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Effects of Interaural Time and Level Differences on the Binaural Interaction Component of the 80 Hz Auditory Steady-State Response

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Abstract

The auditory steady-state evoked response (ASSR) is a scalp-recorded potential elicited by modulated sounds or repetitive transient sounds presented at a high rate. The binaural interaction component (BIC) of the ASSR equals the difference between the response to binaural stimuli and the sum of the responses to a monaural stimulus presented to the left ear and the right ear. This study examined the effect of the interaural time (ITD) and level (ILD) difference on the BIC of the 80 Hz ASSR. Sixteen human participants with normal hearing were tested. The ITD and ILD were varied from -1.6 to +1.6 msec and from 0 to +12 dB, respectively. The ITD function of the BIC showed a "V" shape, with a 0 value of BIC at ITD 0 msec and a positive BIC at ITD +0.8 to +1.6 msec. For ILD conditions, the BIC displayed negative values, and its amplitude became more negative as the ILD was increased. The results indicate that the ITD and ILD may be processed by different groups of binaural neurons in different pathways. It is suggested that the 80 Hz ASSR provides an objective means for evaluating binaural functions in patients such as those with central auditory processing disorders.

Key Words: Auditory steady-state evoked response, binaural interaction, brainstem, click, human, interaural level difference, interaural time difference

Abbreviations: ABR = auditory brainstem response; AEP = auditory evoked potential; ASSR = auditory steady-state evoked response; BIC = binaural interaction component; CANS = central auditory nervous system; EE = excitatory-excitatory neuron; EEG = electroencephalogram; FFT = fast Fourier transform; IE = inhibitory-excitatory neuron; ILD = interaural level difference; ITD = interaural time difference; LSO = lateral superior olivary nucleus; MSO = medial superior olivary nucleus; SOC = superior olivary complex

Sumario

Las respuestas evocadas auditivas de estado estable (ASSR) son potenciales de registro en el cráneo generados por sonidos modulados o sonidos repetitivos transitorios presentados a una tasa alta. El componente de interacción bi-auricular (BIC) de los ASSR iguala la diferencia entre la respuesta a estímulos bi-auriculares y la suma de respuestas a estímulos mono-auriculares presentados al oído derecho y al oído izquierdo. Este estudio examinó el efecto de la diferencia interauricular de tiempo (ITD) y de nivel (ILD) a partir del BIC de un ASSR de 80 Hz. Se evaluaron dieciséis participantes humanos con

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audición normal. Las ITD y ILD se variaron de -1.6 a +1.6 mseg y de 0 a + 12 dB, respectivamente. La función ITD del BIC mostró una forma en "V", con un valor 0 del BIC con un ITD de 0 mseg y un BIC positivo con un ITD +0.8 a +1.6 mseg. Para condiciones ILD, el BIC mostró valores negativos, y su amplitud se hizo más negativa conforme aumento el ILD. Los resultados indican que el ITD y el ILD pueden ser procesados por grupos diferentes de neuronas bi-auriculares en diferentes vías. Se sugiere que el ASSR de 80 Hz proporciona un medio objetivo para evaluar las funciones bi-auriculares en pacientes como aquellos con trastornos centrales de procesamiento auditivo.

Palabras Clave: Respuestas evocadas auditivas de estado estable, interacción bi-auricular, tallo cerebral, clic, humano, nivel de diferencia interauricular, tiempo de diferencia interauricular

Abreviaturas: ABR = respuesta auditiva del tallo cerebral; AEP = potencial evocado auditivo; ASSR = respuesta evocada auditiva de estado estable; BIC = componente de interacción bi-auricular; CANS = sistema nervioso auditivo central; EE = neurona excitadora-excitadora; EEG = electro-encefalograma; FFT = transformación rápida de Fourier; IE = neurona inhibidora-excitadora; ILD = nivel de diferencia interauricular; ITD = tiempo de diferencia interauricular; LSO = núcleo del lemnisco olivar superior; MSO = núcleo olivar medial superior; SOC = complejo olivar superior

The central auditory nervous system (CANS) compares the difference in the arrival time of a sound (interaural time difference [ITD]) and the difference in the intensity level of a sound at one ear with that of the other ear (interaural intensity/level difference [ILD]). This binaural processing in the CANS is essential in localizing sound in the horizontal plane. The ITD and ILD cues for localization are first extracted at the level of the nuclei of the superior olivary complex (SOC) in the auditory brainstem (Goldberg and Brown, 1969; Yin and Chan, 1990). Binaural information is then sent to higher levels of the CANS for further processing.

The understanding of physiological activity underlying binaural processing is incomplete. Much of the physiological evidence concerning the effect of binaural cues in the CANS comes from single neuron studies, which allows minute examination of neural coding but cannot provide a general picture of binaural processing. Moreover, single neuron recording is an invasive approach that cannot be performed in humans. A noninvasive means of determining how the human brain processes binaural cues is to use scalp-recorded auditory evoked potentials (AEPs), which are the synchronized electrical responses of active neurons responding to acoustic stimulation.

Dobie and Berlin (1979) described a procedure of computing the binaural interaction component (BIC) in the auditory brainstem response, allowing investigation of the effect of binaural cues on the BIC across participants, conditions, and recording sites (Ainslie and Boston, 1980; Dobie and Norton, 1980; Ito et al, 1988; McPherson et al, 1989). According to Dobie and Berlin, the BIC is derived by subtracting the sum of monaural responses elicited by stimuli to the right and left ear from the response evoked by binaural stimulation. This method has been used in BIC studies with the auditory brainstem response (ABR) and middle latency response (MLR) (Debruyne, 1984; McPherson and Starr, 1993; Zaaroor et al, 2003).

Previous examinations of AEP-BIC have generally focused on the ABR. Most studies used clicks as stimuli (Dobie and Berlin, 1979; Dobie and Norton, 1980; Furst et al, 1985; Furst et al, 1990; Levine and Davis, 1991; McPherson and Starr, 1993, 1995; Pratt et al, 1997). The BIC in the ABR, occurring at a time corresponding to wave IV or V and above, is suppressive (Furst et al, 1985; McPherson and Starr, 1993). This means that the binaural response is smaller than the sum of monaural responses. Because the wave IV and V are generated from the SOC, the BIC of ABR suggested that the SOC is the site where binaural interaction first occurs in the CANS (Moore, 2000). The amplitude of ABR-BIC is influenced by the difference in arrival time of a sound between both ears (ITD) or the difference in the intensity level of sound arriving at both ears (ILD). Specifically, the ABR-BIC systematically decreases (less suppression) as the ITD or the ILD moves away from a value of 0 (i.e., the sound source localization moves away from the midline, McPherson and Starr, 1995; Ungan et al, 1997). Moreover, there is a significant correlation between the amplitude of the ABR-BIC and the ability to behaviorally localize a sound image as a function of ITD and ILD. This indicates that the ABR-BIC may reflect the spatial processing of sound in the horizontal plane in the brainstem, and it might act as an objective index used in diagnosis of some diseases such as multiple sclerosis and central auditory processing disorders (Furst et al, 1985; Furst et al, 1990; McPherson and Starr, 1995; Gopal and Pierel, 1999; Riedel and Kollmeier, 2002).

There are some unsolved questions about how the ITD and ILD cues of click stimuli are processed in the ABR-BIC studies. For example, are the ITD and ILD of click stimuli processed in the same or different pathways in the brainstem? Are the same or different binaural neurons responsible for processing ITD and ILD (McPherson and Starr, 1993; Melcher, 1996; Gopal and Pierel, 1999; Ungan and Yagcioglu, 2002)? Investigating BIC with another type of auditory evoked potential generated from the brainstem might provide more information for the above questions. Additionally, analysis of the ABR and the ABR-BIC is typically based on subjective visual evaluation (Ito et al, 1988; McPherson et al, 1989; Cone-Wesson et al, 1997). The calculation of the ABR-BIC involves algebraic summation or subtraction of waveforms that may have different latencies, resulting in an imprecise BIC (Spivak and Seitz, 1988).

Recent interest has focused on the auditory steady-state evoked responses (ASSRs), which are elicited by amplitude/frequency-modulated sounds. ASSR can also be evoked by repetitive transient sounds presented at a high rate (Galambos et al, 1981). Unlike other AEPs evoked by transient sounds in which the response to one stimulus is complete before the next stimulus is presented, the ASSRs evoked by successive stimuli at a higher rate overlap so that a consistent "steady state" sinusoidal waveform with a frequency at the presentation rate is elicited (Galambos et al, 1981; Champlin, 1992; John et al, 1998). In the frequency domain, the ASSRs are analyzed in an objective manner, consisting of comparison of the ASSR amplitude at an excitation frequency to surrounding (nonexcitation) frequencies (Kuwada et al, 1986; Picton et al, 1987; Stapells et al, 1987; Cohen et al, 1991). The ASSR elicited by stimuli at a presentation rate of 80 Hz mainly reflects brainstem activities (Cohen et al, 1991; Levi et al, 1993). The 80 Hz ASSR, which is less likely to be influenced by an individual's arousal state than the ASSR evoked with sounds of lower presentation rates (Cohen et al, 1991; Levi et al, 1993; Rance et al, 1995), has been suggested as a means for hearing threshold detection. Despite much information about 80 Hz ASSR at the threshold level, only a few studies have examined the 80 Hz ASSR at suprathreshold levels (Dimitrijevic et al, 2004; Wong and Stapells, 2004). Data of BIC in the 80 Hz ASSR were rare. One study found that the binaural response of the 80 Hz ASSR evoked by amplitude-modulated tones did not differ from the sum of the monaural responses from the left and right ears (Lins et al, 1995). To the best of our knowledge, there have been no studies of the effect of binaural cues on the BIC of the 80 Hz ASSR.

As the first step of a long-term project, the current study was designed to measure the BIC of 80 Hz ASSR elicited by clicks with binaural ITD and ILD cues. This is helpful in exploring the binaural mechanism in the auditory brainstem, which has not been sufficiently revealed in ABR studies with clicks as stimuli. Data from the current study provided a foundation for developing objective tests of binaural processing for patients with abnormal binaural function, particularly in a difficult-to-test population such as infants.

METHODS

Participants

Sixteen healthy, young female human participants (20–29 years) with normal hearing (pure-tone air-conduction thresholds were ≤15 dB HL at audiometric frequencies of 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz) participated. Participants had no history of neurological disease, excessive noise exposure, or use of ototoxic drugs. The hearing thresholds for the click trains used for ASSR recording were 21–31 dB peSPL (peak equivalent sound pressure level re 1 kHz pure tone). The threshold difference for click trains between ears in each participant did not exceed 5 dB. The tympanograms for all participants were normal (type A), and their acoustic reflex thresholds (ART) were within the range of 80–115 dB SPL for pure tones at 0.5 and 1 kHz. Informed consent was obtained from each participant. The protocol of this project was approved by the Institutional Review Board at the University of South Alabama.

Acoustic Stimuli

Stimuli were 0.1 msec rarefaction clicks presented at a rate of 80.466/sec (for convenience, referred to as 80 Hz). The rate of 80.466/sec was employed so that an integer number of response cycles were contained within each 335.544 msec data epoch. This would avoid energy at 80 Hz spreading to the neighboring frequency bins. Clicks were calibrated with a Quest Sound Level Meter 1800, a 7023 microphone, a 2-cc coupler, and a Tektronix oscilloscope. The experimental clicks were generated with SigGenRP software and presented with BioSigRP software on a Tucker-Davis Technologies (TDT) System 3 electrophysiological workstation. The signals were routed from a 16-bit D/A converter (25 kHz sampling rate) to a programmable attenuator (Tucker Davis Technologies, Model PA5). Stimuli were presented via insert earphones (Etymotics, ER-3A).

Recording

All tests were performed in a sound-treated booth (Industrial Acoustic Company). For all participants, the active electrode was attached to the skin at the midline of forehead. To avoid the influence of electrode placement on the BIC, two different placements for reference and ground electrodes were made, respectively, in two groups of participants. In half of the participants (n = 8), the reference electrode was placed on the left mastoid and the ground electrode on the right mastoid. In the remaining eight participants, the reference electrode was on the right mastoid and the ground electrode on the left mastoid. The currently used electrode placement has been used in previous ASSR studies (Levi et al, 1993). The ear opposite to the reference electrode was referred to as the "reference contralateral ear" (for convenience, referred to as the "contralateral ear"), and the ear on the same side of the reference electrode was referred to as the "reference ipsilateral ear" (for convenience, referred to as the "ipsilateral ear"). Interelectrode impedance was kept below 5 kΩ for electroencephalogram (EEG) recordings. Participants were instructed to sleep or lie quietly to keep muscle and movement artifact to a minimum. EEG recordings were amplified using a low-impedance Medusa digital biological amplifier, with a filter band pass of 10 to 300 Hz (24 dB/octave) and a gain of 80,000. An analog/digital (AD) conversion rate of 6.104 kHz was used. An artifact rejection algorithm was used to exclude extraneously high voltages from the averaged waveform (Boettcher et al, 2001).

Experimental Protocol

The baseline stimulus intensity was 60 dB peSPL. Stimuli were presented under monaural conditions (left ear alone or right ear alone) and binaural conditions (with ITD or ILD cues). For ITD conditions, the ITD was varied from -1.6 to +1.6 msec in 0.4 msec steps. To create positive ITD values, the stimulus to the contralateral ear was fixed and the stimulus to the ipsilateral ear was delayed so that the stimulus to the contralateral ear led. To create negative ITD values, the stimulus to the ipsilateral ear was fixed and the stimulus to the contralateral ear was delayed so that the stimulus to the ipsilateral ear led. The maximum value of the ITD was set at 1.6 msec because this ITD range covered the range needed for a fused sound image with corresponding location in the horizontal plane perceived by human subjects

(Furst et al, 1990). For ILD conditions, stimuli were presented simultaneously. The sound intensity to the ipsilateral ear was fixed at 60 dB peSPL, and the sound intensity to the contralateral ear was varied to create different ILDs. Because sound intensities up to 12 dB lower than 60 dB peSPL did not constantly elicit significant 80 Hz ASSR in different participants, negative ILDs were not investigated. Only positive ILDs, in which the contralateral stimulation was louder than the ipsilateral stimulation, were used in the current study. There were a total of 11 recordings for ITD protocol (2 monaural conditions and 9 binaural conditions) and 11 recordings for ILD protocol (6 monaural conditions and 5 binaural conditions) (see Table 1). There were two different sessions with a duration of 1.5 h for each, one for ITDs and the other for ILDs. The presentation sequence of the conditions in each session was randomized.

For each condition, 48 averages of 16 epochs were recorded. The data collecting time for one recording condition was approximately 4.3 minutes (48 x 16 x 335.544 msec). Each epoch consisted of 2,048 data points. In each session, a total number of 176 ASSR epochs (16 epochs per condition x 11 conditions) for each participant were stored in the SigGenRP program for off-line analysis. To measure the test-retest reliability, approximately 20–40% of conditions (2 to 4 out of 11) were randomly recorded twice at different times in the same session.

Analysis

For each recording condition, 16 epochs of responses were averaged so that a single sweep was obtained. This single sweep was submitted to fast Fourier transform (FFT), which transformed the time domain into the frequency domain, with a frequency resolution of 2.98 Hz (1/335.544 msec). The real (X) and imaginary data (Y) were used to calculate the amplitude of the 80 Hz ASSR (square root of $[X^2 + Y^2]$) (John et al, 1998). The amplitude of ASSR in nV for each recording condition was calculated. The presence of an 80 Hz ASSR required that the response at 80 Hz was greater than the average noise level plus two standard deviations in the neighboring two frequency bins (5.96 Hz) on either side of 80 Hz (Champlin, 1992). Only data from participants whose 80 Hz ASSR under monaural conditions were significant were used, since the responses under these two conditions were the basis for calculating the BIC under ITD conditions. Data from 1 out of 16 participants were not used because of nonsignificant response under monaural conditions.

After the amplitude of the 80 Hz ASSR was derived from the spectrum for each recording condition, the BIC was determined for each ITD and ILD condition. The BIC was the difference between the binaural response and the algebraic sum of the monaural responses, that is, BIC = B - (C + I) (B: response for binaural presentation; C: response for contralateral presentation alone; I: response for ipsilateral presentation

Table 1. Summary of the Testing Protocols

Interaural Difference	Monaural Presentation (contralateral ear)	Monaural Presentation (ipsilateral ear)	Binaural Presentation
ITD (msec)	60 dB peSPL	60 dB peSPL	ITD = 0 ITD = -0.4 ITD = -0.8 ITD = -1.2 ITD = -1.6 ITD = 0.4 ITD = 0.8 ITD = 1.2 ITD = 1.6
ILD (dB)	60 dB peSPL 63 dB peSPL 66 dB peSPL 69 dB peSPL 72 dB peSPL	60 dB peSPL	ILD = 0 ILD = 3 ILD = 6 ILD = 9 ILD = 12

Note: For ITD conditions, stimuli to both ears were fixed at 60 dB peSPL. Positive ITDs indicated that the stimuli to the contralateral ear led. Negative ITDs indicated that the stimuli to the ipsilateral ear led. For ILD conditions, sounds were presented simultaneously for binaural presentation; the stimulus intensity to the ipsilateral ear was fixed at 60 dB peSPL, and the stimulus intensity to the contralateral ear was increased to create positive ILDs.

alone). The grand average of the BIC across all participants for each ITD or ILD condition was obtained. For each BIC, a negative value indicated that the binaural response was smaller than the sum of the monaural responses, defined as suppression. A positive value indicated the opposite, defined as facilitation. The within-subject factor was the ITD or the ILD. The electrode placement was the between-subject factor. The dependent variable was the BIC amplitude.

General linear model repeated analysis of variance (ANOVA) was carried out with statistical SPSS (Version 12.0) software to investigate the effects of ITD or ILD on the BIC amplitude. Polynomial tests were performed for follow-up analysis. Pearson correlation analysis was conducted to calculate the test-retest reliability.

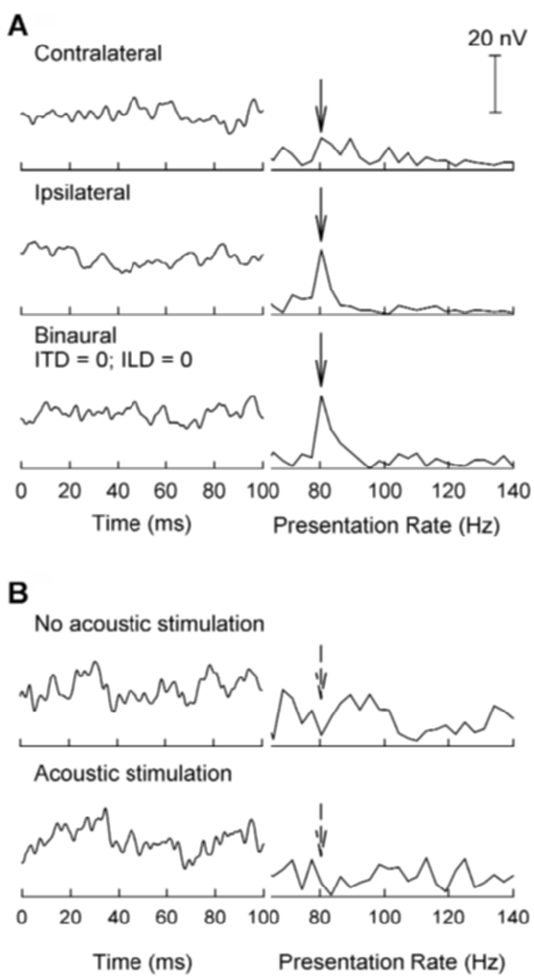

Figure 1. *A*: The 80 Hz ASSR recorded from one participant with clicks presented at a rate of 80/sec. Left panel: waveforms. Right panel: spectra. Each recording is the average of 768 responses (16 epoch x 48 averaging). Solid arrow: significant response. *B*: Examples of EEG without presenting acoustic stimulation and with acoustic stimulation, but the 80 Hz ASSR is not present. Short-dashed arrow: nonsignificant response.

RESULTS

The steady-state response to clicks at a rate of 80/sec has a periodic waveform, which might not be smooth due to a limited number of averaging sweeps. The presence of a response in the spectrum under most conditions was evidenced by the component at 80 Hz that is greater than neighboring components with the aforementioned criterion (Figure 1a). Figure 1b illustrates examples of recordings without acoustic stimulation and with acoustic stimulation, but the spectrum shows the lack of 80 Hz ASSR. These examples suggest that the significant 80 Hz ASSR is not nonphysiological artifact. The amplitude of the 80 Hz ASSR ranged from tens to hundreds of nV across participants, depending upon the presentation mode (monaural or binaural) and the value of ITD or ILD. The mean amplitudes of the monaural response from the contralateral and ipsilateral ears were 21.93 (SD = 11.71) and 23.10 (SD = 8.60) nV, respectively (not shown). Paired t tests showed no significant difference between monaural responses. The correlation coefficient was 0.77, and the slope was 0.81 for the repeatedly recorded data. The correlation coefficient was statistically significant ($p < 0.01$), indicating a satisfactory reliability when the response was repeated at different times.

Effects of ITDs on the BIC of 80 Hz ASSR

Figure 2 shows the BIC as a function of ITDs in four representative participants. The amplitude of the BIC ranged from -45 nV (suppression) to +246 nV (facilitation). The majority of ITD functions displayed a "V" shape with a descending trend at the ends of two branches of the "V" shape. The dips of individual ITD functions across participants varied along the ITD scale. Generally, a relatively prominent dip was located within the ITD range of -0.4 to +0.4 msec while the two peaks were within the ranges of -0.8 to -01.2 msec and +0.8 to +1.2 msec.

Table 2 and Figure 3 show the mean BIC as a function of ITD. This ITD function showed a "V" shape with a dip at an ITD of 0 msec (M = +1.43, SD = 22.19) as well as two peaks at ITDs of -0.8 msec (M = +17.76, SD = 65.72) and +1.2 msec (M = +17.25, SD = 33.07). Due to the large intersubject

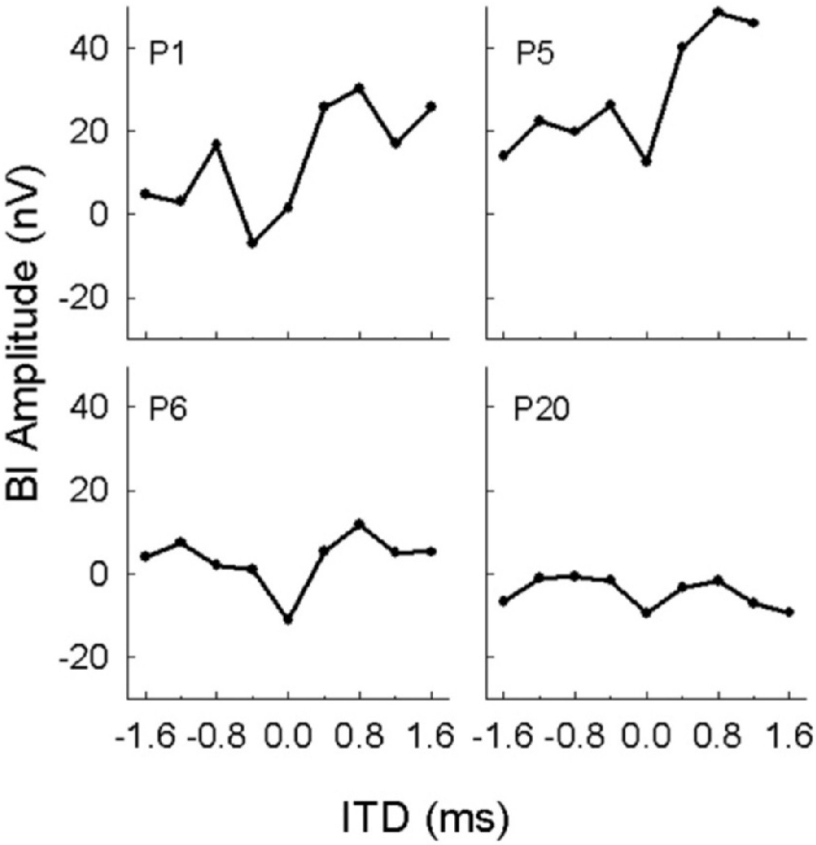

Figure 2. The BIC amplitude of the 80 Hz ASSR (nV) as a function of ITDs (msec) for four representative participants.

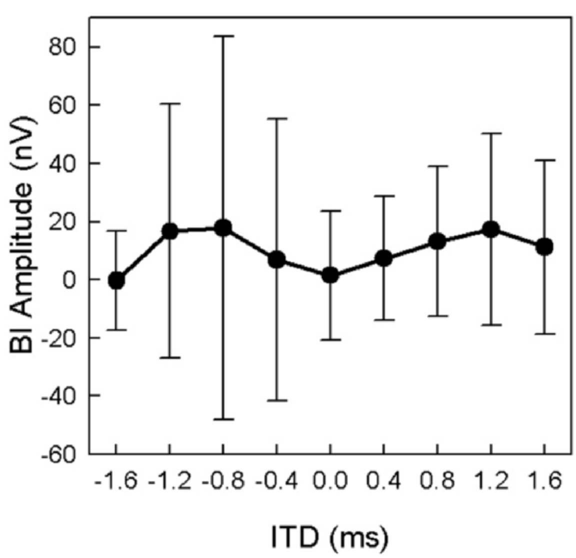

Figure 3. The mean BIC amplitude of the 80 Hz ASSR (nV) as a function of ITDs (msec) (n = 15). Error bar represents one standard deviation.

variability of the ITD function of BIC, especially for negative ITDs, one-way repeated ANOVA did not show any significant effect of ITD condition ($F_{(8, 2)} = 4.20$, $p = 0.21$), electrode placement ($F_{(1, 9)} = 3.01$, $p = 0.12$), and interaction between the two factors ($F_{(8, 2)} = 0.57$, $p = 0.77$). The data were collapsed across electrode placement, and only the conditions of ITD 0 to +1.6 msec were included for a one-way repeated ANOVA. The effect of ITD was significant ($F_{(4, 10)} = 6.01$, $p = 0.01$). A polynomial test showed a significant linear relationship ($F_{(1, 13)} = 6.04$, $p = 0.03$), indicating that BIC increased (more positive) linearly as the ITD was greater. Post hoc analyses showed that the BIC amplitude at ITD 0 msec was significantly lower than that at ITD +1.2 msec ($t = -3.36$, $p = 0.01$, $df = 14$) and +1.6 msec ($t = -2.22$, $p < 0.05$, $df = 13$), respectively.

Table 2. Summary of Participants' BIC under ITD Conditions

ITD (msec)	-1.6	-1.2	-0.8	-0.4	0	0.4	0.8	1.2	1.6
M (nV)	-0.38	16.66	17.76	6.82	1.43	7.34	13.07	17.25	11.25
SD (nV)	17.01	43.65	65.73	48.40	22.19	21.25	25.75	33.07	29.87

Note: The means (M) and standard deviations (SD) of BIC under ITD conditions (n = 15). The BIC was the difference between the binaural response and the algebraic sum of the monaural responses, that is, BIC = B - (C + I) (B: response for binaural presentation; C: response for contralateral presentation alone; I: response for ipsilateral presentation alone).

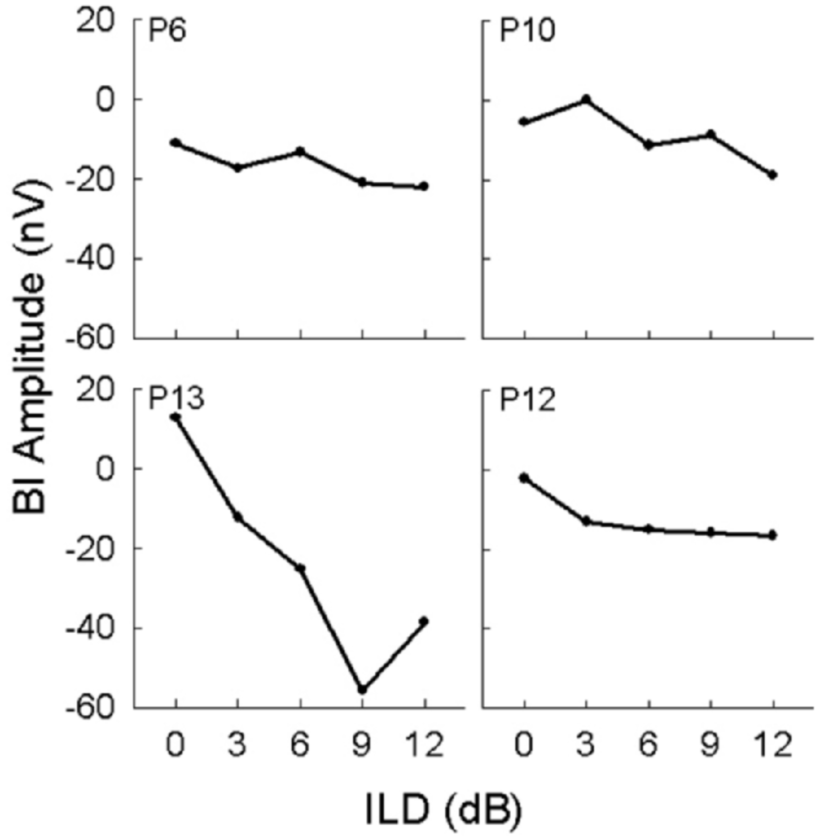

Figure 4. The BIC amplitude of the 80 Hz ASSR (nV) as a function of ILDs (msec) for four representative participants.

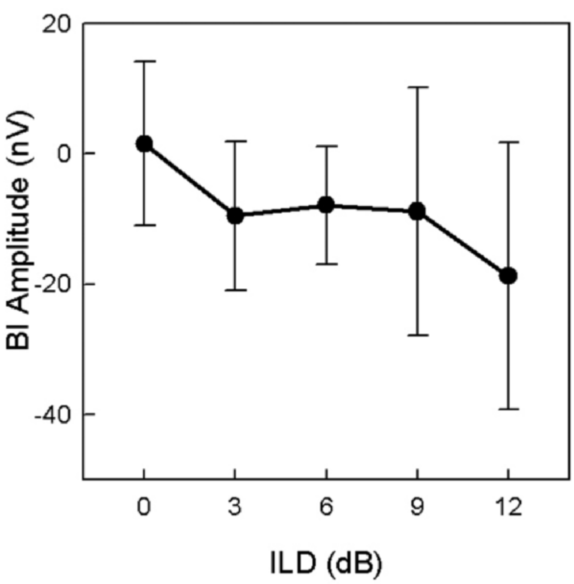

Figure 5. The mean BIC amplitude of the 80 Hz ASSR (nV) as a function of ILDs (dB) (n = 15). Error bar represents one standard deviation.

Effects of ILDs on the BIC of 80 Hz ASSR

The amplitude of the BIC under ILD conditions was within the range of -73 nV (suppression) to +28 nV (facilitation). Figure 4 shows the BIC as a function of the ILD in four representative participants. There was a general trend that the BIC under ILD conditions was suppressive, which was more suppressive as the ILD increased.

Table 3 and Figure 5 show the mean BIC under different ILD conditions. The suppression BIC is relatively greater (more negative) for ILD +3 dB (-9.53 nV, SD = 11.42) than that for ILD 0 dB and keeps relatively steady till ILD is +9 dB (-8.85 nV, SD = 19.99). At ILD of +12 dB, the suppression BIC reaches the maximum value (-18.74 nV, SD = 20.51), which was approximately 31.95% of the sum of monaural responses.

Table 3. Summary of Participants' BIC under ILD Conditions

ILD (dB)	0	3	6	9	12
M (nV)	1.152	-9.53	-7.89	-8.85	-18.74
SD (nV)	12.56	11.42	9.05	18.99	20.51

Note: The means (M) and standard deviations (SD) of BIC under ILD conditions (n = 15). See the caption of Table 2 for the calculation of BIC

A two-way mixed model ANOVA (Electrode placement x ILD condition) showed that there was a significant main effect of ILD condition ($F_{(4, 6)} = 6.17$, $p = 0.03$), but no significant effect of electrode placement ($F_{(1, 9)} = 1.96$, $p = 0.20$), and the interaction between the two factors ($F_{(4, 6)} = 3.89$, $p = 0.07$). The data were collapsed across electrode placement, and only the ILD condition was investigated with a one-way repeated ANOVA. There was a significant effect of ILD condition ($F_{(4, 7)} = 7.22$, $p = 0.01$). Post-hoc analyses suggested that the BIC amplitude with ILD 0 dB (+1.52, SD = 12.56) was significantly different from that with ILD +12 dB (-18.74 nV, SD = 20.51, $p = 0.02$). A polynomial test showed a significant linear effect of ILDs on the BIC amplitude ($F_{(4, 10)} = 13.12$, $p < 0.01$).

DISCUSSION

The magnitude of the 80 Hz ASSR was approximately tens to hundreds of nV, consistent with that reported in previous studies (Rees et al, 1986; John et al, 1998; John et al, 2003). The amplitude of the 80 Hz ASSR displayed a large intersubject variability. Such large intersubject variability has been observed in other studies of ASSRs at suprathreshold levels (Picton et al, 1987; Boettcher et al, 2001, Boettcher et al, 2002). It is not clear what factors result in the large intersubject variability in the amplitude of the 80 Hz ASSR. The difference in electrode placement and hearing threshold across subjects cannot be excluded.

There is the lack of data for the BIC of the 80 Hz ASSR with clicks as stimuli from other studies, although some studies reported the BIC data with ASSR elicited by other stimuli or lower stimulus rates. For example, the 40 Hz ASSR displays a suppressive BIC, which is 50–60% of the summed monaural responses (Suzuki et al, 1991; Boettcher et al, 2003; Zaaroor et al, 2003). The 80 Hz ASSR with amplitude-modulated tones did not show significant BIC when the stimuli with the same level were presented simultaneously (Lins et al, 1995). The current study showed that the BIC of the 80 Hz ASSR responding to clicks varied when the ITD or ILD was changed, although the BIC was nearly zero when ITD and ILD was zero (i.e., stimuli with the same intensity level were presented to the two ears simultaneously). The fact that the BIC of 80 Hz ASSR is dependent on the ITD and ILD in our study indicates that the 80 Hz ASSR is related to the processing of binaural cues.

Effects of Binaural Cues on the BIC of 80 Hz ASSR

The BIC-ITD function was typically a “V” shape in individual participants, with the dips located within the ITD range of -0.4 to +0.4 msec while the two peaks were located within the ITD ranges of -0.8 to -1.2 msec and +0.8 to +1.2 msec. However, the mean difference of the BIC amplitude across ITDs did not reach statistical significance. One reason may be that the current study had a small sample size. Another reason was the large intersubject variability of the BIC. However, after excluding data with negative ITDs, there was a significant effect of ITDs on the BIC. Specifically, the BIC at ITD 0 msec was significantly lower (less facilitation) than that at ITD +1.2 msec and + 1.6 msec. Moreover, the facilitation BIC followed a linear relationship as the ITD was increased (i.e., greater facilitation BIC for larger ITD values in the range of 0 to +1.6 msec).

Unlike the ITD functions, ILD functions of the BIC in the 80 Hz ASSR show exclusively suppressive effects. The BIC linearly increased (more suppression) as the ILD increased, with a maximal BIC when the ILD was +12 dB. Binaural response at positive ILDs is smaller than the sum of monaural responses, indicating that inhibition occurred in binaural hearing when the stimulus to the contralateral ear was louder than the stimulus to the ipsilateral ear (McPherson and Starr, 1993; Ungan and Yagcioglu, 2002).

It has been accepted that the SOC acts as the first location in the CANS for binaural processing. The SOC contains three main nuclei: the medial superior olivary nucleus (MSO), the lateral superior olivary nucleus (LSO), and the medial nucleus of the trapezoid body (MNTB). These three nuclei are associated with sound localization capability across species (Brugge and Geisler, 1978; Smith et al, 1991; Tollin, 2003).

Binaural neurons in the SOC are responsible for binaural interaction with their computed responses to inputs from both ipsilateral and contralateral sides. These neurons display a response to binaural stimulation that is different from the sum of responses to monaural stimulation of both ears providing excitatory input. For example, inhibitory-excitatory

(IE) neurons are those predominantly excited by stimulation from the ipsilateral ear and inhibited by stimulation from the contralateral ear. Excitatory-excitatory (EE) neurons are those excited by the stimulation from both ears (Goldberg and Brown, 1969; Covey et al, 1991). There is a differential distribution of binaural neurons in different divisions of the SOC. The majority of binaural neurons in the MSO are EE type and ITD sensitive whereas the majority of neurons in the LSO are IE type and ILD sensitive. Although the current study cannot indicate which structure is associated with the processing of ITD and ILD cues, the different effects of ITD and ILD on the BIC of 80 Hz ASSR may suggest that the ITD and ILD of clicks are processed by different groups of binaural neurons in different pathways in the auditory brainstem.

Although Riedel and Kollmeier (2002) suggested that ITD and ILD of clicks were not processed independently because of the similar dependence of the ABR-BIC on both cues, other studies with ABR-BIC have suggested the opposite. For example, Pratt et al (1997) reported that binaural activity of the click-evoked ABR across the same psychophysical lateralizations differed between ITDs and ILDs, indicating different pathways for the processing of ILDs and ITDs of clicks in the auditory brainstem. The different-pathway theory appears to be supported by some psychophysical studies, in which patients with caudal pontine lesions due to brainstem infarcts and multiple sclerosis are more sensitive to ITDs than ILDs (Furst et al, 2000). Our current results support the different-pathway hypothesis, because the ITD and ILD functions of ASSR-BIC showed different shapes.

Comparison of Results with the Auditory Brainstem Response

Like the ABR, the 80 Hz ASSR is generated primarily in the brainstem (Starr and Hamilton, 1976; Cohen et al, 1991; Levi et al, 1993; Lins and Picton, 1995; Aoyagi et al, 1999; Herdman et al, 2002; Kuwada et al, 2002). However, this study shows distinct differences in the processing of the binaural cues between the ABR-BIC and the ASSR-BIC. In general, the ABR-BIC is considered to show a suppressive effect, which decreases (less suppression) with the increase of the ITD and ILD (Dobie and Berlin, 1979; Wrege and Starr, 1981; Furst et al, 1985; McPherson and Starr, 1995; Brantberg et al, 1999). In contrast, the 80 Hz ASSR displayed nearly zero BIC at ITD and ILD of zero but facilitation BIC for positive ITDs and suppression BIC for positive ILDs. The change of the BIC of 80 Hz ASSR with ITDs and ILDs in this study seemed to be different from that of ABR. However, by considering the factor of electrode placement in different studies, the current data do not contradict data from the ABR results. In previous ABR studies, the active and reference electrodes were put on the midline of the head skin, that is, active electrode at vertex and reference electrode at the nape of the neck (Furst et al, 1985; Ito et al, 1988; Furst et al, 1990; McPherson and Starr, 1995). In the current study, the active electrode and reference electrode were put on the midline of the forehead and one side of mastoid, respectively. It is likely that, in ABR-BIC studies, binaural neurons from both sides contribute to the ABR-BIC because of the midline-located electrodes. However, in this study, the active binaural neurons from the ipsilateral side may contribute more to the BIC of the ASSR than those from the contralateral side due to the location of the reference electrode.

Using the above hypotheses, we can explain results of the ITD and ILD function of the BIC in this study. The binaural system contains two sets of symmetrical binaural neurons whose behavior can be used to predict psychophysical phenomena in binaural hearing (Hall, 1965). When stimuli are presented simultaneously at the same level, that is, when the ITD and ILD are zero, the binaural neurons from both sides receive sound input. Due to the electrode placement used in this study, the excitatory (EE cells) or inhibitory (IE cells) input from the contralateral side travels a longer tract to reach the ipsilateral binaural neurons. Thus, the ipsilateral excitation is not initially enhanced or reduced. When the ITD is positive, the response to contralateral stimulation presented first travels in advance to reach the ipsilateral binaural neurons. When the ILD is positive, the response to contralateral stimulation at higher intensities travels with a faster speed to reach the ipsilateral binaural neurons. This would overcome the longer path of neural transmission from the contralateral side. Consequently, stimuli from both sides are likely to reach the ipsilateral binaural neurons simultaneously, generating facilitation or suppression of ipsilateral excitation (Joris et al, 1998; Irvine et al, 2001).

Implication and Future Studies

Results of this study demonstrate a systematic change in the BIC of the 80 Hz ASSR with changes in ITDs or ILDs. These results would be improved by increasing the sample size and controlling the intersubject variability. Our results suggest that the information contained in the BIC component of 80 Hz ASSR at suprathreshold levels can reflect the sensitivity of the auditory brainstem to ITDs or ILDs. Because the BIC of the 80 Hz ASSR is analyzed objectively without the involvement of the subtraction or summation of response waveforms, it may have a useful application in the objective assessment of the binaural function in patients with central auditory deficits, especially in those difficult-to-test patients. There are some concerns regarding the possibility of using the BIC of 80 Hz ASSR in a clinical setting. First, the signal-noise ratio of 80 Hz ASSR is small. Future studies may use higher stimulus levels and a greater number of recording sweeps to further increase the signal-noise-ratio (Rees et al, 1986). Second, future study will be aimed at finding the correlation of the BIC change of ASSR caused by binaural cues to the psychophysical results in subjects with normal and abnormal binaural hearing.

Summary

The present study suggests that the ASSR analysis based on objective measurement in the spectral domain provides reliable measures of the BIC. This study showed that the BIC of the 80 Hz ASSR displayed a "V" shape as a function of ITDs. The facilitation BIC displayed a linear correlation as the ITD was increased. The BIC of the 80 Hz ASSR showed suppressive value under ILD conditions, with more suppressive BIC for higher ILDs. The results indicate that ITDs and ILDs may be processed by different groups of binaural neurons in different pathways in the auditory brainstem in humans. Because the BIC of the 80 Hz ASSR can be evaluated with fully objective methods and the BIC data showed systematic change as the ITD or ILD was changed, the BIC of the 80 Hz ASSR might be suggested as a good measure of ITD or ILD processing in clinical situations.

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