Frequency-Following Response: Effects of Interaural Time and Intensity Differences

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Abstract
This research investigated whether brainstem neural mechanisms that mediate lateralization of sounds can be extracted from the frequency-following response (FFR). Monaural and binaural FFRs were obtained from normal-hearing subjects to low-frequency (500 Hz) linearly gated tone bursts (4-4-4 msec) at 40, 50, and 60 dB SL and four interaural time differences (ITDs) (0, 333, 500, and 667 μsec). FFRs were also recorded to ITDs and intensity presented in concert and in opposition (lateralization stimuli). The results show that overall intensity and interaural time differentially affect the FFR. The FFRs evoked by ITDs and intensity (in concert and in opposition) are strikingly different. The normalized amplitudes of the binaural interaction component (BIC) are minimally altered by ITDs and intensity. The study presents strong evidence that ITDs of 0, 333, 500, and 667 μsec and lateralization stimuli, easily discriminated perceptually, evoke clearly distinguishable FFR waveforms. These ITDs provide the cues that mammals use to localize sound in a freefield. The BIC is essentially unaffected by overall intensity, ITDs, and lateralization stimuli. Based on the findings of this study, the FFR has the potential to become a tool for identification of normal and abnormal binaural processing at lower brainstem levels.

Key Words: Auditory evoked potentials, binaural hearing, binaural interaction component, frequency-following response, lateralization

Abbreviations: ABR = auditory brainstem response, BIC = binaural interaction component, EEC = electroencephalographic, FFR = frequency-following response, IID = interaural intensity difference, ILD = interaural level difference, ITD = interaural time difference

The stimulus parameters for localization of sound sources in the horizontal plane of a freefield are interaural intensity and time differences (IIDs, ITDs) at each ear. ITDs and IIDs mediate low- and high-frequency localization, respectively (Stevens and Newman, 1936). In psychoacoustic studies of lateralization (earphones), the sound image can be centered or made to move intracranially by altering the time or intensity difference between the ears. Studies have also shown that such sounds may be localized as if emanating in a freefield (Jeffress and Taylor, 1961). When both sound cues favor the same ear (in concert, time lead, and more intense), the image is fused and easily lateralized (Moushegian and Jeffress, 1959); when they are in opposition (one ear leading, the other more intense), the trained listener may hear two sounds, one dependent on intensity and the other on time (Whitworth and Jeffress, 1961).

The neuroanatomic and neurophysiologic studies of binaural hearing have identified several auditory aggregates within the superior olivary complex as brainstem sites for binaural processing (Galambos et al, 1959; Moushegian et al, 1964, 1975; Goldberg and Brown, 1969), the lateral lemniscus (Brugge et al, 1970); and inferior colliculus (Stillman, 1971a, b; Erulkar, 1975; Kuwada and Yin, 1983; Yin and Kuwada, 1983 a, b). Neurons within these nuclei are differentially sensitive to ITDs and IIDs.

In humans, two types of volume-conducted potentials have been recorded from brainstem
regions. The most widely studied is the auditory brainstem response (ABR), a series of waves (I–VII) evoked by brief sounds such as clicks or tone bursts that originate from neurons located caudal to the inferior colliculi (Jewett et al., 1970). The frequency-following response (FFR), another evoked potential, mimics the tonal stimulus (Marsh and Werden, 1968; Moushegian et al., 1973; Ballachanda et al., 1994) and reflects phase-locked activity from the same caudal brainstem levels (Gardi et al., 1979; Bledsoe and Moushegian, 1980; Bledsoe et al., 1982; Hoormann et al., 1992).

The binaural interaction component (BIC) is a derived response, obtained by subtracting the sum of the right and left monaurals from the binaural waveforms of the ABR. It appears between 5 and 8 msec after stimulus onset (Dobie and Berlin, 1979; Dobie and Norton, 1980). The BIC is believed to reflect binaural activity of the superior olivary complex of the auditory neuraxis, a conclusion based on human and animal studies (Jewett et al., 1970; Dobie and Berlin, 1979; Caird et al., 1985; Jones and Van der Poel, 1990).

Since the initial report on binaural interaction in ABR, the effects of stimulus frequency, intensity, rate, interaural intensity, and ITDs on the latency and amplitude of the derived BICs have been described (Blegvald, 1975; Hosford et al., 1979; Ainslie and Starr, 1980; Dobie and Norton, 1980; Prasher et al., 1981; Wrege and Starr, 1981; Arslan et al., 1982; Gerull and Mrowinski, 1984; Dobie and Wilson, 1985; Fowler and Leonards, 1985; Wilson et al., 1985; Fullerton et al., 1987; Furst et al., 1985, 1990; DeVries and Decker, 1988; Fowler and Broadard, 1988; Ito et al., 1988; Spivak and Seitz, 1988; Parthasarathy and Moushegian, 1993). Furthermore, the relationship between perceptual features of binaural signals and the BIC has also been addressed. Furst et al. (1985) reported, for instance, that the BIC appeared when the binaural clicks were perceptually fused and localized intracranially; the BIC was absent, however, when ITDs exceeded 1.2 msec. Jones and Van der Poel (1990) stated that the latency of the BIC varied from 0 to 1.0 msec of ITDs; similar effects were not observed for amplitude measures.

Clinical findings suggest that the BIC is absent in patients with multiple sclerosis who have difficulty in discriminating ITDs (Furst et al., 1990). McPherson and Starr (1995) compared perception of binaural clicks to alterations in the BIC with ITDs and IIDs. They noted that BIC latencies shifted and amplitudes decreased to ITDs of 1.6 msec and IIDs greater than 30 dB; in both instances, the perception of the acoustic image was lateralized.

Some monaural characteristics of lower brainstem function and dysfunction have been uncovered in ABR research using clicks as stimuli. However, click-evoked brainstem responses have limitations in understanding how binaural sounds are processed at the brainstem level. The reasons are (1) the differential effect of interaural time and intensity parameters cannot be identified, because clicks are broadband signals; (2) click-evoked ABRs are a consequence presumably of onset type of neurons at the brainstem level; (3) each of the ABR waves (I–V) are time locked to the onset of click stimuli. A delay in the click onset at one ear shifts the latencies of these peaks, resulting in a displaced BIC; (4) some investigators maintain that the BIC is sensitive to ITDs (Furst et al., 1985; 1990), whereas others contend that they are not (Gerull and Mrowinski, 1984); and (5) Wrege and Starr (1981) believe that BIC is evoked by low-frequency energy within the click stimuli, whereas Gardi and Berlin (1981) consider it to be primarily of high-frequency origin.

The FFR was chosen to study binaural processing because low-frequency sounds produce periodicities related to the stimulus in the evoked responses; such periodicities cannot be addressed by click stimuli. It is known, too, that neurons located in the brainstem phase lock both to monaural and binaural stimuli (Moushegian et al., 1975). The FFR, therefore, may be used as a measure of binaural brainstem integrity, particularly if it can be ascertained that interaural time cues differentially affect it. The purpose of this study was to determine whether ITDs affect the FFRs and their derived BICs in a predictable manner.

**METHOD**

Eight females, 20 to 30 years of age, participated in this study. Their audiometric thresholds were no greater than 20 dB HL (ANSI, 1969) at octave and interoctave frequencies from 0.25 to 8.0 kHz. Each subject had normal middle-ear functions based on acoustic immittance measured to 226-Hz probe tone (peak pressures at or to −50 daPa and ear canal volumes >0.65 and <2.5 cm³) and normal acoustic reflex thresholds (70–100 dB HL) at 0.5 and 1.0 kHz. In addition, the threshold to a 0.5-kHz linearly gated tone burst with a 4.0-msec rise–fall time and plateau of
Table 1 Description of In-Concert and In-Opposition Stimuli

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Identifiers</th>
<th>Right Ear</th>
<th>Left Ear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensity (dB SL)</td>
<td>Phase/Time</td>
<td>Intensity (dB SL)</td>
</tr>
<tr>
<td>Neutral</td>
<td>R + 10 - 0°</td>
<td>65</td>
<td>0°/0 μsec</td>
</tr>
<tr>
<td>In concert</td>
<td>R + 10 - 60°</td>
<td>65</td>
<td>60°/333 μsec</td>
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<tr>
<td>In concert</td>
<td>R + 10 - 90°</td>
<td>65</td>
<td>90°/500 μsec</td>
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<tr>
<td>In concert</td>
<td>R + 10 - 120°</td>
<td>65</td>
<td>120°/667 μsec</td>
</tr>
<tr>
<td>Neutral</td>
<td>R - 10 - 0°</td>
<td>55</td>
<td>0°/0 μsec</td>
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<tr>
<td>In opposition</td>
<td>R - 10 - 60°</td>
<td>55</td>
<td>60°/333 μsec</td>
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<td>R - 10 - 120°</td>
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<td>120°/667 μsec</td>
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4.0 msec was determined for each subject by the method of limits. It was also ascertained that thresholds for the stimuli were equal for both ears and threshold differences between subjects for the tone bursts were never greater than 5 dB.

The procedures for stimulus generation, data acquisition, response averaging, data analysis, and waveform plotting were implemented by a PDP 11/73 computer using software developed specifically for evoked potential research. The output of the attenuators was coupled to mu-metal shielded earphones (TDH-49) designed to minimize electrical leaks. The stimuli were low-frequency linearly gated 0.5-kHz tone bursts (4.0-msec rise-fall, 4.0-msec plateau) of 40, 50, and 60 dB SL presented at rates of 8/sec. ITDs were produced by a phase-shifter (Grason-Stadler, E3520B). In the first set of stimulus conditions, the left ear served as the reference ear where the stimulus phase was fixed at 0°, whereas the phase in the right ear was at 0°, 60°, 90°, and 120°. In the binaural condition, these phase differences correspond to time leads of 0 μsec (0°), 333 μsec (60°), 500 μsec (90°), and 667 μsec (120°), respectively, in the right ear. The spectra of the reference (left ear) and variable (right ear) channels were identical for all stimulus conditions.

The second set of stimulus conditions included the 0.5-kHz linearly gated tone presented in concert, where one ear had the time lead and greater intensity compared to the opposite ear; when the stimuli were in opposition, the ear leading in time had a lesser intensity than the opposite ear (Table 1).

Recordings were obtained from subjects seated in an electrically shielded sound booth. Gold-plated cup electrodes were attached at the vertex (Cz noninverting), on the neck (Cz inverting), and the forehead (ground); the impedance between any two electrodes was less than 5.0 kOhms. The electroencephalographic (EEG) potentials were amplified 100 times (Grass, 511P), bandpass filtered between 0.3 to 3.0 kHz, and averaged at a sampling rate of 20 kHz. The EEG waves were viewed on a dual-trace oscilloscope to monitor subject state; EEG amplitudes greater than 2.5 volts were automatically eliminated from the averages by an artifact reject program. Subjects participated in four sessions of 1½ hours each; test conditions were completely randomized across subjects. Waveforms were obtained from all subjects twice to ensure that the traces were replicable. All data were extracted from the averages of the two traces, each of which was obtained to 1000 stimulus presentations. Data were stored on hard disk for offline analysis.

As in all electrical measures from body surfaces, amplitude variabilities also appear in evoked potential research. Therefore, comparisons of data within and between subjects cannot be meaningfully interpreted. To obviate this problem and obtain a measure that may be generalized for all subjects and experimental conditions, each waveform (monaural, summed monaural, binaural, and BIC) was integrated between 5 and 20 msec, disregarding the positive and negative values. The single number for every waveform was then divided by each subject's monaural right 60-dB integrated value. The ratios across all conditions provided the normalized indices that were expressed as percentages.

An analysis of variance for repeated measures of the normalized indices identified the main effects of (1) overall intensity, (2) ITD, (3) ITDs and intensity presented in concert and in opposition, and (4) the interactions between them. A within-subject design was used to minimize individual differences.
RESULTS

Frequency-Following Responses to Overall Intensity and Interaural Time Differences

Robust waveforms were obtained from subjects for all stimuli. Even the smallest response at 40 dB SL exhibited easily identifiable periodicities. Figure 1 illustrates representative waveforms from one subject. The waveforms to monaural right and left stimuli, although similar, were not identical; such asymmetries have been reported previously (Ballachanda et al, 1994). The binaural response from all subjects was larger, but not by a factor of two, than either of the monaural waveforms. The onset latencies for all recordings occurred between 6 and 7 msec and the response was complete within 20 msec after stimulus onset, which is consistent with previous findings (Moushegian et al, 1973). Each of the successive peaks in the evoked waveform occurred at 2.0-msec intervals, corresponding to the period of the 500-Hz tone. The traces to right and left ear stimulation were added to give the summed monaural. The BIC, consisting of positive and negative peaks (A–G) occurring between 8.4 and 14 msec, was obtained by subtracting the binaural from the summed monaural.

The effect of stimulus level on evoked responses from one subject is illustrated in Figure 2. Near putative monaural FFR thresholds (e.g., 40 dB SL), the amplitudes of the FFR, although small, are still periodic. With intensity increases, the evoked monaural waveforms, clearly phase lock, become larger, and occur at somewhat shortened latencies. All binaural traces were distinctly periodic with greater amplitudes than either monaural waveforms.
The means of the normalized indices from all subjects for each stimulus condition, as well as the BIC as a function of intensity, are shown in Figure 3. Binaural responses are clearly greater than either monaural but less than the sum of the monaural response across intensities. Intensity effects on the BIC are minimal.

Although phase locking was preserved in the FFR for all phase/time settings, the FFR amplitudes from subjects tended to be greater at 0° for all intensities than at any other interaural phase shift (Fig. 4). Changes in the phase of the stimulus altered noticeably the morphology of the FFR without loss of periodicities.

Figure 5 displays the means of the normalized indices to interaural time at three intensities (40, 50, and 60 dB SL) for all subjects. The effect of increases in interaural time (phase) is
clear regardless of intensity. Magnitudes of all of the indices decrease with increasing time differences. The interaural times, ranging between 0 and 667 μsec, correspond to time differences at the ears of sounds originating from immediately in front (or back) to 90° in freefield.

Figure 6 compares the means of normalized indices of summed monaural, binaural, and BICs for all subjects at three intensities. The summed monaural functions exhibit the greatest interaural effects between 0° (0 μsec) and 90° (500 μsec). The binaural functions follow the same pattern except the normalized indices are smaller than the summed monaural indices. This is evidence that the binaural is not simply a sum of the monaural responses. The BICs, also, are minimally altered by overall intensity and essentially unaffected by ITDs. Statistical analyses for repeated measures of the data were conducted to determine main effects of intensity, mode (binaural, BIC, and summed monaural), time, and their interactions. Each of the sources, namely, intensity, mode, ITD, intensity-mode, and mode-ITD, influenced the responses significantly (p < .05). The effects of intensity-ITD and intensity-mode-ITD, however, were not significant.

### Frequency-Following Responses to Interaural Time Differences and Intensity In Concert and In Opposition

In this experiment, tones were presented in concert and in opposition; in the former, the ear leading in time had the greater intensity; when in opposition, the leading ear received the lesser intensity. Perceptually, an in-concert stimulus is lateralized to the side with a time lead and greater intensity, both of which determine the extent of the lateralization; for a stimulus in opposition, the perception may be either a single sound that is more medial than when the stimuli are in concert or two sounds, one mediated by ITD and the other by IID (Moushegian and Jeffress, 1959; Whitworth and Jeffress, 1961).

The frequency-following waveforms to ITDs and IIDs, in concert and in opposition, exhibited periodicities occurring at 2.0 msec (Fig. 7). In the binaural condition, where no time differences exist (0°), the traces are essentially similar whether the right (R + 10 dB) or left (R − 10 dB) stimulus level was more intense. No conflict exists between interaural time and interaural intensity because interaural time is 0 msec. When both binaural cues, intensity and time, are present in the stimulus, the resulting waveforms for in-concert stimulation (R + 10 dB) are easily distinguished from those to stimuli in opposition (R − 10 dB), regardless of ITD. The greatest contrast is at 120° (667 μsec), where the in-concert (R + 10 dB) is considerably smaller than the in-opposition waveform (R − 10 dB). Also, the amplitudes of the evoked FFRs to in concert stimuli tend to get smaller with ITD, whereas to in-opposition stimuli they do not.

The grouped data support this observation. Large differences occur in the binaural and summed monaural waveforms to stimuli in concert and in opposition (Fig. 8). All functions are indicative of distinct and separate interactions of ITD and intensity on the FFR. For example, when time and intensity are in concert, the binaural amplitudes decrease with increasing interaural time; for stimuli in opposition, they remain essentially unaltered, except at interaural time 667 μsec. The normalized indices of the BIC waveforms are relatively unaffected by interaural time.

Analyses of variance of the normalized data for in concert and in opposition revealed that mode (binaural, summed monaural, or BIC) and mode × in concert × in opposition show significant interactions. The in-concert and
Figure 7 Waveforms to binaural in-concert and in-opposition sounds. At 0°, R + 10 dB indicates right ear at 65 dB SL, left at 55 dB SL; R - 10 dB, right, 55 dB SL and left, 65 dB SL. For the 60°, 90°, and 120° conditions, R + 10 dB (in-concert), right is leading and 10 dB higher than left (R 65 dB SL, L 55 dB SL); R - 10 dB (in-opposition), right leading and 10 dB less than left (R 55 dB SL, L 65 dB SL). Every waveform is the average of two traces, each obtained to 1000 presentations of the stimulus.

Figure 8 The mean normalized amplitudes of binaural, summed monaural, and binaural interaction components for stimuli with interaural level and time differences in concert and in opposition. N = 8.

in-opposition values, however, fail to show significant effects because two obviously disparate conditions are averaged, rendering the absence of true differences.

Figure 9 was composed to present three binaural normalized amplitude functions in order to summarize some of the findings. It shows (1) the effect of interaural time when two ears have the same intensity, (2) the effect of interaural time where the leading ear receives the more intense sound (in concert), and (3) the effect of interaural time when the leading ear is less intense than the lagging (in opposition). The first simulates a freefield condition where only time cues are operative (-); the in-concert lateralization function (● — ●) parallels somewhat the first and shows that intensity is an effective cue in a lateralization paradigm even though the sound is a low-frequency tone; and the third function (▲ — ▲) indicates that intensity offsets time in a lateralization paradigm.

DISCUSSION

For humans, freefield sounds in the median plane (directly ahead) produce no ITD at the ears (0° azimuth); those off the interaural axis (90° azimuth) have differences of 667 μsec (Woolworth, 1938, p. 523). In a lateralization paradigm, sounds at the earphones mimic freefield conditions. When the time difference at the ears
is 0 μsec, a sound is perceived as being in the middle of the head. With an ITD and ILD, the perception is an intracranial one nearer the ear with the advantages (i.e., time lead and louder sound level).

The interaural time and intensity cues that affect localization may produce double images in a lateralization paradigm when these cues are presented in opposition (Shaxby and Gage, 1932). It is known, too, that a time difference may be offset by intensity, the so-called “time-intensity trade” (Moushegian et al, 1959). Whitworth and Jeffress (1961) reported that the “time-image” was affected minimally by intensity differences, and the “intensity-image” had a trading ratio of 20 μsec/dB. Jeffress (1971) suggested that two mechanisms were involved, one based on interaural differences in both intensity and time and the other on only ITDs for frequencies below 1.5 kHz.

This study was undertaken to determine whether the FFR evoked by stimulation of both ears is reflective of binaural processing and whether the FFR and BIC are sensitive to stimulus cues that mediate localization and lateralization phenomena. The findings provide evidence that (1) the binaural FFR is not simply the sum of two monaurals; (2) the FFR is affected differentially by interaural time changes without recourse to computational or derived manipulations; (3) in a lateralization paradigm, FFRs not only contain evidence of binaural processing emanating from the brain stem, but also the waveforms to in-concert and in-opposition sounds are easily distinguished; (4) these results support earlier findings that lower brainstem structures are the initial sites where such sounds are processed; and (5) the normalized amplitudes of the BIC are minimally, if at all, sensitive to time and intensity cues.

Daly et al (1976) found, as this study has, that the binaural FFRs generated were not simple sums of the right and left FFRs but were indicative of binaural processing that takes place in the lower auditory neuraxis. Their conclusion was based on a comparison of monaural and binaural FFRs from normal-hearing adults and subjects with profound unilateral sensorineural hearing losses. The present results support this conclusion. In contrast, however, Gerken et al (1975) wrote that the putative binaural FFR was simply the sum of the monaurals possibly emanating from two separate sources. Daly et al (1976) attributed the contrasting conclusions to methodological differences. Using a beat-frequency stimulus paradigm, Hink et al (1980) reported also that the FFR contains evidence of binaural processing. When the monaural waveforms to two monaural frequencies, differing by 40 Hz at each ear, were added, the summed traces were larger than those to binaural stimuli. They concluded that the binaural FFR originates at or below the inferior colliculi.

Analysis of the data shows that binaural FFR is differentially modified by ITDs between 0 and 667 μsec, the range that occurs naturally in a freefield for humans. The functions in Figure 5 have the greatest slope changes in the normalized binaural waveforms between 0 and 500 μsec, with lesser slopes between 500 and 667 μsec. This trend is the same at all intensities. When time and intensity are in concert, the FFR indices also decrease as the time differences increase; this parallels what happens psychophysically, the ILD supplements the ITD. However, when these cues are in opposition, the effect of ITD is minimized (see Figs. 8 and 9), as reported by Moushegian and Jeffress (1959).

Parthasarthy and Moushegian (1993) described low-frequency BICs that resembled FFRs with latencies longer than those evoked by either clicks or high-frequency tones. They demonstrated that the BIC was affected by rate, frequency, and intensity. The present investigation has revealed that a BIC can be extracted from waveforms evoked by low-frequency tone bursts and that multiple peaks and valleys are present in the BIC but absent in click-evoked BICs. Studies on the BIC to click-evoked responses reported that the amplitudes of the
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BIC were altered as a consequence of intensity or time changes (Furst et al, 1985, 1990; McPherson and Starr, 1995). Click-evoked waveforms contain peaks that are time locked to the stimulus onset; a delay in the click at one ear shifts these peak latencies, resulting in a displaced BIC. Amplitudes of the BICs were unaffected in the present study, where an interaural time delay was produced by shifting the phase/time of the binaural tonal stimulus. These disparities in results are most probably a consequence of stimulus type, clicks versus tone bursts.

This study has shown that the BIC normalised amplitudes are minimally affected by ITDs between 0 and 667 \( \mu \text{sec} \), even when both intensity and time cues, whether in concert or in opposition, are operative (see Figs. 6 and 8). Sontheimer et al (1985) recorded ABRs in animals in concert and in opposition to click stimuli. They reported that when the sound is leading in one ear and louder in the other, the amplitude of the BIC was considerably larger than when the stimulus parameters were in concert; again, as before, this difference in results is best attributable to differences in stimuli.

There is considerable heterogeneity in how brainstem neurons respond to sounds (Moushegian and Rupert, 1974). If a neuron discharges at integral multiples of the period of the stimulus, it is said to phase lock. Measures of phase locking, synchronization index (Anderson, 1973), and vector strength (Goldberg and Brown, 1969) have shown that the interspike intervals of neuronal discharges at best range over the entire half cycle of a sound's period; a single neuron, therefore, cannot capture the veridical period and the frequency of a sound.

Clark et al (1997) undertook to ascertain whether an aggregate response in the guise of the volume-conducted FFR coincided more closely than neuronal discharges to the stimulus period. They wrote in fact that “the averaged FFR periodicity to all stimulus conditions from all subjects was 2.29 ms, differing only 6.8 microseconds from the period of 450 Hz stimulus” (Clark et al, 1997, p. 308) that was used in their investigation. They believed that their results were evidence of brainstem neuronal networks, which maintain “a closer correspondence to the period of a low-frequency, whether monaural or binaural, than the discharge patterns of single neurons” (Clark et al, 1997, p. 308). This was the case whether the binaural sound was simulated intracranially at 0° (no time difference) or off the interaural axis with one ear leading 660 microseconds.

The relevance of all of these findings is that the FFR, when evoked by appropriate stimuli, is differentially responsive to lateralization cues. For this reason, it is an excellent candidate for assessment of normal and abnormal functions of the lower brainstem auditory neuraxis.

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REFERENCES


