.1 msec (Starr et al, 1977; Picton et al, 1981; Barajas, 1982; Pratt et al, 1995). Also, the adults' air-conduction contralateral ABR and AMLR amplitudes were slightly smaller than the ipsilateral amplitudes (Picton et al, 1981). In animals, Gross et al (1967) reported that the contralateral AMLR responses in cats are more extensive and have a larger cortical area of representation but that the maximum response amplitude was found in auditory area I with ipsilateral or contralateral stimulation. These slight ipsilateral/contralateral differences in normal adults indicate that contralateral recording could be useful for the precise identification of later waves and for the verification of the ipsilateral responses for enhanced accuracy of interpretation and diagnosis in otoneurologic cases.

Despite an increasing number of human ASSR amplitude and phase studies (Galambos et al, 1981; Rickards and Clark, 1984; Roß et al, 2000; Stapells et al, 1984; Suzuki and Kobayashi, 1984), most recordings have been made from a single channel. Multichannel recordings were used to study only intracranial sources of the ASSR. Ipsilateral/contralateral interchannel ASSR amplitude and latency to different MFs have not been studied in normal hearing adults. To our knowledge, the only available information is from two unpublished presentations by Stapells and colleagues (Small and Stapells, 2005; Stapells and Van Mannen, 2005). In addition, these two unpublished studies have reported ipsilateral/contralateral ASSR response amplitude and latency differences mainly from infants and to multiple high MF (>70 Hz) with low-level stimuli (i.e., at threshold). Little, however, is known about the combined relationship between MF (39 and 79 Hz) and electrode montages (ipsilateral and contralateral) to single AM (amplitude modulation) tones on the ASSR amplitude and latency on large numbers of adults.

Based on meager unpublished results and on the posited close association between ABR and 80 Hz ASSR, and between AMLR and 40 Hz ASSR, it is hypothesized that ipsilateral/contralateral ASSR responses to high (79 Hz) and low (39 Hz) MF would be absent or slightly asymmetrical. The present study was designed to compare ipsilateral/contralateral response amplitude and latency at (1) the brainstem level (79 Hz ASSR) and (2) the thalamus or the cortical level (39 Hz ASSR) across the carrier frequency, in normal-hearing young, female adults. The findings from the present study could be used as preliminary normative data in otoneurologic assessment.

METHODS

ASSR responses were recorded in 25 normal-hearing, right-handed young females (age range, 18–28 years old; mean age, 24.5 ± 1.6 years). All participants had normal hearing sensitivity in both ears (≤20 dB HL re ANSI S3.6-2004 at octave frequencies between 250 and 8000 Hz). None of the participants demonstrated a history of auditory or neurological pathology, and all of them demonstrated normal middle ear function as determined by otoscopic and tympanometric examinations. The Missouri State University Institutional Review Board approved this protocol. All participants signed consent forms before the protocol was administered, and they participated voluntarily in the study.

The Intelligent Hearing System (IHS) SmartEP-ASSR System 3.63 (research version) was used to record and generate stimuli for ASSR. The generated stimuli were sinusoidal air-conduction 500, 2000, and 4000 Hz carrier frequencies (Fc) that were 100% amplitude modulated. Assigning 100% AM means that the stimulus fluctuates between the maximum and total minimum of the amplitude. The ASSR was recorded at each of the carrier frequencies (i.e., single recording) to 39.06 and 79.10 Hz MF. For simplicity, we will refer to the two MF as 39 and 79 Hz (i.e., 39 and 79 stimulus presentations/sec). The AM stimuli were calibrated in dB SPL using corrections for the ER-3A insert earphones as specified by ANSI (American National Standards Institute) standards (S3.6-1996 [ANSI, 1996]) for hearing-level calibration. Measurements were performed using an Impulse Sound Level Meter (Quest Model 1700), Octave Band Filter (Model OB-300 1/1–1/3), OB-20 sound calibrators with a QE 4170 microphone, a 2-cc coupler (Brüel & Kajær type DB 0138 artificial ear, with GSI 1700–2005 rigid tube insert), and acoustic calibrators (Model QC-20: dual-frequency and dual-amplitude calibrator).

The electroencephalographic (EEG) activity was simultaneously recorded from two channels using four gold-plated electrodes. The noninverting electrode was placed on the vertex and the inverting electrodes were placed on both mastoids (Cz/M2 and Cz/M1) with the low forehead (Fpz) as the ground. The EEG was amplified 100,000 times and filtered using a 30–300 Hz filter (for the 79 Hz MF) and a 10–300 Hz filter (for the 39 Hz MF), and the slope of the filter was −6 dB/octave. The EEG data acquisition was recorded for a total of 100 averaged sweeps for each test condition. Every EEG recording sweep was made up of 20 epochs per block size, with an acquisition rate of 1024 points per second. Every sweep of data was one second. The analog-to-digital conversion rate was 20 kHz. This was down-sampled to 1 kHz, which gave a final spectral fast Fourier transform (FFT) resolution of 0.9765 Hz over the range of 23 to 152 Hz. The artifact rejection region was set to the range of 40–400 msec, and the artifact rejection was set to eliminate epochs of EEG activity that exceeded ±31 μV in amplitude (e.g., muscle artifacts). The FFT algorithm converts the original amplitude-time waveform into a series of cosine waves. Specific frequencies are each represented as a vector in a two-dimensional plane. For each frequency represented in the FFT spectrum, the real (X) and imaginary (Y) coordinates define a vector. Each vector can be represented by its amplitude (the length of the vector) and by its phase (the rotation of the vector in relation to the x-axis as calculated from the arctan [Y/X]). The ASSR response is therefore characterized by this amplitude and phase. The ASSR amplitudes were measured baseline-to-peak and expressed in microvolts (μV). The measured phase values were converted to phase delays (in degrees) and latency (in msec).

Procedure

All testing was completed in a single-walled, sound-attenuated booth in the Auditory Research Laboratory at Missouri State University. An interacoustics AC 40 diagnostic audiometer, calibrated to ANSI standards (2004), was used to estimate the behavioral hearing threshold or each participant. A GSI TympStar was used for tympanometric evaluation to exclude middle ear pathology, and the IHS SmartEP ASSR was used for ASSR recording. The subjects were seated in a reclining chair and were instructed to relax and keep their eyes closed but to remain awake during testing. To assure that they were awake during testing, the examiner (first author) verbally communicated with the subjects between stimulus presentations and provided breaks to participants upon their requests. The interelectrode impedances were less than 2 kΩ. The ASSR stimuli, Fc and MF, were randomly presented to the right ear at 65 dB SPL via an Etymotic ER-3A insert earphone. This moderate-level stimulus is not expected to affect the recording response differences between the two channels. This is because ipsilateral/contralateral symmetry or asymmetry could be recorded at suprathreshold and threshold levels (Sininger and Don, 1989; Small and Stapells, 2005; Stapells and Van Mannen, 2005). In addition, Dobie and Wilson (1998) suggested that 40 Hz modulation frequency might be optimal for ASSR detectability at moderate-signal level (e.g., 38 and 58 dB peSPL) in adults. Given moderate-level stimulus and interaural attenuation by the use of insert earphone, the stimulus level at the nontest ear (the left ear) would be low enough to prevent stimulating the left ipsilateral pathway.

Two recordings per stimulus condition were collected, and each recording was comprised of 100 accepted sweeps. A total of 12 randomized stimulus conditions were recorded (3 [Fc] × 2 [Rates] × 2 [trials]). Recordings were acquired using a split-buffer technique, which allowed comparison of signal and noise characteristics at each frequency. The response amplitude and phase were automatically measured using spectral techniques at the MF via an F-ratio test. This statistical test evaluates whether the response at the MF is different from the noise at adjacent frequencies by computing the ratio between the power measured at the signal frequency and the average power in the neighboring frequency bins (based on F[2,10] corresponding to five frequency bins or 4.88 Hz on each side of the MF). Averaging was continued until a response was significantly different ($p < 0.05$) from noise.

The ASSR amplitudes and phase data were determined for each MF (39 and 79 Hz) across Fc for the ipsilateral and contralateral channel to the test (right) ear. A response was determined to be "present" if the p value was $\leq$0.05, or when the signal-to-noise ratio (SNR) was at least 6.13 dB above the noise at the given frequency bin, which corresponds to the MF and about 5 Hz on either side. A response was considered to be "absent" if any of these criteria were not met, the mean amplitude of the noise level of the recording at and around the MF was >0.05 μV, or the mean amplitude of the response was <0.0125 μV. In the present study, all participants had significant responses at $p \leq 0.01$ and when the SNR was higher than 6.13 dB.

Data Analysis

The recorded amplitude and phase data from the IHS were transferred to SPSS via ASCII format. Mean spectral amplitude values (in microvolts, μV) were averaged across subjects to 39 and 79 Hz MF at 500, 2000, and 4000 Hz Fc for each recording montage (ipsilateral and contralateral). The measured cosine onset phase values (θ) from the IHS were converted into phase delays (P, in degrees) and latencies (L, in msec) using three mathematical steps. First, the measured phase values of the polar plots (θ) were adjusted by adding 90° to compensate for the phase delays due to the 90° shift caused by the stimulus modulation being coded sinusoidally while the onset phase of the response was measured as a cosine (Rodriguez et al, 1986; John and Picton, 2000). Second, the adjusted onset phase values were converted to phase delays (P, in degrees) by subtracting it from 360°. Third, the P values were then converted to latency values (L, in msec), using the equation: $L = P/(360 \times f_m) + (1/f_m)$, where f_m is the modulation frequency, and $(1/f_m)$ is defined as a period to a full cycle. The addition of $1/f_m$ was recommended to compensate for the travel time delay between the cochlea and brainstem, and between the brainstem and cortex. This was done because it is impossible to determine number of cycles that occurred between the stimulus and the recorded cycle (John and Picton, 2000). The resulting latency value (in sec) was then multiplied by 1000 to be estimated in msec. The latency values were averaged across subjects to each MF and carrier frequency for each recording channel.

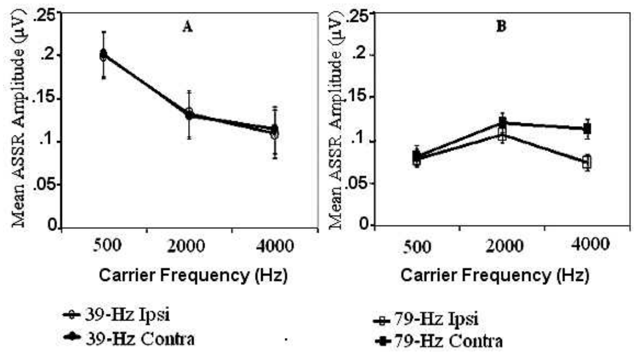

Figure 1. Mean and standard error (±1 SE) of ipsilateral/contralateral ASSR amplitudes asymmetry to 39 and 79 Hz at 500, 2000, and 4000 Hz carrier frequencies (Fc) at 65 dB SPL stimulus level. *(A)* Ipsilateral and contralateral ASSR amplitudes to 39 Hz modulation frequency (MF) are nearly equal across all Fc. *(B)* Ipsilateral/contralateral ASSR amplitudes to 79 Hz MF are similar at 500 Hz but contralateral amplitudes are slightly larger at 2000 and 4000 Hz.

ASSR amplitudes (μV) and latencies (msec) between recording montages for each MF and across Fc were compared for statistical significance by computing two-way repeated measures ANOVAs (SPSS version 15.0). For each MF, montage (ipsilateral vs. contralateral) is considered a between-subject factor, and the carrier frequency (500, 2000, and 4000 Hz) is a within-subject factor. The two 2 × 3 ANOVA (montage and carrier frequency) were computed for response amplitude and latency values. Depending on the outcomes of the ANOVA, least significant difference (LSD) post hoc comparisons were performed for significant main effects and interactions. Differences were considered significant at the $p < 0.05$ for all inferential analysis.

RESULTS

Figure 1 (A and B) depicts the mean ASSR amplitudes to 39 and 79 Hz MF at 500, 2000, and 4000 Hz for each recording montage. Figure 1A shows that 39 Hz ASSR amplitudes to the ipsilateral and contralateral recording are nearly equal and are aligned with decrease of the amplitude with increasing carrier frequency. Figure 1B reveals that 79 Hz ASSR contralateral amplitudes across carrier frequencies are slightly larger than the ipsilateral responses by .02 μV due mainly to larger contralateral responses at 2000 and 4000 Hz. The ipsilateral response did show larger amplitude to the 39 Hz MF compared to the 79 Hz amplitudes, mainly at 500 Hz by .12 μV. When contralaterally recorded, the 39 Hz response amplitudes at 500 Hz were also larger by .12 μV than the 79 Hz amplitudes at 500 Hz.

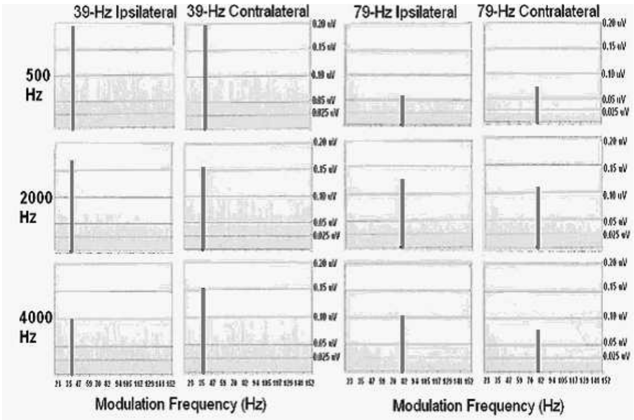

Figure 2. Air-conduction ASSR response sample from two subjects. ASSR responses were recorded using two-channel EEG recording (ipsilateral and contralateral) to 39 and 79 Hz modulation frequency. The x-axis is the modulation frequency over the range of 23 to 152 Hz. The y-axis is the response amplitude (μV). The amplitude (baseline-to-peak in μV) spectra resulting from the FFT analysis of the ASSRs are shown as peaks (thick lines) in the spectrum at 39 and 79 Hz modulation frequency. These peaks differ significantly from the background noise (background, faint gray areas) ($p < 0.01$). In both subjects, the 39 Hz ASSR amplitudes to ipsilateral and contralateral recording are nearly equal at all Fc with larger amplitudes at 500 Hz. Also the 79 Hz ipsilateral and contralateral ASSR amplitudes are similar with little differences in the amplitude across Fc. As can be seen in the spectra, the 39 Hz ASSR amplitudes are larger than the 79 Hz ASSR amplitudes regardless of the recording montage.

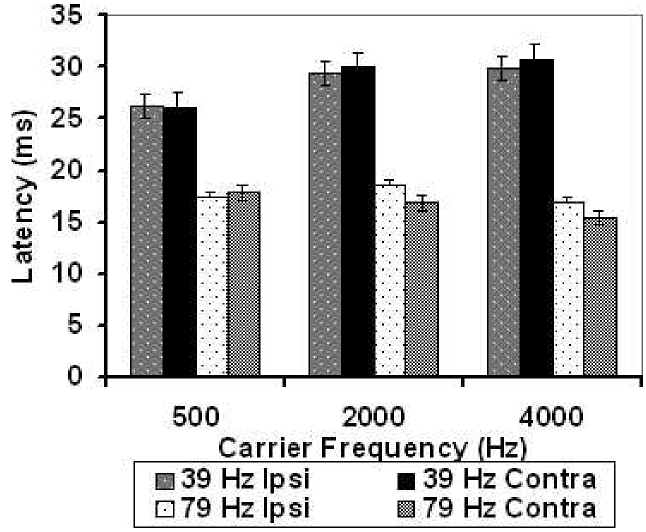

Figure 3. Effect of modulation frequency (39 and 79 Hz) and recording montage (ipsilateral vs. contralateral) on latency of the ASSR as a function of carrier frequency are shown. The figure represents the mean (±1 SE) data of the estimated latency in msec (P/[360 × fm] + [1/fm] × 1000) from the 25 female participants. ASSR latencies are shown for 39 and 79 Hz modulation frequency for both ipsilateral and contralateral recordings. The figure shows a negligible ipsilateral/contralateral latency difference for 39 and 79 Hz modulation frequencies. The 79 Hz latency decreases slightly with increasing carrier frequency, except at 2000 Hz. For 39 Hz responses, latency increases slightly with increasing carrier frequency. The figure also illustrates that 39 Hz responses are prolonged compared to 79 Hz responses across carrier frequency.

Results of the 2 × 3 ANOVA comparing the mean ASSR amplitudes across montage and carrier frequency revealed no significant effect for montage for 39 Hz responses ($F_{[1,48]} = 0.005$, $p = 0.944$, Eta squared $\varepsilon^2 = 0.112$) and 79 Hz responses ($F_{[1,48]} = 0.368$, $p = 0.547$; $\varepsilon^2 = 0.541$). There was significant effect for carrier frequency only for the 39 Hz responses ($F_{[2,96]} = 8.170$, $p < 0.005$; $\varepsilon^2 = 0.321$), but not for the 79 Hz responses ($F_{(2,96)} = 0.1.575$, $p = 0.212$; $\varepsilon^2 = 0.145$). There was no significant interaction between montage and carrier frequency for 39 Hz ($p = 0.985$) and 79 Hz ($p = 0.650$). LSD comparisons indicated that the significant effect of carrier frequency for the 39 Hz response amplitude was explained by the larger amplitude at 500 Hz compared to those at 2000 and 4000 Hz. Figure 2 demonstrates ipsilateral/contralateral mean amplitudes to the 39 and 79 Hz MF at the three carrier frequencies from two representative subjects. It replicates the same findings of the group data (Figure 1).

Figure 3 and Table 1 represent the mean data of the estimated latency (in msec) from the 25 female participants. Figure 3 illustrates the effect of MF (39 and 79 Hz) and recording montage (ipsilateral vs. contralateral) on the mean response latency (in msec) across the carrier frequency. For 79 and 39 Hz responses, the estimated latency values from the ipsilateral recording to 79 Hz (17.5 ± 3.4 msec, 18.6 ± 4.0 msec, 16.9 ± 4.6 msec) and to 39 Hz (26.2 ± 4.2 msec, 29.5 ± 3.9 msec, and 29.9 ± 4.3 msec at 500, 2000, and 4000 Hz, respectively) were nearly similar to the contralateral response latencies with less than 1 msec difference. As can be seen from Figure 3 and Table 1, the 39 Hz latency increased with an increase in carrier frequency for both montages, whereas the latency for 79 Hz responses decreased with increasing carrier frequency, with the exception of latency at 2000 Hz to ipsilateral recording.

To rule out the effect of individual variability as the cause of the negligible difference in the ipsilateral/contralateral channels, the mean group data and the individual data variability were examined. First, when the mean data variability was examined, it showed that the ANOVA assumption of homogeneity was met. Second, the mean individual amplitude data for ipsilateral/contralateral differences to 39 and 79 Hz MFs as a function of carrier frequency were calculated (Table 2). Individual data from Table 2 shows that the response amplitudes were present from all ears at 500, 2000, and 4000 Hz to both MFs and on both channels. It also shows that the mean individual ipsilateral/contralateral response amplitudes, across frequency and MF, were similar to or only slightly different (.01–.13 μV) between the two channels.

Table 1. Estimated Mean Latency Responses to Ipsilateral and Contralateral Recording Montages at 39 and 79 Hz Modulation Frequencies (MF) as a Function of Carrier Frequencies (in Hz)

MF (Hz)	*39 Hz modulation*		*79 Hz modulation*	
Montage	Ipsilateral	Contralateral	Ipsilateral	Contralateral
500 Hz	26.2 (4.2)	26.1 (2.5)	17.5 (3.4)	17.8 (3.0)
2000 Hz	29.5 (3.9)	30.0 (5.8)	18.6 (4.0)	16.8 (4.1)
4000 Hz	29.9 (4.3)	30.7 (6.5)	16.9 (4.6)	15.4 (4.4)
Mean Latency	**28.5 (4.4)**	**28.9 (5.5)**	**17.7 (4.0)**	**16.7 (4.0)**

A 2 × 3 ANOVA comparing the mean latency across montage and carrier frequency indicated no significant effect of montage for 39 Hz modulation ($F_{[1,48]} = 0.203$, $p = 0.654$, $\varepsilon = 0.121$) or for 79 Hz modulation ($F_{[1,48]} = 0.912$, $p = 0.344$, $\varepsilon = 0.128$), but there was a significant effect of carrier frequency for only the 39 Hz latency values ($F_{[2,96]} = 13.01$, $p < 0.0005$, $\varepsilon = 0.213$). There was no significant montage × frequency interaction ($p = 0.858$). LSD comparisons revealed that the significant effect of carrier frequency was explained by prolonged 39 Hz mean latency for 500 Hz compared to the 2000 and 4000 Hz values ($p < 0.005$). Table 1 and Figure 3 also show that 39 Hz response latencies across carrier frequency are prolonged compared to 79 Hz response latencies.

DISCUSSION

Ipsilateral/Contralateral Amplitude Asymmetries at the Brainstem Level (79 Hz ASSR) and at the Thalamus and/or Cortical Level (39 Hz ASSR)

At the outset of the present study, there were no previous published reports directly comparing air-conduction 39 and 79 Hz ASSR amplitudes to ipsilateral and contralateral recordings at moderate stimulus level in adults. Since there is little information about adults' air-conduction ipsilateral/contralateral responses in the ASSR literature for comparison, the current findings were compared to ipsilateral/contralateral ABR and AMLR results.

The current results of negligible interchannel differences between ipsilateral and contralateral ASSR amplitudes at the 79 Hz MF are almost in agreement with those ipsilateral/contralateral ABR results in adults. For example, several researchers reported no ipsilateral/contralateral difference for ABR wave V amplitude (Edwards et al, 1985; Hashimoto, 1979; Rossi et al, 1979; Stapells and Mosseri, 1991). The negligible interchannel difference for both 79 Hz ASSR and wave V of the ABR suggests that the 79 Hz ASSR is probably analogous to wave V of the ABR. Our findings of 79 Hz amplitudes to 500 and 4000 Hz tend to be lower in amplitude than the 2000 Hz amplitude. This is similar to those previously reported for both adults' air-conduction ASSR amplitudes (John and Picton, 2000) and ABR amplitudes (Gross et al, 1967; Erwin and Bauchwald, 1986).

In contrast, our findings differ from those reported for ipsilateral/contralateral air-conduction ABR amplitudes in infants. Hatanaka et al (1988), for example, found that ipsilateral ABR amplitudes are larger than contralateral responses. Accordingly, it was assumed that the neural generators of the ABR in infants are viewed differently from the ipsilateral and contralateral electrode montages. Another assumption is that the maturation of the contralateral auditory pathway is incomplete in infants when stimulated via air-conduction ABR (Hatanaka et al, 1988). The immaturity of the contralateral pathway is, thus, considered to be the cause of the smaller ABR amplitudes when contralaterally recorded in infants. Furthermore, when the individual ipsilateral/

Table 2. Mean Individual Amplitude Data for Ipsilateral/Contralateral Differences to 39 and 79 Hz Modulation Frequencies Are Shown as a Function of 500, 2000, and 4000 Hz Carrier Frequency (Fc)

		Number of Subjects (range of difference)		
Fc	MF	*No Ipsi/Contra difference*	*Ipsi > Contra*	*Contra > Ipsi*
500 Hz	39 Hz	5 (0)	14 (.01 to .08)	6 (.01 to .03)
	79 Hz	1 (0)	15 (.01 to .13)	9 (.01 to .05)
2000 Hz	39 Hz	—	13 (.01 to .13)	12 (.01 to .07)
	79 Hz	1 (0)	13 (.01 to .07)	11 (.01 to .08)
4000 Hz	39 Hz	5 (0)	8 (.01 to .06)	12 (.01 to .02)
	79 Hz	1 (0)	16 (.01 to .05)	8 (.01 to .06)

Note: The number of subjects is shown and the range of individual amplitude differences between electrode montages is shown in (parenthesis). N = 25 subjects, 25 right ears. Ipsi = ipsilateral; contra = contralateral.

contralateral amplitudes were compared, our finding showed "present" responses from all ears to both EEG channels with slight ipsilateral/contralateral difference (Table 2), suggesting that ipsilateral/contralateral pathways at the brainstem level in young, female adults are completely mature and that the noninverting electrode is viewing the response amplitudes the same for either ipsilateral or contralateral recordings in adults. The results of the current study, thus, suggest that the noninverting electrode is viewing the response amplitudes the same for either ipsilateral or contralateral recordings in response to moderate-level, air-conduction AM stimuli in young, female adults.

In regard to 39 Hz response amplitudes, the present finding of negligible difference between ipsilateral and contralateral amplitudes differs from those of the AMLR amplitudes that showed asymmetrical ipsilateral and contralateral recordings in both human and animal studies (Gross et al, 1967; Tucker and Ruth, 1996). Possible explanations are that 39 Hz ASSR and AMLR responses largely arise from different neurons and generator sites (Basar et al, 1987). For example, brain mapping has shown that 40 Hz ASSR represents simultaneous activation over widely spaced areas of the brain in both humans (Ross et al, 2005) and cats (Gross et al, 1967). Herdman et al (2002) have reported that 40 Hz ASSRs have dominant cortical generator sites in humans and that they are predominantly in the left auditory cortex (Yamasaki et al, 2005). This widespread activation of the brain mainly at the left auditory cortex and the interaction between the right and left auditory cortices may be the cause of eliciting nearly equal interchannel ASSR amplitudes. Another possible explanation of the slight interchannel amplitude difference may be the orientation of the electrodes (vertex to both mastoids), wherein the noninverting electrode is, again, viewing the 39 Hz response amplitude the same for ipsilateral and contralateral ASSR recording in adults. In contrast, when electrodes were placed on the temporal lobe at T3 and T4 areas, larger 40 Hz amplitudes and shorter latencies were recorded on the contralateral side to the stimulated ear (Yamasaki et al, 2005). They also reported that 40 Hz ASSR amplitudes to 500 Hz are larger and showed laterality when recorded from the temporal electrodes contralateral to the stimulated ear. This may suggest that T3 and T4, or T5 and T6 two-channel electrode placements may be a better montage than vertex to mastoids to probe for ipsilateral/contralateral 40 Hz amplitude asymmetry for recording in otoneurologic diagnosis. Our current finding of the absence of significant ipsilateral/contralateral 39 Hz amplitude difference across Fc is in contrast to findings from Yamasaki et al (2005) and Ross et al (2005). This may be due to the use of tone-burst stimuli and multichannel MEG recording by Yamasaki et al (2005) and whole-head MEG recordings by Ross et al (2005) versus 100% AM tones and two-channel recording from vertex to both mastoids in the present study.

The presence of enhanced ipsilateral and contralateral 39 Hz responses at 500 Hz compared to those at 2000 and 4000 Hz, where the amplitude at 500 Hz is twice as large as that at 2000 and 4000 Hz, is consistent with those findings from Ross et al (2003). They reported that the amplitude of ASSR at 250 Hz is three times larger than that at 4000 Hz. It is also consistent with previous studies using single AM carrier frequencies (Galambos et al, 1981; Stapells et al, 1984; Ross et al, 2000, 2003) or from the use of brief tone-bursts (Rodriguez et al, 1986; Pantev et al, 1996). Regardless of the electrode montage, the 39 Hz ASSR amplitudes at 500 Hz being larger than at higher carrier frequencies could be explained by one or more of the following:

1. The 39 Hz response has dual generator sites from the brainstem and cortex, wherein the 500 Hz brainstem response has a broader and a later waveform that might combine with the cortical response (Herdman et al, 2002);
2. At 500 Hz the recorded ABR wave V and the AMLR have significant energy and similar frequency spectra around 30 to 50 Hz; these can add to produce larger amplitudes in the 40 Hz ASSR (Suzuki et al, 1977, 1983). While at the 4000 Hz tone the recorded ABR was shown to have more energy content at faster frequency spectra (100, 550, and 1100 Hz) than the AMLR spectra (30–50 Hz), causing the ABR wave V and the AMLR to be less likely to combine (Suzuki et al, 1982);
3. Stimulus presentation of the 500 Hz tone at 40/sec causes both ABR wave V and AMLR waves Pa and Pb to be very close together, causing them to add, resulting in larger amplitude; and
4. Low frequencies have a broader activation pattern in the cochlea to high-level stimuli, more synchronicity of the responding cells in cortex, and shorter distance between the responding cells and the surface recording electrodes.

Ipsilateral/Contralateral Latency Asymmetries at the Brainstem Level (79 Hz ASSR) and/or at Thalamic or Cortical Level (39 Hz ASSR)

The ambiguity of the phase measurements of the ASSR is mainly related to its circularity (0–360°) and its steady state nature. Therefore, the phase of the response should be converted into latency (as explained earlier) in contrast to transient AEPs where the phase of the response can be directly measured as latency. After converting phase measures to phase delays (in degrees) and latencies (in msec), the estimated 79 and 39 Hz ASSR latencies to ipsilateral and contralateral recordings were not statistically different (Figure 3). This may support the evidence that the ipsilateral and contralateral pathways in young female adults are completely mature and that the noninverting electrode is viewing the 39 Hz response latency the same for either ipsilateral or contralateral recordings in adults. Our estimated latency of 29 msec, on average, for ASSR to AM tones at 39 Hz, is in agreement with findings from Schimmel et al (1974), who reported that auditory responses with peak latencies between 20 and 40 msec could be efficiently recorded at stimulus rates of 40–45 Hz. The current findings are also comparable to the apparent latency previously reported (25 msec from Cohen et al, 1991; 25–41 msec from Herdman et al, 2002; 32 msec from Kuwada et al, 1986; 36 msec from Linden et al, 1985; 38 msec from Picton et al, 1987; and 34 and 41 msec from Stapells et al, 1984, 1987). To the contrary, our finding of a negligible ipsilateral/contralateral latency difference to 39 Hz latency does not agree with those findings from Yamasaki et al (2005), who reported that contralateral 40 Hz latency was significantly smaller than those of ipsilateral recording. This, perhaps, could be explained by their use of multichannel recording that detected differences at the temporal lobe while the use of two-channel vertex to ipsilateral/contralateral mastoid electrodes may not be a good tool to probe for asymmetries.

In addition, the current estimated latency values for ipsilateral 79 Hz modulation frequency (17.5, 18.6, and 16.9 msec at 500, 2000, and 4000 Hz, respectively) agree with those of John and Picton (2000). They recorded air-conduction ASSR to high MF (80–100 Hz range). John and Picton (2000) reported that the apparent latencies were 19.9, 17.0, and 15.4 msec at 750, 1500, and 3000 Hz, respectively. On average, our 79 Hz response latencies (17.7 msec) and those of John and Picton (2000) (17.4 msec) are more prolonged than those (13 msec) of Cohen et al (1991). The shorter latency in Cohen et al (1991) may be because the response was recorded to binaural mixed modulation stimuli with higher multiple MFs (90–190 Hz), or because of the difference between transduction times of distal and rostral brainstem levels, which are suggested as the generator sites for ASSR to high (90–190 Hz) modulation frequencies. Our latency difference of 11.6 msec between 39 and 79 Hz responses may reflect the differences between the travel time from the brainstem source for 79 Hz responses and the cortical source for the 39 Hz responses (Herdman et al, 2002).

As mentioned earlier, it was hypothesized that 80 and 40 Hz ASSR responses can be predicted from the superimposition of overlapping transient ABR and AMLR, respectively (Galambos et al, 1981; Azzena et al, 1995). This suggests that latencies for 80 and 40 Hz responses may be similar to those of transient ABR and AMLR (Picton et al, 1974; Rickards and Clark, 1984; Hari et al, 1989; Roβ et al, 2000). In comparison to transient AEPs, the current latency findings to 79 Hz are prolonged than ABR wave V latency, while the 39 Hz latency responses are similar to AMLR Pa wave latency. Presence of prolonged latency to 79 Hz ASSR compared to ABR wave V latency may suggest that ASSR and wave V of the ABR may have different neural generators. This is supported by Basar et al (1987), who indicated the presence of specific neurons that are activated only to rapid stimuli, as is the case of ASSR. For low carrier frequency (e.g., 500 Hz) with a low MF (e.g., 39 Hz), subjects were likely to demonstrate delayed latencies with either ipsilateral or contralateral recording. The underlying reasons of our finding of delayed 39 Hz response latency at 500 Hz may be attributed to several factors. At low frequency, the 39 Hz responses are believed to be generated at later, cortical regions of the auditory system that increase travel time. The cochlear mechanical activities in response to low frequency stimuli travel slowly at the apex (Kiang, 1965), most probably due to less myelinated nerve fibers per inner hair cells, less density of inner and outer hair cells at the apex (Bohne et al, 1982; Ehret, 1979), and less innervation at the apex (Bohne et al, 1982). These factors would result in increasing response latency at low frequencies. Also, the total activity that is time-locked to the stimulus decreases as the stimulus rate decreases, resulting in delayed latency (Kiang, 1965). In addition, at moderate stimulus level, similar to what was used in the current study, the cochlear partition responds mainly to the frequency of maximal sensitivity (e.g., 500 Hz) with less basal spread of excitation of the dominant cochlear locations, causing delayed latency at low frequency (Kiang, 1965).

Our overall current findings, thus, support the hypothesis that interchannel ASSR amplitude and latency responses in adults are nearly symmetrical at the brainstem and at the thalamus and cortical levels. These results, though these were a relatively small to moderate effect size (ε^2), clearly show that ASSR could be recorded from either EEG channel in young, female adults. Additionally, ipsilateral/contralateral recordings of ASSR may view the generators at the brainstem or at the thalamocortical regions from different angles. The results of negligible ipsilateral/contralateral ASSR response differences are consistent with the findings of Durrant et al (1990), who reported a strong correlation between ipsilateral/contralateral ABR mainly at wave V, suggesting a "tight coupling" between the two EEG channels. One limitation of this study, while not expected to affect the overall findings, is that we have not considered the signal-to-noise ratio for response amplitude measures to eliminate the variability introduced by the background noise. The current ipsilateral/contralateral ASSR amplitude and latency trends may be considered as normative data for assessing the integrity of the central auditory pathway at the brainstem level, and at the thalamus or cortical levels in normal-hearing female adults. Given that the data presented from the current study were collected only from healthy, young females then, these data should only apply to females because of the known effect of gender on the amplitude and latency of the AEPs (Jerger and Hall, 1980; Rosenhall et al, 1985; Chambers et al, 1989; Palaskas et al, 1989). Before it can be implemented clinically, more normative data is still needed to determine the normal ipsilateral/contralateral response pattern and its normal variability per gender and age group. Not much, however, can be inferred from the current study about the site of lesions. Further investigations are needed to study the ipsilateral/contralateral relationship in individuals with confirmed brainstem, thalamus, or auditory cortical lesions. The use of other electrode montages, such as vertical electrode orientation (Sininger and Don, 1989), vertex to nape (Pratt et al, 1995), 3-CLT (Durrant et al, 1994), multichannel recording using temporal electrodes (Yamasaki et al, 2005), or multichannel recording using independent component analysis (ICA) to improve ASSR detection (Van Dun et al, 2007), warrant further investigation.

CONCLUSION

Overall, the results suggest that interchannel ipsilateral and contralateral ASSR amplitude and latency to 79 and 39 Hz are not significantly different in normal, young female adults. The response amplitudes to 39 Hz are larger at 500 Hz than at 2000 and 4000 Hz, whereas the 79 Hz amplitudes tend to be larger at midfrequency (2000 Hz) than at 500 and 4000 Hz. The overall results of simultaneous ipsilateral/contralateral recording seem quite encouraging for the use of ASSR clinically. These results may be used to provide a normal baseline for studies concerning the relationship between interchannel ASSR in normal and abnormal auditory pathway at the brainstem and thalamocortical levels. Future investigations to record ipsilateral/contralateral responses are needed on individuals with confirmed otoneurologic pathologies along the central auditory pathway with or without associated hearing loss. This could provide diagnostic information about the site of the lesions in neurological patients. In addition to the current results, future findings could then be used to develop a diagnostic protocol for otoneurologic evaluation. However, some caution should be exercised in interpreting these results in otoneurologic patients because the ASSR generators are still not well known. Additionally, ipsilateral/contralateral ASSR recording at different MFs may be used clinically to confirm the normal maturation of the central auditory pathways at the brainstem level (79 Hz ASSR) and at the thalamus and cortical levels (39 Hz ASSR).

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