

# Multiple-Stimulus Method for Rapid Collection of Auditory Brainstem Responses Using High-Frequency ( $\geq 8$ kHz) Tone Bursts

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## Abstract

Auditory brainstem responses (ABR) to high-frequency ( $\geq 8$  kHz) tone-burst stimuli have shown potential for objective early detection of ototoxicity. In the case of ill, unresponsive, or otherwise difficult-to-test individuals, the patient group for whom this test is targeted, a threshold-seeking process can be too lengthy. A new method is described for obtaining responses to several high-frequency tone bursts in the same amount of time as that used in obtaining a single response. Using 10 normal-hearing subjects, four high-frequency tone-burst stimuli (14, 12, 10, and 8 kHz) were presented singly, then in a multiple-stimulus sequence with onsets separated by 10 msec. Wave V response latencies from the multiple-stimulus sequences are compared to those presented singly, with small but statistically significant longer latencies observed for all stimuli following the initial stimulus (14 kHz) in the multiple sequence. Test-retest reliability was comparable between multiple and single conditions. These findings support the development of this technique for clinical auditory monitoring.

**Key Words:** Auditory brainstem response (ABR), high-frequency tone burst, multiple-stimulus sequence, reliability

**H**earing loss caused by treatment with ototoxic agents typically occurs at the highest audible frequencies and can progress to impair the lower frequencies necessary for speech communication (Huizing and DeGroot, 1987; Kopelman et al, 1988). Thus, early identification of ototoxicity in the high-frequency region has the potential for preventing communicatively disabling hearing loss. This has been demonstrated by behaviorally monitoring high-frequency ( $\geq 8$  kHz) audition

during treatment with potentially ototoxic agents (Fausti et al, 1984a, b, 1992d; Pollera et al, 1988; van der Hulst et al, 1988; Dreschler et al, 1989).

Obtaining reliable auditory thresholds with behavioral techniques requires alert and attentive subjects. Patients receiving therapeutic agents with ototoxic side effects are often quite ill and unable to provide the reliable behavioral responses needed to document ototoxic change. Many of these patients are also unable to report gross subjective symptoms associated with ototoxicity, such as tinnitus or decreased hearing ability and/or imbalance. The inability to respond in order to establish the presence or absence of ototoxic symptoms may place such patients at higher risk for hearing loss (Whelton, 1985). The need exists for a reliable objective monitoring tool that will give health-care providers the earliest possible warning of auditory damage.

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The auditory brainstem response (ABR) evoked by click stimuli has been demonstrated to be an effective objective measure for detecting damage to the auditory system and has proven valuable as an auditory evaluation tool for patients unable to respond reliably to behavioral testing (Bernard et al, 1980; Guerit et al, 1981; Piek, Lumenta, and Bock, 1985; Hall et al, 1986). Click stimuli, however, yield information about hearing sensitivity primarily in the 2- to 4-kHz region (Gorga et al, 1985; Mitchell, Phillips, and Trune, 1989). Since ototoxicity begins at high frequencies and progresses to lower frequencies, considerable loss of hearing sensitivity can occur in the higher frequencies before it can be detected with ABR using click stimuli. The ABR evoked by high-frequency ( $\geq 8$  kHz) tone-burst stimuli is more suitable for identifying high-frequency threshold changes early enough in the ototoxic process to preserve communication ability. Tone bursts produced by commercial evoked-potential systems, however, are generally confined to frequencies  $\leq 8$  kHz (Gorga et al, 1988; Fjermedal and Laukli, 1989; Purdy et al, 1989). Instrumentation to produce reliable ABRs from tone bursts of 8, 10, 12, and 14 kHz has been developed and documented (Fausti et al, 1992c). On patients receiving aminoglycoside antibiotics and cisplatin, ABRs using high-frequency tone-burst stimuli have detected ototoxicity earlier than those using click stimuli, with a detection potential similar to that of behavioral threshold testing (Fausti et al, 1992b).

The use of tone bursts to obtain frequency-specific responses has improved the usefulness of ABR, although the length of time required to obtain tone-burst ABR thresholds remains a limiting factor (Eggermont and Don, 1980; Jerger, Oliver, and Stach, 1985; Burkard, Shi, and Hecox, 1990). While effective in detecting change, threshold determination or complete frequency-intensity information can be obtained from this technique only through lengthy test procedures that are difficult, if not impossible, for ill patients to tolerate. Studies at Portland, Oregon Veterans Affairs Medical Center (PVAMC) with such patients have demonstrated the need for a reliable frequency-specific ABR technique that can be conducted rapidly and that is sensitive to ototoxic change.

The multiple-stimulus ABR technique developed and reported here is based on the concept that auditory stimuli can produce adaptation if they are presented too closely together in time. However, if successive stimuli activate

different neural populations, response adaptation may be minimized or avoided. That is, successive stimuli presented far enough apart in time, frequency, or intensity may avoid adaptation from previous stimuli. This has been demonstrated in paired-stimulus adaptation studies in guinea pigs (Mitchell, Fausti, and Frey, 1994). Thus, several stimuli could be presented within a single averaging period to produce multiple, relatively unadapted evoked potentials. This technique is different from maximum length sequences in which significantly adapted responses are accepted (Eysholdt and Schreiner, 1982; Burkard et al, 1990).

Concurrent investigations into stimulus stacking or sequencing concepts in order to achieve time savings have apparently shown successful results for click stimuli at different intensities (Spoor, 1974; Hamill, Hussung, and Sammeth, 1991, 1992) and for tone bursts at conventional frequencies (0.5–4 kHz) (Hoke et al, 1991). The Hamill group (1991) used different intensity levels of clicks as "chained-stimuli," similar to the method of Spoor (1974), and compared "chained" responses to those of singly presented clicks. In Germany, the Hoke group (1991) used a series of tone-pulse stimuli (0.5–4 kHz) and a "derived-response" technique (Teas, Eldridge, and Davis, 1962; Don and Eggermont, 1978; Parker and Thornton, 1978), but did not make the important comparison between multiple and single responses. Neither of these groups reported test-retest reliability.

The purpose of the present study was to develop a reliable multiple-stimulus method for evoking the ABR with several high-frequency tone-burst stimuli in order to provide maximum information in a minimum amount of time. Instrumentation was designed to deliver customized sequences of high-frequency tone-burst stimuli. Auditory brainstem responses to stimuli presented singly and in multiple-stimulus sequences are compared.

## METHOD

### Subjects

Subjects included four males and six females, with a mean age of 22.8 years (range = 17–27 years), who met the following criteria: negative history of ear disease; normal aural acoustic-immittance results (Wiley, Oviatt, and Block, 1987; Shanks et al, 1988); conventional frequency ( $\leq 8$  kHz) hearing thresholds no greater than 15 dB HL; high-frequency ( $> 8$

kHz) thresholds no greater than one standard deviation of the mean reported by Schechter et al (1986); and repeatable ABRs to 14-, 12-, 10-, and 8-kHz tone-burst stimuli delivered at 90 dB peSPL.

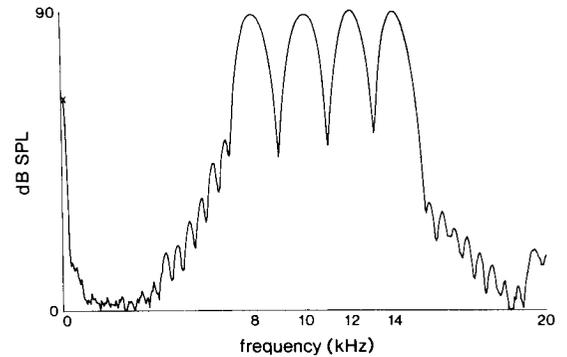
### Instrumentation

A new stimulus generator was developed for this study (Tucker-Davis Technologies, Gainesville, FL), consisting of a portable PC with a customized 16-bit D/A board. Controlling software is fully user-programmable to deliver a train of custom-designed tone bursts at various frequencies and/or intensities with control of waveform configuration (windowing), stimulus phase at onset, frequency, intensity (100 dB in 1-dB steps), rise-fall times, plateau duration, and time separation between stimuli. The stimulus generator can be triggered by positive or negative electrical square waves (condensation or rarefaction clicks from a conventional ABR system). In the present study, a Bio-logic (Mundelein, IL) Brain Atlas was used to produce click stimuli for triggering the stimulus generator and synchronizing it with the averaging window.

Subjects were tested in a double-walled, RF-shielded sound suite (Model 19701A, Acoustic Systems, Austin, TX). Conventional (0.25–8 kHz) and high-frequency (9–20 kHz) behavioral auditory evaluation was conducted with a Model 320 (Virtual Corporation, Portland, OR) audiometer. Headphone transducers for conventional-frequency testing were Telephonics TDH-50P with MX 41/AR earcushions. High-frequency transducers were modified Koss Pro/4X Plus (Fausti et al, 1990). The same headphones were used for high-frequency behavioral testing and presenting high-frequency tone-burst stimuli. Pure-tone calibration methods were as described in Fausti et al (1990). Calibration of ABR tone-burst stimuli was as described in Fausti et al (1991, 1992a, b). Immittance screening (tympanometry at 226, 630, and 1000 Hz, and ipsilateral and contralateral acoustic reflexes at 500, 1000, and 2000 Hz) was conducted with a Model 310 (Virtual Corporation, Portland, OR) aural acoustic-immittance system.

### Stimuli

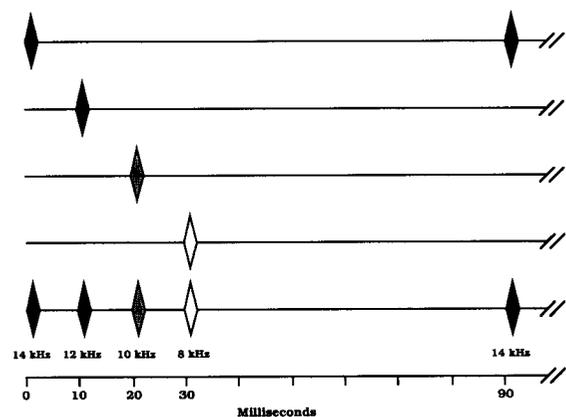
Tone bursts of 2-msec duration were ramped with 1-msec rise-fall times and no plateau. A Hanning (Cosine<sup>2</sup>) window was utilized to obtain the desired spectral characteristics of



**Figure 1** Spectra of the multiple sequenced stimuli at 90 dB SPL (HP 3561A Dynamic Signal Analyzer).

frequency sharpness at the peak and distance to the initial side lobes (Fig. 1). All stimuli were presented at 90 dB peak equivalent (pe)SPL, determined via the oscilloscope displacement-matching method described in Fausti et al (1991, 1992c). Briefly, the acoustic output of a tone burst is displayed on an oscilloscope and its displacement is measured. The scope displacement of a known pure-tone signal is then matched to this and the resulting sound pressure level assigned as the peSPL of the tone burst.

Figure 2 demonstrates the stimulus presentation paradigm. Tone-burst stimuli at 14, 12, 10, and 8 kHz were first presented singly at the same time position in which they occurred within the multiple-stimulus sequence. Next, these high-frequency tone bursts were delivered as a multiple-stimulus sequence, with each of the four stimuli separated by 10 msec between onsets. Animal studies have shown



**Figure 2** Block diagram of stimulus sequencing. Single stimuli were presented in the same sequence time period in which multiple stimuli were presented.

minimal adaptation using this separation interval between stimuli (Mitchell et al, 1994). All stimuli, single and multiple, were presented at a rate of 11.1 per second.

**Procedures**

Case history, behavioral testing, immitance screening, and high-frequency tone-burst ABRs were obtained initially to establish subject eligibility. ABR test sessions were then scheduled on 2 separate days for accepted subjects. ABRs were recorded from gold-cup surface electrodes attached at the forehead (common), vertex (non-inverting), and both mastoid prominences (inverting), with two channels (ipsilateral and contralateral) recorded simultaneously. Absolute electrode impedance did not exceed 2 kΩ, and the interelectrode impedances were at or below 1 kΩ. Bioamplifier filter settings were at 100 and 1500 Hz, and the response was averaged with a time window of 45 msec. Data-collection trials consisted of three averaging runs of 1000 presentations for each stimulus condition at each session.

**Waveform Identification**

ABR wave-identification techniques for click stimuli (Chiappa, Gladstone, and Young, 1979; Beattie et al, 1986; Picton et al, 1988) were employed as a guideline for peak marking of high-frequency tone-burst responses. Peak latencies were measured from the onset of the relevant tone burst. Contralateral recordings and summing of the three separate averages within a session were utilized for additional information in latency determinations. Three trained audiologists scored each average independently. Only wave V data are reported here.

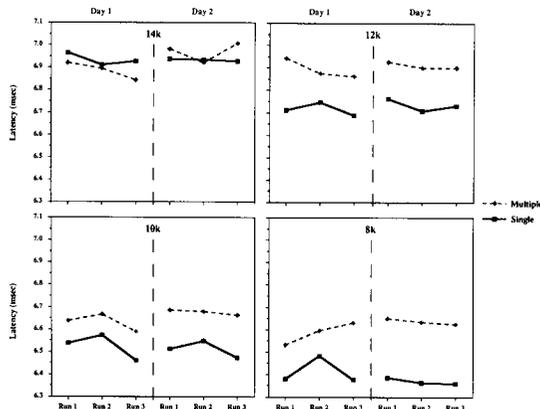
**RESULTS**

A two-way (days × runs) repeated measures analysis of variance (ANOVA) was completed on response data from the stimuli presented singly for each scorer. At all frequencies, main effects for days and runs, as well as the two-way interaction, were not significant ( $p > .05$ ). This established the reliability of each scorer within and across days. Multiple-response data were analyzed in the same way as for the single stimuli. None of the ANOVA produced significance ( $p > .05$ ), indicating that the multiple-stimulus presentations also resulted in reliable responses.

Although these analyses indicated that each scorer did not detect a change in responses over time, there was the possibility that scorers were consistently identifying peak waveforms differently from each other. To address potential interscorer differences, a one-way repeated measures ANOVA was done at each frequency on day 1, run 1 for both the single-stimulus and multiple-stimulus data. No significant differences were seen ( $p > .05$ ), allowing the conclusion that scorers were marking wave V peaks consistently.

With interscorer reliability determined, latencies were then averaged across scorers for each day and run (Fig. 3). Note that the mean latencies of multiple-stimulus responses were longer than those of the corresponding single-stimulus responses at all frequencies except 14 kHz, the first stimulus in the multiple-stimulus sequence. Latency differences between single- and multiple-stimulus conditions, however, were not statistically significant ( $p > .05$ ), except at 8 kHz ( $p < .01$ ), the final stimulus in the multiple sequence.

To compare mean responses between single and multiple stimuli, a two-way (averaging run × single/multiple) repeated measures ANOVA was done at each frequency. Orthogonal t-tests were then used to make corresponding comparisons, using the appropriate error term derived from the ANOVA. For example, the mean response to the *single* stimulus on day 1, run 1 was compared to the mean response to the *multiple* stimulus on day 1, run 1 and so forth for each of the six day/run combinations. Table 1 shows probability values from each orthogonal t-test. No significant differences were seen for



**Figure 3** Responses averaged across subjects and scorers for each test session (day) at each test frequency.

**Table 1 Probability (p) Values for Comparisons of Mean Latency of Single and Sequenced Stimuli**

Frequency (kHz)	Day 1			Day 2		
	Run 1	Run 2	Run 3	Run 1	Run 2	Run 3
	14	.67	.86	.41	.65	.91
12	<.001	.026	<.010	<.010	<.001	<.010
10	.091	.105	.025	<.010	<.050	<.001
8	<.050	.095	<.001	<.001	<.001	<.001

14 kHz ( $p > .05$ ), while most of the comparisons for the subsequent 12, 10, and 8 kHz were significant ( $p < .05$ ).

Because intrasession data were determined to be reliable, mean latencies were then collapsed across averaging runs within each session to evaluate intersession reliability of multiple-stimulus responses in relation to reliability of single-stimulus responses. Mean latencies and standard deviations ( $\pm 1$ ) for multiple- and single-stimulus responses at each frequency are shown in Table 2 for each test session (day). A one-way repeated measures ANOVA revealed that in each case, the single-stimulus intersession difference did not differ significantly from the corresponding multiple-stimulus difference ( $p > .05$ ).

Table 3 shows the overall mean latencies for multiple- and single-stimulus responses (3 scorers  $\times$  10 subjects  $\times$  6 runs = 180 potential data points for each mean) with standard deviations ( $\pm 1$ ). As previously noted from data pooled across subjects and scorers in Figure 3, no latency delay (adaptation) can be seen between single- and multiple-stimulus conditions at 14 kHz. These overall mean data reveal a latency delay of 0.18 msec with the second stimulus in

**Table 2 Intersession Reliability. Mean Latencies (in msec) for all Scorers and Subjects by Day (Session)**

Frequency (kHz)	Single		Multiple	
	Day 1	Day 2	Day 1	Day 2
	14	6.92 (.36)	6.94 (.37)	6.88 (.20)
12	6.69 (.31)	6.74 (.24)	6.89 (.23)	6.90 (.24)
10	6.52 (.32)	6.51 (.24)	6.63 (.18)	6.68 (.23)
8	6.41 (.38)	6.37 (.26)	6.59 (.26)	6.63 (.26)

Standard deviation ( $\pm 1$ ) in parentheses.

**Table 3 Overall Mean Latency (in msec) with Differences between Single and Multiple Presentations**

Frequency (kHz)	Single	Multiple	Difference
14	6.93 (.36)	6.93 (.36)	.00
12	6.71 (.25)	6.89 (.24)	.18
10	6.52 (.26)	6.65 (.21)	.13
8	6.39 (.33)	6.61 (.23)	.22

Standard deviations ( $\pm 1$ ) in parentheses.

the sequence, 12 kHz, which thereafter remains relatively stable for subsequent stimuli in the sequence, 10 and 8 kHz ( $\leq 0.09$  msec).

The previous analyses have shown that the multiple-stimulus wave V responses were as reliable across sessions as responses to the stimuli presented singly. These analyses did not, however, rule out the possibility that high variability existed between the three runs within a session. To address this concern, standard deviations of response scores were calculated, based on means derived from each of the three duplicate averages within each session. All standard deviation values were less than 0.3 msec. This range was divided into 10 0.03 msec increments, and each standard deviation was placed into its appropriate category, as shown in Table 4. Each row represents the single or multiple condition for each frequency. With all traces scored, a maximum of 60 values would be distributed across each row (2 sessions  $\times$  10 subjects  $\times$  3 scorers). In a very few instances, however, unscorable traces resulted in missing data points and, thus, the inability to calculate standard deviations. Consequently, not all of the rows add up to 60. Although the multiple-stimulus responses are seen to "spread out" slightly more than the single-stimulus responses, most standard deviations for both fall within 0.0 to 0.2 msec. These results clearly demonstrate reliability of intrasubject and intrasession responses and, further, that single- and multiple-stimulus reliability were comparable.

Responses from one of the subjects in this study are shown in Figure 4. Traces depicted are the summation of three averages for 1 test day. Note how the amplitude of responses increases with sequentially lower stimulus frequency in both single- and multiple-stimulus conditions and how responses correspond to the diagram demonstrating stimulus-presentation sequence (Fig. 2).

**Table 4** Number of Occurrences of Standard Deviations of Response Scores Derived from Daily Averages\* for 10 Subjects, 3 Scorers, and 2 Days, for Single (S) and Multiple (M) Presentations at Each Test Frequency

Frequency		Standard Deviations (msec)									
(kHz)		.00- .03	.03- .06	.06- .09	.09- .12	.12- .15	.15- .18	.18- .21	.21- .24	.24- .27	.27- .30
14	S	3	15	8	15	8	4	3	0	0	0
	M	3	10	16	5	11	8	3	1	0	1
12	S	4	9	22	5	9	2	3	2	0	0
	M	5	6	19	10	12	5	1	1	1	0
10	S	5	18	22	1	8	2	1	0	0	0
	M	3	21	24	7	2	1	1	0	0	0
8	S	0	25	20	11	1	2	0	0	0	1
	M	5	15	26	4	3	1	2	0	0	3

\*Unable to calculate standard deviation when missing data points (unscorable traces) result in too few occurrences.

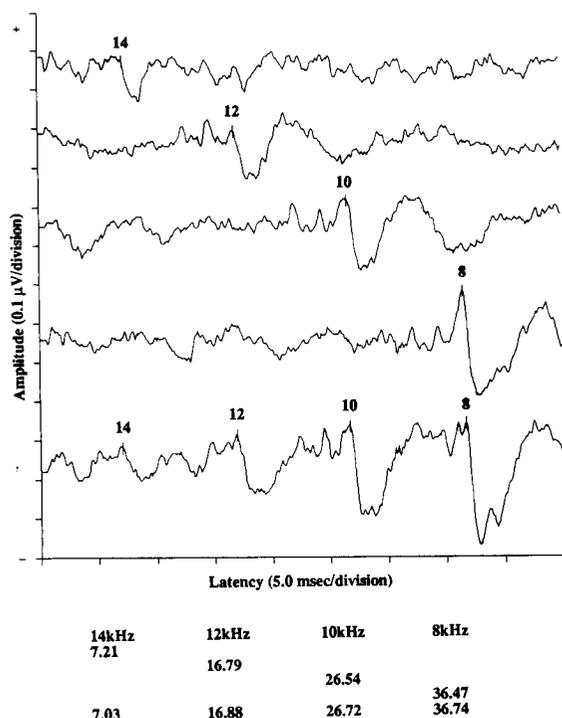
**DISCUSSION**

The criteria with which an auditory serial ototoxicity monitoring technique should be measured are its reliability, sensitivity, and length (time) of administration. Reliability of the multiple-stimulus sequencing technique is demonstrated in this preliminary study, as is rapidity of test administration. Sensitivity refers to the ability to accurately detect a change

in auditory function. Previous single-stimulus studies (Fausti et al, 1992a, b, c) have addressed the sensitivity of high-frequency tone-burst stimuli in the early detection of ototoxicity. The sensitivity of multiple stimuli to changes in threshold, however, remains to be addressed.

There is some evidence in guinea pigs that adaptation occurring at suprathreshold levels does not change at threshold (Mitchell et al, 1994). This issue will be explored further in humans. Eggermont et al (1974) compared adaptation of the cochlear action potential (AP) in humans and guinea pigs. Using fast repetition rates, they found adaptation to be about four times greater in humans than in guinea pigs. A comparison of our current findings in humans with data from the accompanying study in guinea pigs (Mitchell et al, 1994) does not demonstrate such large differences in adaptation. This may be attributed to methodologic differences. For example, when fast repetition rates induce adaptation, adaptation time constants obtained have at least three components: *rapid and slow adaptation* (Smith and Brackman, 1982), as well as *forward masking*. It is possible that only one of these components, rapid adaptation, was involved in our current studies using paired or 4-stimulus sequences. Thus, adaptation differences between humans and guinea pigs may be large when adaptation is induced by faster repetition rates but small when paired- or multiple-stimulus sequences are used.

In the present study, mean latencies for both single- and multiple-stimulus presentations can be seen to decrease with successively lower frequency (Tables 2 and 4). Although this



**Figure 4** Auditory brainstem responses from a 24-year-old female subject to the single- and multiple-stimulus presentations. These are shown summed across the three averages for 1 test day.

may seem counterintuitive with respect to information showing that latency typically decreases with *increasing* frequency, it must be remembered that tone-burst SPL was held constant at 90 dB for all frequencies. With average pure-tone thresholds for the subjects in the present study at 37.5, 28.5, 22.0, and 14.5 dB SPL at 14, 12, 10, and 8 kHz, respectively, it seems reasonable that the decreasing latency seen with decreasing frequency was a result of increasing sensation level.

There were no latency differences between multiple- and single-stimulus responses at 14 kHz in this study. There was some degree of latency delay (response adaptation) seen in responses to stimuli following 14 kHz in the multiple presentation. The differences, however, between multiple- and single-stimulus responses at 14, 12, and 10 kHz were not statistically significant. Only 8-kHz responses were seen to be significantly different from the others. In any case, latency differences were small ( $X \leq .22$ ), and responses were demonstrated to be reliable.

This is the first report describing a high-frequency multiple-stimulus evoked ABR in humans. The stimulus generator and electrophysiologic technique presented is designed to rapidly monitor auditory function. A 400 percent increase in efficiency (obtaining four responses in the time that one response could previously be obtained) reported in this study over single-stimulus ABR methods can be further improved. This multiple-stimulus technique, for the purpose of this study, used four sequenced stimuli. Averaging and display of responses was accomplished using commercially available auditory evoked potential systems. Although the multiple-stimulus generator can be programmed for delivery of 20 stimuli, a significant limitation to this larger number of stimuli is imposed by input and display capabilities of current commercial signal averagers.

These preliminary data demonstrate the reliability of this multiple high-frequency tone-burst ABR technique. It is also clear that this technique can be accomplished far more rapidly than the current single-stimulus method, and its use should minimize the discomfort that is common in lengthy test procedures with ill patients. Although additional data are being collected, the findings obtained thus far strongly suggest that the multiple, high-frequency stimulus technique has significant potential for monitoring subjects receiving ototoxic agents for the purpose of early detection of hearing change.

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