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THE EFFECTIVE DURATION OF THE STIMULUS FOR THE AUDITORY BRAINSTEM AND MIDDLE LATENCY RESPONSES

by

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A dissertation submitted to the Graduate Faculty in Speech and Hearing Sciences in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Abstract

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Advisor: Professor David R. Stapells

ABR and MLR are considered "onset" responses, reflecting the auditory system's response to stimulus onset rather than its continuance. The studies in this dissertation were designed to determine the effective duration of the stimulus for ABR and MLR elicited by different stimuli and by stimulation of different regions of the cochlea using the "constant-slope" rise-time paradigm in which the slope of the rise (rather than intensity) for different rise times is kept constant.

ABRs and MLRs were recorded from 12 normal-hearing adults. In the first study, the acoustic stimuli consisted of 500- and 2000-Hz tones and broadband noiseburst stimuli with rise times ranging from 0.5 to 12 ms.

Results indicate that the effective duration for the ABR and MLR is stimulus dependent, with 500-Hz exhibiting the longest effective duration (~12 ms), broadband noiseburst exhibiting the shortest effective duration (~2 ms), and 2000-Hz falling in between (~4 ms). No significant differences were seen between the effective duration of the ABR and MLR.

In the second study, ABR and MLR responses to brief broadband noisebursts were recorded using the high-pass masking noise (HP) subtraction technique. One-octave-wide narrowband derived responses were centered at 500-, 1000- and 2000 Hz.

Results indicate that the effective duration of the stimulus for the ABR and MLR is cochlear place dependent, with 500-Hz derived response exhibiting the longest effective duration (~8 ms), 2000-Hz derived response exhibiting the shortest effective duration (~2 ms), and 1000-Hz results falling in between (~4 ms). No significant differences were seen between ABR and MLR effective durations.

Thus, the effective duration of the stimulus for ABR and MLR is cochlear place dependent with responses from the apical regions of the cochlea integrating longer portions of the stimuli. The lack of significant differences between the effective durations of the ABR and the MLR suggests that the time it takes to achieve maximum output is determined by peripheral processing, not by where the response is generated.

PREFACE

The focus of this dissertation in on the effective duration of the stimulus for the auditory brainstem (ABR) and middle latency (MLR) responses. The dissertation consists of four chapters: (1) a review of the literature on stimulus parameters affecting the auditory brainstem and middle latency responses; (2, 3) two research papers; (4) a brief summary, and (5) a references-cited section. The research papers include: (1) "The effective duration of the stimulus for the auditory brainstem and middle latency responses", and (2) "Cochlear place determinants of the effective duration of the stimulus for the auditory brainstem and middle latency responses". Each research paper is intended as a stand-alone research paper. Therefore, there is necessarily some overlap between papers and some of the information presented in the literature review at chapter 1. To minimize some of this repetition, references cited are listed at the end of the dissertation.

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CHAPTER 1: REVIEW OF LITERATURE

INTRODUCTION

The auditory brainstem (ABR) and middle latency (MLR) responses evoked by tones have often been recommended to assess auditory sensitivity in individuals who are unable to participate in conventional behavioral audiometry (e.g., Kraus & McGee, 1990, 1993; Stapells & Oates, 1997). When assessing auditory sensitivity, the primary objective of using the ABR and MLR is to specify, as accurately as possible, the patient's hearing status for different frequencies. The ABR and MLR are elicited by stimuli of relatively short duration and short rise/fall times. These brief stimuli generate the synchronized discharge of the auditory nerve fibers which are required to elicit the far-field brainstem and middle latency responses (Møller, 1993).

The following literature review is a brief discussion of how cochlear, VIIIth nerve, and brainstem anatomy and physiology determines the properties of the ABR and MLR. The literature review continues with a brief description of the acoustics of brief stimuli and ends with a discussion on how various stimulus parameters affect the auditory brainstem (ABR) and middle latency (MLR) responses.

A. Description of the ABR and MLR

The auditory brainstem and middle latency responses are "far-field" auditory evoked potentials usually recorded between an electrode at the vertex and an electrode on the mastoid (or earlobe) of the ear being stimulated. The ABR appears during the first 20 ms following stimulus onset when elicited by a moderately high intensity click at a rate of 20/s or less. The ABRs evoked by clicks with an intensity above 60 dB nHL typically consist of five to seven vertex-positive peaks that are identified by Roman numerals, a labeling system developed by Jewett and Williston in 1971 (Jewett & Williston, 1971). The ABR evoked by

low-intensity clicks and by tonal stimuli consists primarily of Wave V followed by a large negativity (e.g., Beattie & Boyd, 1985; Beattie & Kennedy, 1992; Stapells & Picton, 1981; Wu & Stapells, 1994). ABR wave V to tonal stimuli in normal-hearing adults has been defined as the maximum vertex-positive peak occurring between 6 and 20 ms following stimulus onset. If several peaks of equal amplitude occur within this range, the peak preceding the largest negativity is labeled as wave V (Oates & Stapells, 1997a; Stapells & Picton, 1981; Wu & Stapells, 1994; Wu & Stapells, submitted).

The middle latency response consists of three negative-positive waves (Na, Pa, and Nb) which occur after the ABR and before the slow cortical auditory evoked potentials, usually between 15 and 80 ms after the onset of an acoustic stimulus (e.g., Goldstein & Rodman, 1967; Kileny, 1983; Kraus & McGee, 1993; Ozdamar & Kraus, 1983; Picton, Hillyard, Kraus, & Galambos, 1974). Wave Pa is a robust positive wave seen between 20 and 50 ms and wave Nb is the largest negativity following Pa and occurring between 30 and 75 ms (Mackersie, Down, & Stapells, 1993; Wu & Stapells, 1994; Wu & Stapells, submitted). A following positive wave, Pb, which is probably wave P1 of the slow cortical response (Erwin & Buchwald, 1986), is not included in this study. Figure 1 shows the grand mean ABR and MLR waveforms from 12 normal-hearing subjects evoked by 500- and 2000-Hz stimuli presented at 66 dB ppe SPL.

B. Auditory processing - From the cochlea to the auditory cortex

The auditory evoked potentials provide information about the central auditory pathways as well as about the cochlea and the auditory nerve. The study of the ABR and MLR provides a "window" into the processes which occur at the cochlea, brainstem and cortical levels.

The following is a brief discussion of how cochlear, VIIIth nerve, brainstem and cortical physiology determines the frequency-selectivity of the auditory system.

The Cochlea

The function of the cochlea is to convert the mechanical energy arriving from the middle ear into electro-chemical energy that can be processed by the central auditory mechanism. It transforms the rapid fluctuations in atmospheric pressure into a neural code in auditory nerve fibers (for an in-depth review of the cochlea, see Patuzzi, 1996).

The human cochlea is about 35 mm in length, located in the temporal bone and forms a cone-shaped spiral with $2\frac{5}{8}^{th}$ turns. The cochlea is composed of a bony labyrinth which includes the otic capsule, as the external boundary of the cochlea, and the modiolus which forms the central axis of the cochlea. The interior of the bony labyrinth spirals around the modiolus from base to apex. It partitions into three chambers: scala vestibuli, scala media and scala tympani. Scala vestibuli and scala tympani are filled with perilymph, a fluid high in sodium and low in potassium. Scala media is filled with endolymph, a fluid high in potassium and low in sodium. The scala tympani and scala vestibuli are connected at the apical tip of the cochlea through a narrow opening called helicotrema. The scala media is separated from the scala vestibuli by Reissner's membrane, and from the scala tympani by parts of the osseous spiral lamina and the basilar membrane (BM) (Dallos, 1996; Slepecky, 1996). The BM contributes to the stiffness and mass of the cochlear partition. von Békésy reported the BM to be approximately 32 mm long, with width varying from 0.5 mm at the cochlear apex to 0.1 mm at the cochlear base (von Békésy, 1960). The BM is thicker at the base of the cochlea than at its apex causing the BM's

stiffness to decrease progressively from base to apex (Slepecky, 1996; von Békésy, 1960).

The organ of Corti rests longitudinally along the basilar membrane. It contains both sensory and supporting cells. The organ of Corti consists of a single row of inner hair cells (IHCs), three rows of outer hair cells (OHCs), supporting cells, and the pillars forming the tunnel of Corti. In a cross section of the organ of Corti, the IHCs are stationed medially and the OHCs laterally to the tunnel pillars. There are approximately 12,000 OHCs and 3,500 IHCs in human ears (Ulehlova, Voldrich, & Janisch, 1987; Wright, Davis, Bredberg, Ulehlova, & Spencer, 1987). The organ of Corti is covered by a gelatinous and fibrous flap called the tectorial membrane. The tectorial membrane extends from the spiral limbus, passes over the inner and outer hair cells, and connects laterally to the Hensen's Cells (Steel, 1983). The longest of the three rows of the OHCs stereocilia are attached to the tectorial membrane (Steel, 1983).

The IHCs are flask shaped with a centrally placed nucleus (Lim, 1988). They form one continuous row along the length of the basilar membrane. The IHC stereocilia are arranged in a "U" shape. The basal end of the IHCs synapses directly with the VIIIth nerve afferent fibers. The IHCs are completely surrounded by support cells so that they do not touch the BM directly (Lim, 1988).

There are almost four times more OHCs than IHCs. The OHCs are long and cylindrical in shape with a more basally placed nucleus. The OHCs are supported by Deiter's cells located at the base of each hair cell (Slepecky, 1996). The OHCs stereocilia are arranged in a "W" pattern, and are longer and thinner than those of the IHCs. The OHCs vary in length with the shortest OHCs located at the base and longest at the apical end of the cochlea. The tips of the tallest OHCs cilia are

embedded in the tectorial membrane, whereas the other shorter cilia remain free-standing (Lim, 1988).

The cochlea is innervated by about 30,000 afferent sensory neuron fibers (Spoendlin, 1972). The afferent fibers cell bodies are located in the spiral ganglion in the modiolus on the inner wall of the spiral lamina. One branch of the cells projects to the hair cells and the other to the cochlear nucleus. Approximately 90-95% of the afferent nerve fibers entering the cochlea innervate the IHCs (Spoendlin, 1972). The nerves are unbranched and each fiber terminates on one IHC. The number of nerve fibers contacting each IHC vary with the highest neural density located at frequency regions which are functionally useful. Consequently, in humans, the middle region of the cochlea exhibits the greatest neural density (Slepecky, 1996). The remaining 5-10% of the afferent fibers innervate the OHCs with each fiber terminating at numerous OHS synapses (Dannhof & Bruns, 1993). Thus, one neuron fiber can receive information from 6 to 100 OHCs, most often from within the same row. The branching pattern for these fibers are not uniform across the cochlea. It differs by the row innervated and changes systematically from base to apex (Dannhof & Bruns, 1993).

Efferent fibers coming from the central nervous system enter the cochlea, reach the organ of Corti, and continue in the osseous spiral lamina along with the afferent fibers. The efferent fibers that innervate the IHC region are thin and unmyelinated. These fibers originate ipsilaterally or contralaterally from the lateral portion of the superior olivary complex and terminate on the afferent neural fibers of the IHCs (Slepecky, 1996). The OHC's efferent path consists of myelinated fibers originating from the medial portion of the superior olivary nucleus which become unmyelinated after passing through the habenula perforata to reach the OHC region (Spoendlin, 1979). Once

reaching the OHC region, ipsilaterally or contralaterally, the efferent fibers branch immediately with each branch ending at the base of an OHC. The difference in the efferent fibers connections to the IHCs and OHCs suggest that the efferent fibers act pre-synaptically on the OHCs and post-synaptically on the IHCs (Slepecky, 1996)(for a more-complete review of cochlear anatomy see Slepecky, 1996; Yates, 1995).

Frequency selectivity of the cochlea depends on the mechanics of the basilar membrane, the cochlear fluids, and the integrity of the hair cells. Vibrations of the stapes in the round widow causes displacement of the basilar membrane which results in a traveling wave (von Békésy, 1960). The wave's speed and properties are determined by the physical characteristics of the BM and organ of Corti, as well as by stimulus characteristics. Due to differences in BM stiffness, the traveling wave progresses from the cochlea base to its apex. As the traveling wave progresses, BM displacement increases until it effectively halts (i.e., point of maximal displacement) and than decays. The location of the wave's maximal displacement depends on stimulus frequency. Each location on the basilar membrane has a characteristic frequency which is largely determined by the BMs stiffness. High-frequency steady-state stimuli cause displacements only at the basal regions of the cochlea, while steady-state low-frequency stimuli cause displacements in all regions of the cochlea with the point of maximal displacement occurring in the apical region. As a result, low-frequency stimuli stimulate the whole cochlea, while high-frequency stimuli stimulate the basal region only (von Békésy, 1960). Thus, the traveling wave results in "place coding" for frequency along the basilar membrane. Greenwood reviewed cochlear coordinates in several species in relation to empirical frequency-position functions. The distance from the cochlear apex to the place of maximum displacement varied as a function of species and

stimulus frequency. For the human ear, maximum wave displacement occur at approximately 5, 15 and 21 mm away from the apex for 500-, 1000-, and 2000-Hz tonal stimuli (Greenwood, 1990).

von Békésy's traveling wave model was based on the passive response of the BM (von Békésy, 1960). Later research determined the traveling wave to be to be non-linear and more sharply tuned (Khanna & Leonard, 1982; Rhode & Greenberg, 1992; Robles, Ruggero, & Rich, 1986; Ruggero, 1992b; Sellick, Patuzzi, & Johnstone, 1982). Tuning curves obtained for the basilar membrane at low intensities demonstrate that it is sharply tuned with high degree of selectivity for both low- and high-frequencies especially at the lower intensities. At moderate to high intensities (above 60 dB SPL), the BM response becomes more broadly tuned and the tip of the tuning curves shifts toward the lower frequencies (Dallos, 1996; de Boer, 1996; Khanna & Leonard, 1982; Patuzzi, 1996; Robles, Ruggero, & Rich, 1986; Ruggero, 1992b). This occurs because as stimulus level increases, saturation of the BM occurs for tones at or near the characteristic frequency, while the response continues to grow linearly to frequencies below characteristic frequency.

Tuning curves of the BM are similar in characteristics to those obtained for the IHCs and for the auditory nerve (Khanna & Leonard, 1982; Robles et al., 1986; Ruggero, 1992b; Russell & Sellick, 1978). The IHC tuning curves are characterized by low-threshold, sharply-tuned tips at the stimulus CF, and a high-threshold, less steeply sloping low frequency tail (Russell & Sellick, 1978). Since the tuning curves of the IHCs correspond to the mechanical response of the BM, it appears that the tuning curves of the IHCs are derived from the tuning of the BM (Pickles, 1988, page 64). The intensity functions for the IHCs (and BM mechanics) for a CF tone show an approximately linear increase in

potential at the lower intensities followed by a nonlinear saturation at higher intensities. For non-CF frequencies, especially those below CF, the response grows linearly with intensity increase (Pickles, 1988, page 64; Russell & Sellick, 1978).

OHC tuning curves are similar to those obtained for the IHCs (Cody & Russell, 1987). The intensity functions for the OHCs are comparable to those of inner hair cells; however, the responses of the OHCs saturates more abruptly at high stimulus intensities. Damage to the OHCs causes losses in frequency tuning, sensitivity, and non-linearity (Dallos, 1996; Patuzzi, 1996).

In addition to mediating a frequency-to-place coding in the auditory system, the traveling wave results in a delay, because it takes time for the vibrations to move along the basilar membrane. The traveling wave delay is frequency dependent and consists of cochlear transport time and cochlear filter build-up time (Don, Ponton, Eggermont, & Kwong, 1998; John & Picton, 2000). Cochlear transport time delay is the time between the arrival of the acoustic energy at the oval window and the beginning of activity at the location of the basilar membrane where transduction occurs (Eggermont, 1979). High frequencies activate the BM close to the oval window and low frequencies activate the BM at some distance away from the oval window. The transport time delay is in the millisecond range increasing exponentially from 1 ms to approximately 5 ms with increase in distance along the basilar membrane (Ruggero, 1994). Thus, the cochlear transport time is the delay associated with the linear component of the BM filter. The transport time delay is independent of stimulus level because it is mostly reflects the passive response time of the BM filter (Hall, 1974). Eggermont estimated this "mechanical" time (in ms) as $f^{-0.5}$, where f is the characteristic frequency (in kHz)(Eggermont, 1979).

In addition to the being affected by transport time delay, the cochlear response time is effected by filter "build-up time". Filter build-up time is the additional time required for the acoustic energy to pass through the active filtering process of the hair cells that are sensitive to the frequencies of the sound in the stimulus (Don et al., 1998; John & Picton, 2000; Ruggero, 1994). The increase is due to the cochlear amplifier which sharpens the tuning of the BM and shifts the place of resonance for a particular stimulus frequency to a more apical location (Don et al., 1998). This increase in time is dependent on filter sharpness, stimulus intensity and the CF of the BM location (Don et al., 1998; John & Picton, 2000; Ruggero, 1994). Filter build-up time is usually measured by the number of stimulus cycles necessary to reach a maximum amplitude response. According to Don and colleagues, filter build-up time for 2000 Hz one-octave-wide region is approximately one cycle longer than the filter build-up time for a 500-Hz one-octave-wide region, but shorter by approximately 2.5 cycles than for 6000-Hz one-octave-wide region (Don et al., 1998).

The auditory nerve

The auditory nerve fibers provide a direct connection between the hair cells of the cochlea and the cochlear nucleus. Each human ear has about 30,000 VIIIth nerve fibers connecting the organ of Corti to form the auditory nerve (Pickles, 1988). The auditory nerve is organized tonotopically with fibers from the apical end of the cochlea (i.e., low-frequency fibers) positioned in the nerve center and fibers originating in the basal end (i.e., high-frequency fibers) located in the outer layers. The bulk of the auditory nerve consists of afferent neurons. There are two types of afferent cochlear neurons, type I which innervates a single IHC, and type II which innervate many OHCs. All

single neuron recordings have been obtained from type I afferent neuron (Palmer, 1995; Pickles, 1988; Ruggero, 1992b).

Single auditory nerve fibers discharge in an all-or-none manner. With no acoustic stimulation, the neurons discharge spontaneously at rates ranging from less than 1/s to as high as 140/s (Kiang, Watanabe, Thomas, & Clark, 1965). This spontaneous activity is related to the sensitivity of individual fibers and the release of neurotransmitters by the inner hair cells (Liberman, 1982). In response to an auditory stimulus, the fiber discharge rate increases above the cell's spontaneous rate (Kiang et al., 1965). Increasing the intensity level of the stimulus causes an increase in the rate at which the auditory nerve fibers discharges. Due to the characteristics of the basilar membrane, each fiber can be activated by a restricted range of frequencies. The firing patterns of the nerve fibers are studied by constructing post-stimulus time (PST) histograms, which represent the latency of firing from the initiation of the stimulus. To make such a histogram, the stimulus is presented many times, and the occurrence of each action potential is plotted as a function of the time it takes for the fiber to fire. PST histograms of the neural response to tonal stimuli show an initial burst of activity at stimulus onset, followed by a gradual decline, ending with a transient off-suppression of the spontaneous activity at the end of the stimulus (Kiang et al., 1965). Frequency-threshold curves (FTC) represent the changes in the discharge rate of the auditory neuron as a function of stimulus intensity across a frequency spectrum. The frequency at which the threshold of a single neuron is the lowest is the characteristic frequency (CF) of that particular neural fiber. The CF of a neuron provides information about the cochlear location of the hair cell which it innervates. Low-CF fibers innervate hair cells close to the apex of the cochlea and high-CF

fibers innervate hair cells close to the base (Liberman, 1982). The sharpness of the neural tuning is frequency dependent, with sharper tuned FTCs obtained for the high-frequency fibers. The FTCs obtained for fibers innervating the hair cells along the basilar membrane suggest an overlapping series of band-pass filters that form the auditory hearing range for that cochlea (Palmer, 1995). At threshold, a single tone will activate only a small group of fibers with CFs at the tone frequency. As the intensity of the stimulus increases there is an increase and an overlap in the FTCs and an upward spread of masking occurs (Palmer, 1995). Tuning curves of the auditory nerve fibers exhibit changes in shape across frequencies. Tuning curves below 1000 Hz are essentially symmetrical. Increases in frequency yield increasingly asymmetric tuning curves with steep high-frequency slopes and less steep low-frequency slopes. A distinction between two parts of the tuning curve occurs at the higher frequencies. The "tip" which is frequency-selective, and a "tail" which is broadly tuned stretching toward the low frequencies. Thus, due to the characteristics of the basilar membrane, single auditory nerve fibers act as bandpass filters with an asymmetric filter shape (Kiang, Sachs, & Peake, 1967).

The nerve fibers' firing rate changes with stimulus frequency. At frequencies above 5000 Hz, nerve fibers fire with equal probability in every part of the cycle. At lower frequencies, the neural discharges are time-locked to individual cycles of the tonal stimulus (Kiang et al., 1965). Although a nerve fiber may not discharge during every stimulus cycle, responses of the auditory nerve fibers to tones of frequency lower than about 5000 Hz are time-locked to the tonal stimuli and will fire in only one phase of the stimulus (Anderson, Rose, Hind, & Brugge, 1970; Hind, 1972; Hind, Anderson, Brugge, & Rose, 1967; Rose, Brugge, Anderson, & Hind, 1967).

When the rate of neural firing is measured as a function of intensity most nerve fibers continue to fire up to 20-50 dB above threshold when a rate plateau is reached (the dynamic range). At frequencies above the fiber's CF, some of the fibers reach saturation levels at even higher intensity levels (Evans & Palmer, 1980; Palmer, 1995). A small group of cochlear nerve fibers have rate-intensity functions that never reach a rate plateau regardless of intensity. A third group of cochlear nerve fibers is theorized to have a straight rate-intensity function (Ruggero, 1992a). Liberman identified three groups of auditory nerve fibers with respect to their spontaneous rates and thresholds (Liberman, 1978). High-spontaneous-rate fibers yielded the lowest thresholds, low-spontaneous-rate fibers yielded the highest thresholds, and medium-spontaneous-rate fibers yielding thresholds in between. Liberman indicates that the three types of fibers innervate each IHC (Liberman, 1982). The three groups are distinguished on the basis of size, morphology and where they attach to the IHC. Thus, type I auditory nerve fibers with similar CFs have a large range of thresholds and dynamic ranges (Ruggero, 1992a).

The responses of the auditory fibers have been examined by Kiang (1965) who obtained PST histograms for 18 auditory nerve fibers of a single cat in response to clicks (Kiang et al., 1965). The PST histograms demonstrate that the response of the neuron fiber to the click stimulus depends on the CF of the fiber. Fibers with low characteristic frequencies exhibit multiple peaks with interpeak intervals corresponding to the period of the fiber's characteristic frequency; and fibers with higher characteristic frequencies exhibiting a single peak only (Kiang et al., 1965).

The responses of the auditory fibers to broadband noise stimuli have been analyzed by correlating the discharge pattern of the nerve

fibers to spectrum of the noise stimulus (de Boer, 1980). Responses of the auditory neurons to noisebursts reflect the sum of responses to the tonal stimuli with each specific nerve fiber being evoked by wavelets of the noise stimulus within its frequency characteristic (de Boer & de Jongh, 1978; Evans, 1977). Due to filter characteristic of the basilar membrane, the cochlear/8th nerve output in response to noise is periodic. Thus, unlike the neural response evoked by the tonal stimuli, the noiseburst stimuli can excite neurons with multiple CFs simultaneously.

The auditory brainstem

The auditory brainstem pathways are a complex system which consist of numerous ipsilateral and contralateral alternate paths to the cerebral cortex. The auditory pathway starts with first order neurons exiting the cochlea and reaching the cochlear nuclei and ends with fourth-order neurons reaching the auditory cortex. Figure 2 presents a schematic illustration of the auditory system. As seen in figure 2, the auditory brainstem pathways are highly divergent and convergent. The pathway originates in the cochlea. From the cochlea, the fibers of the auditory nerve divide into three sections, which synapses at morphologically different divisions of the cochlear nuclei. Some of the cochlear nucleus neurons project directly to the inferior colliculus, whereas others project to different divisions of the superior olivary complex before reaching the inferior colliculus. Portion of the neurons of the cochlear nuclei ascend to higher nuclei ipsilaterally, while most cross over contralaterally. From the inferior colliculus, all branches proceed to the thalamus which is located at the medial geniculate nucleus. The medial geniculate is connected ipsilaterally to the primary auditory cortex, located at the temporal lobes. The auditory

brainstem is tonotopically organized at each level from the cochlear nuclei up to the inferior colliculus. In the next few sections, the tonotopical organization of the cochlear nucleus, superior olivary complex, lateral lemniscus, inferior colliculus, thalamus and the auditory cortex will be discussed.

Cochlear nucleus

The afferent auditory nerve fibers from the cochlea synapse with neurons in the cochlear nuclei in a complex manner. The cochlear nuclei contain a wide variety of cell types. The cochlear nuclei are typically divided into three regions based on the morphology of the cells they contain and the structures with which they connect. These divisions are the anterior ventral cochlear nucleus (AVCN), the posterior ventral cochlear nucleus (PVCN) and the dorsal cochlear nucleus (DCN). The discharge patterns of the neurons at the cochlear nuclei vary from firing constantly, firing at onset only, or firing for prolonged stimuli only. Each of the three divisions of the cochlear nucleus show different response properties and exhibit a unique tonotopic organization (Rhode & Greenberg, 1992; Rose, Galambos, & Hughes, 1960). In the AVCN division, the responses are similar to those of the auditory nerve fibers; in the DCN, the tuning curves are complex, influenced by bands of inhibition and nonmonotonic rate-intensity functions; in the PVCN division the tuning curves take an intermediate form (Pickles, 1988, p. 202; Rhode & Greenberg, 1992).

These three divisions are each associated with a specific pathway. The "Binaural Pathway" begins at the AVCN. Through the binaural pathway, the AVCN provides direct and indirect (via the medial nucleus of the trapezoid body) input to the Superior Olivary Complex (SOC). This pathway is likely to be involved in spatial localization and other tasks

requiring convergence of information from both ears (Rhode & Greenberg, 1992). The PVCN is connected to the periolivary nuclei continuing to the inferior colliculus via the lateral lemniscus. The function of this pathway is not well known. "The Monaural Contralateral Pathway" begins at the DCN. This pathway caries information from the contralateral ear only. This pathway is unique in that it carries a substantial amount of descending input as well (Pickles, 1988; Rhode & Greenberg, 1992). Cells in the DCN have complex frequency intensity tuning curves. The firing rate for each DCN vary greatly in response to a low intensity sound at one frequency and then fall below the spontaneous rate with only a small change in stimulus frequency or intensity.

Functionally, the cochlear nucleus acts as a switchboard distributing auditory information to several different areas in the auditory pathway. It also does a substantial amount of processing of both time and frequency information (Palmer, 1995; Pickles, 1988; Rhode & Greenberg, 1992).

Superior olivary complex

The superior olivary complex (SOC) is the first place in the auditory pathway where neurons receive input from both ears. It is essential in the ability to localize the source of a sound. The SOC processes information about interaural delays and stimulus level. It also acts as a crossover site for spatially oriented auditory information. Studies in which the SOC was selectively damaged have shown that it is essential for sound localization. The auditory SOC is composed of the lateral superior olivary nuclei (LSO), medial superior olivary complex (MSO), and the medial nucleus of the trapezoid body (MTB).

The lateral superior olivary (LSO), is disproportionally innervated by high-frequency neurons (Palmer, 1995; Rhode & Greenberg, 1992). The LSO nucleus receives both ipsilateral and contralateral input from the cochlear nucleus. The neurons in LSO are sensitive to intensity differences between sounds in the ipsilateral and the contralateral ears. They can detect differences as small as 10 dB SPL. Almost all cells of the LSO receive excitatory input from the ipsilateral AVCN and inhibitory input from the contralateral AVCN via the MTB. Thus, the initial processing of interaural level differences takes place at the LSO, with the LSO neurons excited to sounds which are louder in the ipsilateral ear and inhibited by sounds which are louder in the contralateral ear (Palmer, 1995; Rhode & Greenberg, 1992).

The medial superior olivary neurons respond to both binaural and monaural stimuli. The medial superior olivary complex receive input via two different paths. The first input is from the ipsilateral AVCN, and the other input is from the contralateral AVCN via the trapezoid body. The medial superior olivary nucleus is predominantly responsive to low-frequency stimuli (Irvine, 1992; Pickles, 1988). In addition to a characteristic frequency, neurons in the MSO respond best to a specific delay between ipsilateral and contralateral stimulus called "characteristic delay". The MSO neurons are able to detect delay times between ipsilateral and contralateral stimulus by determining the differences in the phase inputs arriving from both ears. This interaural phase difference (IPD) is then transformed into changes in the neural firing rate of the MSO neurons (Palmer, 1995).

The MTB is responsive exclusively to sound presented to the ear contralateral to the nucleus itself. The MTB receives input mainly from the contralateral AVCN. The MTB than sends the input via a short axon to the lateral superior olivary complex to form an inhibitory response.

Like the LSO, the MTB are more responsive to high frequencies (Irvine, 1992; Pickles, 1988).

Lateral lemniscus

The Lateral lemniscus (LL) is primarily a tract of axons ascending from the SOC to the inferior colliculus. Before it reaches the inferior colliculus it passes through a nucleus of cell bodies referred to as the nucleus of the lateral lemniscus (NLL). The NLL contains neurons which are sensitive to changes in both timing and stimulus intensity. Morphologically, the NLL contains two regions, the ventral and dorsal regions. The ventral nucleus of the LL receives an input from the contralateral CN and projects ipsilaterally to the inferior colliculus, whereas the dorsal nucleus of the LL receives bilateral input and projects bilaterally to the inferior colliculus. Only some of the axons traveling in the LL actually synapse there. Most continue directly to the inferior colliculus, medial geniculate body, or other more rostral regions of the brain (Pickles, 1988).

Inferior colliculus

The inferior colliculus (IC) receives afferent neurons from earlier nuclei contralaterally from CN and SOC and ipsilaterally from CN, SOC and NLL. The inferior colliculus contains three morphologically distinct nuclei. The central nucleus, the dorsal nucleus and the pericentral nucleus. The central nucleus is tonotopically organized with cells arranged in an organized frequency bands across the nucleus (Irvine, 1992). The central and lateral nucleus of the IC receive mostly ascending information from the brainstem. The dorsal cortex receives both ascending information from the brainstem and descending information from the auditory cortex. The IC appears to be an

integrative station, as well as a switchboard. It is responsive to interaural delay and amplitude differences. Changes in the spectrum of the stimulus such as amplitude and frequency appear to be processed here (Irvine, 1992; Pickles, 1988). Tuning curves in the IC are more complex than those found in lower levels of the brainstem. The IC neurons vary their responses according to stimulus intensity, frequency, phase and bandwidth (Palmer, 1995). The IC is able to process and detect changes in amplitude modulation of a pure tones. At the IC level, the processing of binaural cues and spatial localization continues (Irvine, 1992; Palmer, 1995; Pickles, 1988).

The thalamus

The thalamus is the last relay site on the way to the auditory cortex. It has been divided into a large number of nuclei. The primary nucleus involved in the auditory pathway is the medial geniculate body (MGB). The afferent neurons from the IC project ipsilaterally and contralaterally into the MGB. The MGB includes both tonotopically and non-tonotopically organized regions. Both types of neurons differ in their frequency selectivity, with the tonotopic cells tuned to a narrower frequency range than the non-tonotopic cells (Clarey, Barone, & Imig, 1992). The MGB consists of the ventral, medial and dorsal regions. The ventral MGB is primarily responsible for relaying frequency, intensity and binaural information to the cortex. It is tonotopically organized. The medial MGB is thought to be primarily responsible for detection of the relative intensity and duration of the stimulus. It is not known wether the medial MGB is tonotopically organized. The dorsal MGB is not tonotopically organized and its function in auditory processing is unknown (Irvine, 1992; Palmer, 1995;

Pickles, 1988). From the MGB, the ascending auditory pathways continue to the auditory cortex.

The auditory cortex

The Auditory Cortex is located in the temporal lobe below the lateral fissure. Damage to this region of the cortex typically results in an inability to hear the sound frequency represented by the damaged neurons. The auditory cortex is divided into the primary and secondary auditory cortex. The primary auditory cortex is tonotopically organized with the anterior region responding to higher frequencies, and the posterior regions responding to lower frequencies. The primary auditory cortex is surrounded by the secondary auditory cortex, which is subdivided into six distinct areas. Unlike the primary auditory cortex, the degree of tonotopicity of the secondary auditory cortex is poor, with cells in the same region having a wide range of characteristic frequencies (Clarey, Barone, & Imig, 1992; Pickles, 1988). The primary auditory cortex receives its input from the ventral medial geniculate body. The secondary auditory cortex receives its input mainly from the other divisions of the medial geniculate. The neurons in the primary cortex are differentiated in their response to the auditory stimuli. They vary in their tuning curves, and response times (Clarey, Barone, & Imig, 1992; Pickles, 1988). It is hypothesized that the auditory cortex is responsible for the analysis of complex stimuli, the localization of sound, the ability of selective attention, the inhibition of inappropriate motor responses, the identification of stimuli on an absolute basis, the discrimination of auditory temporal patterns and is necessary for difficult auditory tasks (Pickles, 1988, p. 233).

Heil and colleagues studied the responses of single auditory cortical neurons of anesthetized cats to tone onsets with parametric

variation of level, rise time, and frequency. Their results indicate that the neural response to stimulus onset is determined by a dynamic interaction of stimulus rise time, and slope (rapidity of signal change), and not by changes in sound pressure levels (SPL) alone (Heil, 1997a, b; Heil & Irving, 1998). Biermann and Heil demonstrated the same relationship between stimulus rise time and slope, and onset responses for N100 and P50 evoked magnetic fields in humans to responses of signal auditory cortical neurons of anesthetized cats (Biermann and Heil, 2000). They suggested that the transmission delay as a function of frequency observed in the single-neuron data, and in the N100 and P50 are consistent with the frequency-dependent delays which exist in the cochlea (Heil, 1997a,b; Biermann and Heil, 2000). In addition, Biermann and Heil reject any "fixed amplitude" model such as Brinkmann and Scherg's "virtual trigger time" concept to explain the stability of the ABR amplitude for responses evoked by rise times up to 5 ms (Brinkmann & Scherg, 1979). They showed that the stimulus amplitudes at which the N100 or P50 peak amplitudes are triggered, are not constant even for a given frequency, but vary systematically with rise time, level, and rise function (Biermann and Heil, 2000). In the following thesis (Chapter 2, 3) stimulus slope remained constant while rise time, level and frequency varied thus enabling us to determine the effective duration of the stimulus for the ABR and MLR without the confounding effects of slope.

C. The origins of the ABR and MLR

The ABR and MLR are the summated activity of many neurons, generated from both action potentials and post-synaptic potentials (Buchwald, 1983; Picton, 1990). The action potentials are triggered by a suprathreshold depolarization of the axonal membrane. The action potential propagates along the axon to the axon terminals. These are

all-or-nothing responses. When a response is generated, a depolarization occurs causing conductance changes across the neural membranes. The biophysical profile of the axon determines the conduction velocity, length of the depolarized segment, and the time it will take before an additional firing can occur (Vaughan & Arezzo, 1988). The action potential lasts 1-2 msec and is followed by an refractory period during which a second action potential cannot be produced. By contrast to the propagated action potentials, postsynaptic excitation is stationary, determined by the location of the active synaptic sites of the postsynaptic neurons. This action of excitation synapses distributed on the dendrites and body of a neuron produces inward current flow, and a slow excitatory postsynaptic potential results. Legatt and colleagues suggest that the slow negativity (SN) reflects predominantly postsynaptic potentials which make contributions to the ABR/MLR waveforms. They conclude that the ABR's phasic peaks (waves I through VII) originate in action potentials, whereas the SN reflects postsynaptic potentials within the brain-stem auditory nuclei (Legatt, Arezzo, & Vaughan, 1988).

The spatial and temporal characteristics of the current flow for individual neurons play a role in the generation of the evoked responses. The evoked responses depend on the temporal synchronization of the neural activity. The responses are optimally generated when the action and/or postsynaptic potentials are activated simultaneously from many neurons within a specific anatomical region. The ABR and MLR are further dependent on the number of cells that are activated in response to the acoustic stimuli, as well as by the geometrical organization of the active membranes. The far-field evoked potentials (such as the ABR and MLR) are best detected when parallel neurons organized in an open electrical field are activated. The fourth factor determining the

evoked potential response is the impedance of the volume conductor between the generator and the recording electrode with the size of the voltage fields recorded vary inversely with its impedance (Picton, 1990).

The ABR and MLR provide far-field measures of the summed activity of numerous generators. Due to the complexity of the ascending auditory pathway, which results in parallel processing of auditory information and almost simultaneous contributions from the different nuclei, it is difficult to identify the generators via far-field recordings only. Thus, the identification of these generators are derived using different methodologies such as surface mapping, intracranial recordings of subcortical auditory pathways, recordings obtained from animals with surgically induced known lesions, and by studying the effects of pathological lesions in humans (e.g., Achor & Starr, 1980; Durrant, Martin, Hirsh, & Schwegler, 1994; Elberling, 1976; Hashimoto, 1982; Hashimoto, 1984; Hashimoto, Ishiyama, Yoshimoto, & Nemoto, 1981; Legatt, Arezzo, & Vaughan, 1988; Martin, Pratt, & Schwegler, 1995). Review of these studies indicate that the ABR and MLR waveforms, except for wave I, have multiple generators, reflecting the complex neuroanatomy of the auditory system. As there are multiple pathways and routes to reach the auditory cortex, the ABR and MLR may represent only part of the system. Furthermore, in addition to their differing anatomical location, the ABR and MLR may represent different functional parts of the system.

The origins of the ABR

Wave I of the ABR has been identified as representing the compound action potential (AP) of the eighth nerve. Its origin is suggested to be in the distal portion of the eighth nerve where the nerve fibers leave the cochlea and enter the auditory canal. These findings are

supported by direct recordings of the eighth nerve potential (Møller & Jannetta, 1981; Møller & Jannetta, 1983), by spatiotemporal dipole models (Scherg & von Cramon, 1985) and by clinical findings in patients with retrocochlear pathology (Starr & Achor, 1975).

The origin of Wave II has been controversial (Legatt et al., 1988; Martin et al., 1995). Initially, some researches suggested that it is generated by the cochlear nucleus (e.g., Hashimoto et al., 1981; Jewett & Williston, 1971). Others suggested that it is generated by the proximal eighth nerve as it enters the brainstem (Elberling, 1976; Møller & Jannetta, 1981). Currently, Martin and colleagues suggest that wave II is generated as a result of physical changes that occur in the posterior fossa (Martin et al., 1995). They suggest that the negativity prior to wave II is generated by the passage of the auditory nerve from the internal auditory canal to the cerebral spinal fluid, and that wave II is generated as the nerve passes from the cerebral spinal fluid to the brainstem (Martin et al., 1995). An auditory nerve origin is also supported by the relationship between the latency of waves I and II and by the presence of a reliable wave II in brain death (Legatt et al., 1988).

In humans, wave III is believed to be generated by the caudal portion of the auditory pons, with possible contributions from the cochlear nuclei and superior olivary complex (Legatt et al., 1988; Moore, 1987). Patients with clinical lesions in this region often have a normal wave II but abnormal wave III. When an ABR of a patient with an asymmetrical lesion exhibits an abnormal wave III in the ear ipsilateral to the lesion, it suggests that the legion is located at or below where the ascending auditory pathways cross (Legatt et al., 1988). Human intracranial recordings demonstrate a positive wave over the dorsal pons coinciding with the scalp-recorded wave III (Hashimoto et

al., 1981). Thus, it is suggested that wave III reflects axonal activity in the trapezoid body and the outflow of activity from the SOC (Legatt et al., 1988; Moore, 1987).

The generators of Wave IV and wave V are believed to be in the same proximity because they are usually either both affected or both unaffected by brainstem lesions (Legatt et al., 1988). Waves IV and V are the first waves that are abnormal or absent in patients with brainstem tumors. Intracranial recordings suggest that wave IV is generated by dorsal pons (Hashimoto et al., 1981). Thus, it is believed that wave IV is generated predominantly by the ascending auditory fibers within the pons probably at the lateral lemniscus (Legatt et al., 1988). Wave V is believed to have multiple generators at the midbrain level and upper pons, predominantly from the lateral lemniscus and inferior colliculus regions (Durrant et al., 1994; Hashimoto, 1982; Legatt et al., 1988; Moore, 1987). Intracranial recordings suggest that the negative wave following ABR (which may also be MLR wave Na) is generated by the inferior colliculus (Hashimoto et al., 1981; Legatt et al., 1988).

The origins of the MLR

The origin of the MLR is believed to be in the auditory cortex with a possibility of contributions from subcortical levels (e.g., Hashimoto, 1982; Scherg & von Cramon, 1986). Wave Pa is believed to be generated, at least in part, by the posterior temporal lobe, specifically the auditory cortex (Scherg & von Cramon, 1986). Case studies of patients with cortical lesions suggest that Wave Pa origins are the temporal lobe and/or the thalamus (Kileny, Paccioretti, & Wilson, 1987; Kraus, Özdamar, Hier, & Stein, 1982; Scherg & von Cramon, 1986; Woods, Clayworth, Knight, Simpson, & Naeser, 1987).

D. Acoustics of brief stimuli

The ABR and MLR are elicited by stimuli of relatively short duration (typically 0.1-10 ms). This shorter stimulus produces more synchronized firing of the auditory neurons which evokes the ABR and MLR (Harris & Dallos, 1979; Kiang et al., 1965; Smith, 1979). The three types of stimuli mostly used in obtaining ABR and MLR are clicks, brief tones, and noise stimuli.

The spectrum of the brief tone depends on the duration of its rise/fall, plateau time, temporal shaping (linear *versus* nonlinear), and the type of transducer employed (Burkard, 1984; Durrant, 1983; Laukli, 1983a; Stapells & Picton, 1981). A brief tone contains its maximal energy at its nominal frequency, with side lobes of energy at higher and lower frequencies (Burkard, 1984; Durrant, 1983; Harris, 1978). A systematic relationship occurs between the duration, frequency and intensity of the stimulus and the stimulus frequency spectrum (Burkard, 1984; Davis, 1976; Durrant, 1983). The total duration of the stimulus determines the width of the main lobes and the amplitudes of the sidelobes in relation to the main lobes (Pfeiffer, 1974). The shorter the rise time, the more "spectral splatter" it contains. Spectral splatter is acoustic energy at frequencies away from the nominal frequency of the stimulus (Durrant, 1983). Increasing the rise time decreases the spectral splatter of the stimulus and thus increases the frequency specificity of the stimulus (Davis, 1976; Durrant, 1983). Figure 3 displays the electrical spectra of 500- and 2000-Hz tonal stimuli and of noisebursts. For the tonal stimuli, the shorter the rise time, the more energy is splattered above and below the main lobe of the spectrum. With increases in rise time, relatively more energy is concentrated around the center of the nominal frequency of the stimulus. Comparison of the spectra of high- and low-frequency tones at equal rise

times (for example at 2 ms, figure 3) reveals less spectral splatter for the higher frequency stimulus. High- and low-frequency stimuli with equal number of cycles, however, have similar frequency spectra (Burkard, 1984; Davis, 1976; Durrant, 1983).

Clicks and noisebursts have a broad frequency spectrum with approximately equal energy across frequency regardless of stimulus envelope. The flatness and the upper frequency cutoff of the spectrum are determined by the transfer function of the transducer for both stimuli, as well as by stimulus duration for the clicks (Pfeiffer, 1974; Stapells, Picton, & Durieux-Smith, 1994). Figure 3 displays the electrical spectra of the noiseburst stimuli with rise times ranging from 1 to 8 ms. Unlike the tonal spectra, the electrical noise spectra are similar across rise times, containing nearly equal energy across frequencies.

E. Review of the Literature on ABR and MLR

E1. Frequency Specificity and the ABR and MLR

The term "frequency specificity" is used to indicate the degree to which a measurement at a given frequency is free of contributions from surrounding frequencies (Stapells et al., 1994; Stapells, Picton, Pérez-Abalo, Read, & Smith, 1985). The term frequency specificity is usually used in relation to the evaluation of auditory thresholds. When frequency specificity is poor, the threshold at the tested frequency may be inaccurate due to responses mediated by other frequencies. A related term is "place specificity", which refers specifically to the portion of the basilar membrane contributing to the response (Stapells et al., 1994; Stapells et al., 1985).

Masking techniques

Several masking techniques have been used to improve and/or investigate the frequency and place specificity of the ABR and MLR to different stimuli. The masking techniques used include tone-on-tone masking, the high-pass/derived response (HP/DR) technique, notched-noise masking and broadband noise masking.

In this thesis, the derived response technique is used to obtain masked responses, as it provides results with the best frequency- and place- specificity (Stapells et al., 1994; Stapells et al., 1985). The following is a review of the different masking techniques.

Tone-on-tone masking

Pure-tone masking has been used to investigate the frequency specificity of the ABR to brief tones (Folsom, 1984; Folsom & Wynne, 1987; Klein, 1983b; Klein & Mills, 1981a; Klein & Mills, 1981b; Mackersie et al., 1993; Wu & Stapells, 1994). In this paradigm, the effect of pure-tone maskers on the evoked potentials to the probe tones are investigated. Klein used a simultaneous pure-tone masking paradigm to investigate the frequency specificity of the slow-wave component of the ABR (Klein, 1983b). Results indicated that the slow-wave component of the ABR for stimulus frequencies above 250-Hz are frequency specific up to at least 77 dB ppe SPL (Klein, 1983b). However, Klein used a 40 per second presentation rate which might have generated the "40-Hz response", which could have interfered with the ABR-slow wave response. Stapells and colleagues demonstrated good frequency specificity for the ABR for low-intensity 500- and 2000-Hz brief-tone stimuli presented at a rate of 10/s (Mackersie et al., 1993; Wu & Stapells, 1994). Folsom and colleagues investigated the frequency specificity of the ABR to filtered clicks at 1000-, 4000- and 8000-Hz at 75- and 95 dB ppe SPL (Folsom,

1984; Folsom & Wynne, 1987). Good frequency specificity was demonstrated at 75 dB ppe SPL (Folsom, 1984; Folsom & Wynne, 1987). However, at 95 dB ppe SPL, the frequency specificity of the response decreases due to the spread of excitation to higher-frequency regions of the cochlea (Folsom, 1984).

High pass noise/derived response technique

High-pass noise was initially used for auditory evoked potentials by Teas, Eldridge, and Davis in 1962 (Teas, Eldridge, & Davis, 1962). Using this technique, the ABR/MLR is elicited by either a click or a tone presented simultaneously with a high-pass noise. The high-pass noise prevents contributions from frequency fibers above the high-pass cutoff frequency from contributing to the response (Beattie & Kennedy, 1992; Burkard & Hecox, 1983; Jacobson, 1983; Kileny, 1981; Laukli, 1983b; Laukli, Fjermedal, & Mair, 1988). With the use of high-pass noise masking, the latencies of ABR evoked by low-frequency tones at moderate to high intensities are longer in comparison to the nonmasked response (e.g., Beattie & Kennedy, 1992; Burkard & Hecox, 1983; Jacobson, 1983; Kileny, 1981; Laukli, 1983b; Laukli et al., 1988). The change in latency is due to removal of the high-frequency contributions to the response.

One technique which eliminates the lack of masking below the nominal test frequency is the high-pass noise/derived response (HP/DR) technique (Stapells et al., 1994; Stapells et al., 1985). The derived response technique was developed by Teas, Eldridge and Davis in 1962 (Teas et al., 1962). The HP/DR technique provides measures of the narrowband regions of the cochlea contributing to the nonmasked response (Don & Eggermont, 1978; Parker & Thornton, 1978a; Parker & Thornton, 1978b). In the HP/DR technique, the response to a tone in high-pass

noise with one cutoff frequency is subtracted from the response recorded in high-pass noise with a higher cutoff frequency. The result is a "derived response" to the frequencies approximately between the two cutoff frequencies. The technique is based on the assumption that the masking noise does not affect responses below the high-pass cutoff frequency due to the steep high-frequency edge of the traveling wave in the cochlea (Stapells et al., 1994; Stapells et al., 1985). The center frequency (CF) of the derived response depends on the slope of the filter employed and the filter cutoff frequencies (Don & Eggermont, 1978; Don, Eggermont, & Brackmann, 1979). The calculated CF for a high-pass noise masking with a 96 dB/Octave is close to the cutoff of the lower high-pass frequency (Don et al., 1979; Nousak & Stapells,1992). Stapells and So (Stapells & So, 1999) demonstrated that, for wave V, the center frequency of the derived bands are close to the lower high-pass (96 dB/Octave) cutoff frequency, with mean CFs of 608-, 1068-, and 1849-Hz obtained for the 500-, 1000-, and 2000-Hz one-octave derived bands, respectively.

The basic assumptions of the HP/DR technique are as follows: (i) the noise in the high-frequency regions can mask responses of high-frequency fibers without affecting fibers with characteristic frequencies lower than the cutoff frequency, so that the response evoked by the unmasked region of the cochlea is independent of the masking noise; (ii) the derived response represents cochlear activity limited to the frequency regions approximately between the two high-pass cutoff frequencies, with recent data suggesting that the center frequency of the derived bands is at the frequency of the lower of the two cutoff frequencies (Stapells & So, 1999); and (iii) the derived responses for all frequency regions add together linearly (i.e., without any interaction) to give a similar amplitude and latency as the non-masked

response (Don et al., 1979; Eggermont & Don, 1982; Stapells et al., 1994).

Several studies have demonstrated the validity of these assumptions (Don et al., 1979; Elberling, 1974; Evans & Elberling, 1982; Parker & Thornton, 1978a; Parker & Thornton, 1978b; Parker & Thornton, 1978c; Stapells & So, 1999). Parker and Thornton compared response amplitude and latency of derived and non-derived responses in order to determine whether each represents response contributions from the same locations along the cochlear partition. The summed derived responses were then compared to the non-derived response. Parker and Thornton's results indicate that the non-masked and the summed derived response waveforms are very similar in both amplitude and latency characteristics, confirming the validity of the technique (Parker & Thornton, 1978a).

In a subsequent study, Parker and Thornton studied the effect of masking within the derived band by simulating a hearing loss in normal-hearing subjects by introducing masking noise which matched the intensity and frequency of the derived band. Results indicate that narrowband masking within the derived band significantly reduces the derived amplitude within the band while leaving the amplitude and latency measures from adjacent bands unaffected (Parker & Thornton, 1978c). Stapells and So determined the CFs and bandwidths of derived-band ABRs through the use of narrowband noise maskers. Clicks and high-pass noise maskers were mixed with 1/3-octave-wide of narrowband noise. Derived-band ABRs for particular narrowband noise conditions were obtained by subtracting the responses recorded in one high-pass noise and narrowband noise from the response recorded in high-pass noise with a cutoff one-octave higher and the same narrowband noise. Results indicate that the derived bands are centered close to the lower high-

pass cutoff frequency, validating the assumption that the derived response represents cochlear activity limited to the frequency regions between the two high-pass cutoff frequencies (Stapells & So, 1999).

Evans and Elberling compared direct cochlear-nerve fiber recordings in cats to the obtained summed derived responses (Evans & Elberling, 1982). Their results indicate that the HP/DR technique yields cochlear-fiber activity which is limited to the regions between the response cutoff frequencies validating the HP/DR technique for obtaining place-specific cochlear responses. Based on comparisons of results obtained for humans and cats, the authors concluded the HP/DR technique to be valid for testing frequencies between 500 and 16,000 Hz in humans (Evans & Elberling, 1982).

The HP/DR technique has been further validated by successfully evaluating audiometric thresholds of hearing-impaired subjects having different hearing loss configurations (Don et al., 1979; Elberling, 1974). A study by Stapells, however, showed that the technique overestimated the hearing-impaired thresholds at 500 Hz (Stapells, 1984).

The advantages of using the derived response technique are as follows: (i) it provides place-specific responses, and (ii) it provides the ability to evaluate specific regions of the cochlea at various intensity levels without being affected by the spread of energy of the stimuli. The disadvantages of using the technique are: (i) the subtraction procedure decreases the signal-to-noise ratio of the response, (ii) the high levels of acoustic noise which are required to mask the evoked potential may cause a temporary threshold shift (Stapells et al., 1994), and (iii) considerable time is required for data acquisition and analysis.

Another technique for obtaining derived responses uses tonal masking (Pantev & Pantev, 1982; Stapells et al., 1985). In this technique the ABR is evoked simultaneously by clicks and a pure tone stimuli. Derived responses are obtained by subtracting these responses from responses obtained by clicks alone. The technique is based on the assumption that the pure-tone activates the neurons responding specifically to that frequency and thus prevents them from responding to the broadband click. Subtraction of the responses yields a derived response presumably equivalent to the response to the tone. Using this technique, derived responses with appropriate wave V latencies are seen when the intensity of the pure tone is 0-20 dB greater than the ntensity of the click (Pantev & Pantev, 1982). When the intensity of the pure tone is greater than 20 dB above the intensity of the click, spread of masking occurs which affects the response (Pantev & Pantev, 1982; Stapells et al., 1985).

Notched noise

In the notched noise technique, either clicks or tonal stimuli are presented simultaneously with broadband noise, from which a band of frequencies has been rejected. The purpose of notched noise masking is to restrict the responsive region of the cochlea to the frequencies within the notch only (Stapells et al., 1994). The notched noise technique provides frequency-specific responses directly without the need for subtractions.

Several researchers have recorded responses to clicks in notched noise (e.g., Abdala & Folsom, 1995; Beattie, Franzone, & Theilen, 1992; Folsom & Wynne, 1986; Laukli, 1983b; Pratt & Bleich, 1982; Stapells et al., 1985; Starr & Don, 1988; Van Zanten & Brocaar, 1984). With the use of clicks in notched noise, frequency-specific responses can be

obtained. However, due to the high amount of masking noise needed to mask the evoked ABR potential to clicks, and the spread of masking into the notch, the amplitude of the evoked potential is small and difficult to identify (Stapells et al., 1994). In addition, ABR thresholds obtained with clicks in notched noise do not correlate well with pure-tone behavioral thresholds in patients with hearing loss (Pratt, Ben-Yitzhak, & Attias, 1984; Stapells et al., 1985).

In contrast, the use of tones in notched noise is a better approach for obtaining frequency-specific responses (e.g., Beattie & Boyd, 1985; Beattie & Kennedy, 1992; Munnerley, Greville, Purdy, & Keith, 1991; Picton, Ouellette, Hamel, & Smith, 1979; Purdy, Houghton, & Keith, 1989; Stapells, Gravel, & Martin, 1995; Stapells & Picton, 1981; Stapells, Picton, Durieux-Smith, Edwards, & Moran, 1990), due to the lower noise intensities required to mask responses from frequencies other than the tone frequency (Picton et al., 1979; Stapells et al., 1990). Thresholds obtained for tones in notched noise are more accurate than those obtained by clicks in notched noise because tones provide greater concentration of stimulus energy at the nominal frequency, resulting in larger amplitudes and more recognizable responses (Picton et al., 1979; Purdy et al., 1989; Stapells & Picton, 1981; Stapells et al., 1994; Stapells et al., 1990). As with the click in notched noise technique, the disadvantage of the technique is the spread of masking into the notch, especially from the low-frequency edge. Despite this upward spread of masking, reliable estimates (within 10 to 20 dB) of the auditory sensitivity at 500- , 1000-, 2000-, and 4000-Hz were obtained for normal and hearing-impaired adults (Munnerley et al., 1991; Purdy et al., 1989; Stapells et al., 1990), and infants and young children (Stapells et al., 1995).

Broadband noise masking

Broadband noise masking is a technique suggested to mask the energy spread in brief tones (Beattie & Boyd, 1985; Picton et al., 1979; Stapells, 1984; Stapells et al., 1994; Stapells et al., 1985). In this technique, the tonal stimuli are presented simultaneously with the broadband noise. The broadband noise masks the side lobes of the tone acoustic spectrum, thus significantly reducing responses to frequencies away from the nominal frequency of the tonal stimulus tested (Beattie & Boyd, 1985; Picton et al., 1979; Stapells, 1984). Broadband noise masking provides similar frequency specificity to responses obtained with notched noise masking. Its response amplitude, however, is approximately 33% lower than those obtained with the notched noise technique, due to the partial masking of energy at the tone's nominal frequency (Picton et al., 1979; Stapells, 1984; Stapells et al., 1994; Stapells et al., 1985). This lower amplitude makes waveform identification difficult, especially at or close to threshold (Stapells et al., 1994).

Frequency specificity and threshold estimation

The frequency and place specificity of the ABR and MLR to click and tonal stimuli can be demonstrated by (i) comparison of evoked potential thresholds with behavioral audiometric thresholds of hearing-impaired subjects having significantly different audiometric thresholds across frequencies; and by (ii) comparison of responses evoked without masking to responses evoked with masking, such as pure-tone, notched noise, and high-pass/derived response masking.

Threshold estimation and frequency specificity using the ABR

The ABR to clicks cannot provide accurate information about hearing threshold levels at different frequencies due to the click's broad frequency content (Eggermont, 1982; Hyde, 1985; Stapells, 1989; Stapells et al., 1994; Stapells et al., 1985). By comparing click-evoked ABR thresholds to behavioral audiometric thresholds, several researchers indicate that the click-ABR thresholds correlate best with hearing sensitivity in the 2000-4000 Hz region for normal and hearing impaired subjects (Coats & Martin, 1977; Gorga, Reiland, & Beauchaine, 1985; Jerger & Mauldin, 1978; van den Drift, Brocaar, & van Zanten, 1978; Yamada, Kodera, & Yagi, 1979; Yamada, Yagi, Yamane, & Suzuki, 1975). However, these results reflect averages across a large group of patients, and can not be used as a reliable estimate of the 2000-4000 Hz thresholds with individual patients (Stapells, 1989; Stapells & Oates, 1997; Stapells et al., 1994). Stapells and colleagues compared the nonmasked click-ABR thresholds and the average of the pure-tone behavioral thresholds at 2000 and 4000 Hz for 161 ears with sensorineural hearing loss (Stapells et al., 1994). No direct relationship is seen between increases in high-frequency hearing loss and elevation in click-ABR thresholds. Thus, with the use of clicks, hearing loss restricted to a particular frequency region will be missed or underestimated due to response contributions originating from regions of the basilar membrane with better hearing sensitivity (Stapells, 1989; Stapells & Oates, 1997; Stapells et al., 1994). Consequently, recorded at threshold, ABR evoked by clicks provides a rough estimate of the patient's best hearing threshold.

Many researchers (e.g., Davis & Hirsh, 1976; Davis & Hirsh, 1979; Gorga, Beauchaine, Reiland, Worthington, & Javel, 1984; Gorga, Kaminski, Beauchaine, & Jesteadt, 1988; Hayes & Jerger, 1982; Hyde, 1985; Klein, 1983a; Kodera, Yamane, Yamada, & Suzuki, 1977b; Laukli et al., 1988;

Munnerley et al., 1991; Picton & Durieux-Smith, 1988; Stapells, 1989; Stapells et al., 1995; Stapells & Picton, 1981; Suzuki, Hirai, & Horiuchi, 1977; Suzuki & Horiuchi, 1981) recorded responses to tonal stimuli in order to obtain frequency-specific threshold responses. Historically, some controversy existed concerning the tone-evoked ABR especially in response to low-frequency tones (Davis & Hirsh, 1976; Gorga et al., 1988; Laukli, 1983a; Laukli et al., 1988; Laukli & Mair, 1986; Scherg & Volk, 1983; Sohmer & Kinarti, 1984; Weber, 1987). In 1976, Davis and Hirsh (Davis & Hirsh, 1976), suggested that the ABR to 500 Hz was difficult to identify because it was mediated by basal regions of the cochlea. Subsequent research has demonstrated that the ABR recorded using 10-40 Hz high-pass EEG filters and appropriate analysis and stimulus parameters will yield 500-Hz ABR thresholds within 10 to 20 dB of behavioral thresholds (e.g., Beattie & Kennedy, 1992; Davis & Hirsh, 1979; Gorga et al., 1988; Jacobson, 1983; Kavanagh, Harker, & Tyler, 1984; Kileny, 1981; Klein, 1983a; Klein, 1983b; Kodera et al., 1977b; Munnerley et al., 1991; Picton et al., 1979; Purdy et al., 1989; Stapells, 1989; Stapells & Picton, 1981; Stapells et al., 1994; Stapells et al., 1990; Suzuki et al., 1977; Suzuki & Horiuchi, 1981).

ABR thresholds in normal-hearing subjects to 500-, 1000-, 2000-, and 4000-Hz tones are frequency specific when the tones are presented at low to moderate intensities (below 70 dB ppe SPL). Comparing behavioral thresholds of normal-hearing and hearing-impaired subjects to their tone evoked ABR thresholds indicate that thresholds for the normal-hearing subjects are estimated accurately whereas thresholds for the hearing-impaired subjects may occasionally be underestimated (e.g., Davis, Hirsh, Popelka, & Formby, 1984; Hayes & Jerger, 1982; Picton et al., 1979; Purdy & Abbas, 1989; Stapells, 1994; Stapells et al., 1995;

Stapells et al., 1990; Stapells et al., 1985). Underestimation of threshold is more likely to occur when large differences in threshold sensitivity are present across frequencies (Davis et al., 1984; Hayes & Jerger, 1982; Picton et al., 1979; Stapells, 1994; Stapells et al., 1995). Furthermore, at higher stimulus intensities, the response may be mediated by regions of the cochlea away from the nominal frequency for both the normal- and hearing-impaired individuals (Beattie & Kennedy, 1992; Burkard & Hecox, 1983; Jacobson, 1983; Klein, 1983b; Picton et al., 1979; Stapells & Picton, 1981). This effect is due to both the upward spread of cochlear excitation and the effects of spectral splatter.

The frequency specificity of the ABR to brief tones was evaluated by comparing tonal responses to those obtained with notched noise centered at the nominal frequency of the stimulus (Abdala & Folsom, 1995; Picton et al., 1979; Stapells, 1984; Stapells & Picton, 1981). The notched noise limited the responsiveness of the cochlea to those regions of the basilar membrane specific to the nominal frequency of the tonal stimulus (Picton et al., 1979). At intensities greater than 80 dB ppe SPL, the latency and amplitude of the response significantly changed between the two recording conditions, indicating some response contributions from frequencies in the spectrum outside the nominal frequency of the tones (Picton et al., 1979; Stapells, 1984; Stapells & Picton, 1981).

The frequency specificity of the response was further evaluated using the high-pass masking techniques which do not allow contributions from the high-frequency regions of the cochlea to influence the response (Burkard & Hecox, 1983; Folsom, 1984; Jacobson, 1983; Kileny, 1981; Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b). Kileny demonstrated that with the use of tones (500-, and 1000-Hz) and high-

pass noise masking, the audiometric thresholds of normal-hearing and hearing-impaired subjects can be correctly estimated (Kileny, 1981). The high-pass masking technique is inappropriate for middle-, and high-frequency tones because it does not prevent the spread of energy to frequencies below the nominal test frequency. This can cause an underestimation of the subjects' degree of the hearing loss at the tested frequency (Purdy & Abbas, 1989; Stapells et al., 1994). Using the HP/DR technique, Oates and Stapells obtained mean derived response amplitude profiles for wave V-V'. Their results demonstrate that the ABR for both the 500- and 2000-Hz tones to 80 dB ppe SPL show good frequency specificity with the maximal amplitude profiles occurring at or within a narrow range of the nominal stimulus frequency (Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b).

Threshold estimation and frequency specificity using the MLR

Compared to the ABR, the MLR has been proposed to be a better indicator for threshold estimation of 500-Hz threshold (e.g., Kavanagh, Harker, & Tyler, 1984; Kileny & Shea, 1986; Palaskas, Wilson, & Dobie, 1989; Scherg & Volk, 1983). This suggestion was based on (i) the observation that the response amplitude of the 500-Hz MLR is larger than that of the ABR, resulting in better response detectability (Musiek & Geurkink, 1981; Scherg & Volk, 1983; Wu & Stapells, submitted), and (ii) the commonly-held belief that the MLR integrates a significantly longer duration of the tone and therefore improves the frequency specificity of the response. The following thesis study is designed to investigate this commonly held belief by determining the effective duration of stimuli for both the ABR and MLR.

Numerous studies have shown that the MLR accurately reflects low-frequency hearing thresholds in normal-hearing adults (e.g., Kavanagh et

al., 1984; Kileny & Shea, 1986; Musiek & Geurkink, 1981; Palaskas et al., 1989; Scherg & Volk, 1983; Wu & Stapells, submitted). Several researchers have proposed that the MLR provides better frequency specificity at 500 Hz than does the ABR (e.g., Kavanagh et al., 1984; Kileny & Shea, 1986; Scherg & Volk, 1983). This notion, however, has not been supported by comparison of the frequency specificity of the ABR and MLR (Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b) or by tone masking studies employing forward- (Smith, Mills, & Schmiedt, 1990) or simultaneous-masking (Mackersie et al., 1993; Wu & Stapells, 1994). The ABR and MLR exhibit similar frequency specificity at 60 dB ppe SPL (Mackersie et al., 1993; Wu & Stapells, 1994) and 80 dB ppe SPL (Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b) in normal-hearing adults for responses evoked by both the 500- and 2000-Hz stimuli.

In this section, the frequency specificity of the ABR and MLR has been assessed. Both the ABR and MLR exhibit good frequency specificity up to about 80 dB ppe SPL. At these intensities the largest cochlear contributions for both the ABR and MLR are generated by regions of the basilar membrane corresponding to the stimulus frequency for normal hearing adults. With the utilization of one of the masking techniques mentioned above, frequency-specific responses for higher intensity tones as well as a more accurate threshold estimation for hearing-impaired ears can be obtained.

E2. Signal Processing

The ABR and MLR recordings always contain both response to the stimulus (i.e., the signal) as well as other unwanted potentials which originate from physiologic and non-physiologic sources (i.e., the noise)

(Hyde, 1994; Picton, Hink, Perez-Abalo, Linden, & Wiens, 1984; Picton & Maru, 1984). The physiological noise is composed of electrical activity from both neural and muscular origin. The non-physiologic noise includes electromagnetically induced potentials from sources such as radio-frequency, high-voltage equipment, 60-Hz power line radiation and internal instrumentation noise (Hyde, 1994). The signal processing models usually assume that the characteristics of the signal and the noise are unrelated. It is assumed that the signal is always identical for each repetition of the stimulus, while the noise is random and statistically stationary and independent (Hyde, 1994; Picton et al., 1984; Picton & Maru, 1984). It is further assumed that the noise has a normal distribution of amplitude (Hyde, 1994). Based on these assumptions, techniques which either enhance the signal or reduce the background noise (or both) have been developed in an attempt to improve the ratio between the signal and background noise. These techniques include averaging, filtering, and artifact rejection (Hyde, 1994; Picton et al., 1984; Picton & Maru, 1984).

Averaging

Averaging is the most widely used signal processing technique for improving the signal-to-noise ratios when recording ABR and MLR. The underlying assumption of averaging is that the signal remains relatively constant from one sweep to the next, whereas the background noise is always different. Therefore, when recordings are averaged, the amplitude of the background noise decreases by the square root of the number of trials averaged (Hyde, 1994; Picton et al., 1984; Picton, Linden, Hamel, & Maru, 1983; Picton & Maru, 1984). For ABR and MLR recordings, the averaging technique effectiveness depends on the signal-to-noise ratio of the response. The lower the intensity, the lower the

response amplitudes, making waveform identification difficult. In order to achieve lower signal-to-noise ratios, the number of sweeps required increases, decreasing collection efficiency.

In order to obtain a good signal-to-noise ratio in this thesis study, eight replications of 1000 sweeps each were averaged for each subject at each condition (for a total of 8000 trials). Eight thousand trials were previously used successfully by Oates and Stapells in a derived response study (Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b). The data was collected in blocks of 1000 sweeps in order to maximize patient comfort.

Filtering

Another way to decrease background noise and improve signal-to-noise ratio in the recording is to filter the response. The underlying assumption of filtering is that the filter passes those frequencies present in the signal while eliminating those frequencies present in the noise but not present in the signal (Boston & Ainslie, 1980; Picton et al., 1984; Picton & Maru, 1984; Picton, Stapells, & Campbell, 1981). The extent to which filtering improves the signal-to-noise ratio depends on the amount of overlap of the signal and noise spectra. When there is an overlap between the signal and noise spectra, analog filtering causes changes in the signal due to the elimination of specific frequencies from the signal, and changes in the relative phase of the signal's frequency components. The low-pass filter causes a latency lag whereas the high-pass filter causes a latency lead (Boston & Ainslie, 1980; Hyde, 1994; Picton et al., 1984; Picton & Maru, 1984; Picton et al., 1981).

Several researchers have endorsed the use of digital filtering of the ABR and MLR (i.e., Domico & Kavanagh, 1986; Doyle & Hyde, 1981;

Lettrem & Laukli, 1995; Marsh, 1988; Møller, 1980; Møller, 1983). Digital filters are much more powerful and flexible than analog filters. Even though the digital filters are non-analog, they can simulate any analog filter. The zero-phase-shift digital filter allows the removal of unwanted frequencies from the response without phase or latency changes. Digital filtering can be utilized post-hoc after averaging without alteration of data (Boston & Ainslie, 1980; Marsh, 1988).

The effect of bandpass filtering on the ABR

Due to the spectral content of the ABR, changes in EEG bandpass filter settings significantly affect the ABR waveforms. The spectral content is the amount of energy as a function of frequency that is present in the electrical spectra of the evoked potential. The major spectral energy present in ABR evoked by clicks and tones is located below 250 Hz, with smaller peaks of energy present at higher frequencies (Elberling, 1979b; Sininger, 1995; Spivak, 1993; Suzuki & Horiuchi, 1977; Suzuki, Sakabe, & Miyashita, 1982). The spectral content of the ABR is intensity-, frequency- and wave-dependent (Elberling, 1979b; Suzuki & Horiuchi, 1977; Suzuki et al., 1982). In response to high-intensity clicks (i.e, above 100 dB ppe SPL), half of the spectral energy is located below 110 Hz, whereas at low intensities (i.e., 35 dB ppe SPL), half the energy is located below 90 Hz (e.g., Elberling, 1979b; Suzuki & Horiuchi, 1977; Suzuki et al., 1982). The lower the frequency of the evoking stimulus, the lower the resulting ABR's spectral content, with frequency spectra of ABR evoked by 500-Hz tones located mostly below 100 Hz (Laukli & Mair, 1981b; Suzuki et al., 1982). The ABR waves consist of different spectral content with waves I and III containing higher EEG frequencies than wave V (Suzuki et al., 1982).

Changes in high-pass EEG filter settings have significant effects on the ABR evoked by clicks. As the high-pass cutoff frequency increases, the amplitude and latency of the ABR decreases (Elberling, 1979a; Elberling, 1979b; Laukli & Mair, 1981a; Laukli & Mair, 1981b; Stapells, 1989; Stapells & Picton, 1981; Suzuki & Horiuchi, 1977). However, because ABR waves (I, III, and V) contain different spectral content, the latency effect on wave V is greater than that on waves I and III (Laukli & Mair, 1981a; Laukli & Mair, 1981b). The amplitude of wave V evoked by moderate-intensity clicks increases when high-pass filters below 100 Hz are utilized (Boston & Ainslie, 1980; Domico & Kavanagh, 1986; Kavanagh et al., 1984).

For ABRs evoked by tones, the effect of high-pass filtering is most pronounced for waveforms dominated by low-frequency energy, such as the ABR evoked by 500-Hz tones (Stapells & Picton, 1981; Suzuki & Horiuchi, 1977). Some early researchers had difficulties identifying responses to 500-Hz tones (e.g., Davis & Hirsh, 1976; Laukli, 1983b; Laukli & Mair, 1986; Scherg & Volk, 1983; Sohmer & Kinarti, 1984; Weber, 1987). Subsequent research, however, showed that when low high-pass filter settings (e.g., 10-30 Hz) are used, wave V can be recorded within 10 to 20 dB of behavioral threshold (Kodera, Yamane, Yamada, & Suzuki, 1977a; Stapells & Picton, 1981; Suzuki et al., 1977; Suzuki & Horiuchi, 1977). At high stimulus intensities, high-pass filtering significantly attenuates the amplitude of the response to 500 Hz compared to the ABR to higher frequency stimuli (Suzuki & Horiuchi, 1977). At low stimulus intensities, where higher EEG frequencies contribute only little to the response, high-pass filtering attenuates the amplitude of ABR evoked by clicks, 500- or 2000-Hz stimuli similarly (Hyde, 1985; Stapells & Picton, 1981; Stapells et al., 1994; Suzuki & Horiuchi, 1977). Studies on the effects of high-pass filtering and rolloff slopes on the ABR to

500-Hz tones have demonstrated that the latency and amplitude of wave V decreased as the high-pass filter or rolloff slope increased. The largest response was recorded with a high-pass filter setting of 10 Hz combined with a rolloff slope of 12 dB/Octave or lower (Hyde, 1985; Stapells & Picton, 1981). Davis and Hirsh, on the other hand, obtained a large-amplitude vertex-negative wave with the use of a 40-Hz high-pass filter with a 24 dB/octave slope and stimuli presented at a rate of 33/s (Davis & Hirsh, 1979). Stapells and Picton demonstrated that the vertex-negative ABR obtained by Davis and Hirsh (1979) was due to the specific recording parameters chosen (Davis & Hirsh, 1979; Stapells & Picton, 1981). The combination of the 40-Hz high-pass filter with a high rolloff slope (24 dB/octave) at a presentation rate of 33/s caused phase distortion to wave V as well as an overlap of wave V with the 40-Hz response (Stapells & Picton, 1981). Thus, to minimize waveform distortions of wave V, researchers have recommended recording the ABR with a low high-pass filter setting (10-20 Hz) with a low rolloff slope (6-12 dB/octave) (Hyde, 1985; Stapells & Picton, 1981).

The effects of changes in low-pass filter settings have received relatively little attention. Because the ABR contains little if any spectral energy above 2000 Hz, decreasing the cutoff frequency from 10,000 Hz to 3000 Hz eliminates noise without distorting the ABR latency or amplitude. Further reductions in the low-pass filter (below 2000 Hz) smooths the waveforms and increases its waves' latencies (Boston & Ainslie, 1980; Elberling, 1979b; Kavanagh et al., 1984; Laukli & Mair, 1981a).

Thus, the optimum filter setting recommended for obtaining ABR recordings in adults include using a high-pass filter setting between 10-30 Hz, a low-pass filter setting between 1500-3000 Hz, and an analog

filter slope no greater than 12 dB/octave or less (Hyde, 1985; Sininger, 1995; Spivak, 1993; Stapells & Picton, 1981).

The effect of bandpass filtering on the MLR

The frequency spectrum of the middle latency response was investigated by Suzuki and colleagues for responses evoked by 80 dB ppe SPL clicks (Suzuki, Kobayashi, & Hirabayashi, 1983). The MLR frequency spectrum was found to be between 20 and 60 Hz (with a peak at 40 Hz), with some energy present between 90 and 180 Hz (Suzuki et al., 1983).

The EEG filter settings, especially the high-pass filter setting, have significant effects on the MLR (e.g., Kavanagh & Domico, 1986; Kavanagh et al., 1984; Kileny, 1983; Kraus, Reed, Smith, Stein, & Cartee, 1987a; Kraus, Smith, & McGee, 1987b; Lane et al., 1974; McGee, Kraus, & Manfredi, 1987; Scherg, 1982; Suzuki et al., 1983). Because the spectral energy of the MLR is predominantly low frequency (below 50 Hz), analog high-pass filters above 20 Hz result in amplitude reductions and phase distortions of the MLR waveforms (Kavanagh & Domico, 1986; Kavanagh et al., 1984; Lane et al., 1974; McGee et al., 1987; Scherg, 1982; Suzuki et al., 1983). As the high-pass filter increases to 40 Hz, the latencies and amplitudes of the MLR peaks (Na, Pa, and Nb) decrease, with complete polarity reversal of waves Pa and Nb (Kraus et al., 1987b; Scherg, 1982; Suzuki, Hirabayashi, & Kobayashi, 1984b; Suzuki et al., 1983). The MLR completely disappears with the use of a 60-Hz high-pass filter. Studies of the effect of filter rolloff slopes on the MLR indicate that increases in steepness (above 12 dB/octave) changes the morphology of the MLR by adding additional components to the response (Kraus et al., 1987b).

With the use of zero-phase-shift digital high-pass filters, the distortion caused by the analog filtering is eliminated, leaving the

morphology of the MLR unaffected by high-pass filters of 30 Hz or below (Scherg, 1982; Suzuki et al., 1984b; Suzuki et al., 1983). However, the use of digital high-pass filters above 30-Hz causes a decrease in response amplitude due to the elimination of the low-frequency spectra from the response (Scherg, 1982).

Due to the low-frequency spectral energy of the MLR, lowering the low-pass cutoff frequency of the low-pass filter from 3000 to 300 results in smoothing of the MLR with no significant changes in amplitude or latency of the response (Kavanagh et al., 1984; Kileny, 1983; McGee et al., 1987; Scherg, 1982). Further decrease in the low-pass cutoff frequency of the low-pass analog filter has very little effect on the MLR amplitude but produces an increase in the MLR latency (Kavanagh et al., 1984; Kileny, 1983; McGee et al., 1987; Scherg, 1982). The increase in latency is due to the phase shifting of the response produced by the analog filtering (Scherg, 1982). Digital filters were used to demonstrate that recording MLR with very narrow bandpass analog filters produces what appears to be an MLR response when a response is not present (such as in children; Kileny, 1983).

Thus, the optimum filter setting recommended for obtaining MLR recordings in adults include using a high- pass filter setting of 10 Hz, a low-pass filter setting of at least 300 Hz, and an analog filter slope no larger than 12 dB/octave (Gould, Crawford, Mendel, & Dodson, 1992; Kileny, 1983; Kraus et al., 1987b; Kraus, Smith, McGee, Stein, & Cartee, 1987c; Suzuki et al., 1984b).

In this thesis study, simultaneous recordings of the ABR and MLR were obtained. For simultaneous recordings of ABR and MLR, a wide bandpass analog filter such as 10-1000 Hz bandpass is usually used (Kraus, Smith, Reed, Stein, & Cartee, 1985; Mackersie et al., 1993;

Oates, 1996; Oates & Stapells, 1997a; Oates & Stapells, 1997b; Özdamar & Kraus, 1983; Scherg & Volk, 1983; Suzuki, Hirai, & Horiuchi, 1981; Wu & Stapells, submitted). In the present thesis study, the EEG signals were amplified and analog filtered using a bandpass of 10-3000 Hz and a rolloff slope of 6 dB/octave. To remove the high-frequency electrical noise present in the recordings, the averaged responses were digitally filtered offline with a 1000-Hz low-pass filter (12 dB/oct slope, zero phase shift).

Artifact rejection

Averaging is often combined with artifact rejection. Artifact rejection improves the signal-to-noise ratio by excluding sweeps with amplitudes above a predetermined rejection level from the averaging process (Don, Elberling, & Waring, 1984; Picton et al., 1984; Picton & Maru, 1984). The rejected sweeps are considered outliers. They can have both neural and/or muscular origins. If included in the response, these sweeps can enhance, suppress, or distort a genuine response (Hyde, 1994). However, when the background noise of the recording is similar to that of the rejection level, most sweeps will be rejected, thus prolonging the collection process (Picton et al., 1984; Picton et al., 1983) and distorting the averaged response (Don et al., 1984). The usual noise levels in a relaxed subject are less than 20 μV (Picton et al., 1984). The typical artifact rejection values range between ± 10-25 μV and ± 20-50 μV for the ABR and MLR, respectively (Picton et al., 1984; Picton & Maru, 1984; Stapells & Oates, 1997).

In this thesis study, artifact rejection was employed. Sweeps exceeding amplitudes of ± 25 μV were automatically rejected.

E3. The Effect of Stimulus Factors on the ABR and MLR

The ABR and MLR are influenced by stimuli parameters such as intensity, rate, frequency, envelope (i.e., rise/fall time and plateau) duration and polarity. In the following section, the effects of each parameter are described.

Stimulus intensity

Stimulus intensity (or level) of brief stimuli is described in terms of decibels and sound pressure level (dB SPL). In this thesis study, the intensity of the stimulus is measured with the peak-to-peak equivalent (ppe) SPL method. The ppe SPL is a measure of sound intensity in which the peak-to-peak voltage measured on an oscilloscope is the same as the peak-to-peak voltage measured for a long duration reference signal (Gorga & Neely, 1994; International Electrotechnical Commission, 1994; Stapells, Picton, & Smith, 1982).

The effect of stimulus intensity on the ABR

The amplitude, latency and morphology of the ABR evoked by clicks are influenced by changes in signal intensity. For the ABR, a decrease in stimulus intensity results in an increase in latency and a decrease in amplitude of the ABR waves. The peak latency of wave V evoked by clicks decreases by approximately 2.6 ms as stimulus intensity decreases from 80 dB nHL to 10 dB nHL (Hecox & Galambos, 1974; Picton et al., 1981; Picton, Woods, Baribeau-Bräun, & Healey, 1977). Although, the latency-intensity function of wave V is not linear, it can be reasonably well fit a linear regression line with a -38 µS/dB slope and an 8.8 ms baseline at 0 dB (Picton et al., 1981). A decrease in stimulus intensity decreases the amplitude of the ABR waves, with earlier waves (waves I, III) declining more rapidly than wave V (Picton et al., 1981).

Thus, wave I and III are detectable down to 25-35 dB nHL, whereas wave V is detectable until five dB nHL (Elberling & and Don, 1987).

When evoked by tones, a decrease in stimulus intensity results in an increase in latency and a decrease in the amplitude of wave V for all stimulus frequencies (e.g., Beattie & Boyd, 1985; Beattie & Kennedy, 1992; Gorga et al., 1988; Kodera et al., 1977b; Picton et al., 1979; Stapells & Picton, 1981; Suzuki et al., 1977; Wu & Stapells, submitted). The increase in latency and the decrease in amplitude are greater for lower *versus* higher frequency tonal stimuli, when not masked by noise (Stapells, 1984; Stapells & Picton, 1981; Suzuki et al., 1977; Wu & Stapells, submitted). When evoked by low-frequency stimuli, wave V latency decreases with increases in intensity due to (1) a true intensity affect, (2) upward spread of excitation to more basal(and thus shorter latency) regions, and (3) excitation by higher-frequency energy (side-lobes) of the brief tones. These three mechanisms also apply to situations in which the ABR is evoked by mid and high low-frequency stimuli. However, when this spread of energy is masked by notched noise, the slope of the latency-intensity function for the ABR to low-frequency tones are similar to those for higher frequency tones. (Picton et al., 1979; Picton et al., 1981; Stapells & Picton, 1981; Stapells et al., 1994). A replicable wave V can be detected at stimulus intensities within 10 dB of behavioral thresholds for 500-, 1000-, 2000- and 4000-Hz tones presented to normal hearing adults (e.g., Beattie & Kennedy, 1992; Davis & Hirsh, 1979; Gorga et al., 1988; Kodera et al., 1977b; Picton, 1990; Purdy et al., 1989; Stapells et al., 1995; Stapells & Picton, 1981; Stapells & Wu, submitted; Suzuki et al., 1977).

The effect of stimulus intensity on the MLR

The effect of intensity on the click evoked MLR is similar to that of the ABR at low to moderate levels. Overall, the peak latency of wave Pa evoked by clicks increases by approximately 1.5 ms as stimulus intensity decreases from 65 dB nHL to 15 dB nHL (Wu & Stapells, submitted). Unlike the ABR, however, further increases in intensity do not yield further decreases in wave Pa latency (Mendel & Goldstein, 1969a; Mendel & Goldstein, 1969b; Özdamar & Kraus, 1983; Thornton, Mendel, & Anderson, 1977; Wu & Stapells, submitted). The amplitude of the MLR evoked by clicks increases with increases in intensity until a plateau is reached where further increases in intensity do not yield further increases in amplitude (Mendel & Goldstein, 1969a; Mendel & Goldstein, 1969b; Özdamar & Kraus, 1983; Thornton et al., 1977; Wu & Stapells, submitted).

The latency of the MLR evoked by tones increases and its ampllitude decreases with decreases in stimulus intensity (Beattie & Boyd, 1985; Beattie et al., 1984; McFarland, Vivion, & Goldstein, 1977; Suzuki et al., 1981; Thornton et al., 19771; Wu & Stapells, submitted). The decline in amplitude is not linear, with the majority of the change occurring between 25 dB ppe SPL and 55 dB ppe SPL (Wu & Stapells, submitted). The amplitude growth between these intensities is larger than the more gradual growth observed for the ABR (Wu & Stapells, submitted). Similar to ABR, the increase in latency and decrease in amplitude of the MLR is greater for the lower *versus* higher frequency tonal stimuli, when not masked by noise (Beattie & Boyd, 1985; Thornton et al., 1977; Wu & Stapells, submitted). With normal-hearing adults, replicable MLR waves can be detected at stimulus intensities of 10-15 dB above behavioral threshold for responses evoked by 500-, 1000-, 2000- and 4000-Hz tones (e.g., Beattie et al., 1984; Davis, Hirsh, & Turpin,

1983; Suzuki et al., 1981; Thornton et al., 1977;; Wu & Stapells, submitted).

Stimulus Rate

The effect of rate on the ABR

Increasing the stimulus repetition rate up to approximately 20/s has very little effect on the morphology of the ABR evoked by clicks (e.g., Burkard, Shi, & Hecox, 1990; Don, Allen, & Starr, 1977; Eggermont & Odenthal, 1974; Hyde, Stephens, & Thornton, 1976; Picton et al., 1974; Picton et al., 1981; Suzuki, Kobayashi, & Takagi, 1985). Increasing stimulus rate above 20/s increases the latency and decreases the amplitude of the ABR (e.g., Don et al., 1977; Hyde et al., 1976; Picton et al., 1974; Picton et al., 1981). Changes in rate, however, affect the various ABR waves differently. Increase in rate from a slow rate of 10/s to a fast rate of 80/s, causes about 50% decrease in wave I amplitude but only 10-30% amplitude decrease in wave V (Picton et al., 1981). In addition, these same increases in rate cause a latency prolongation of approximately 0.4-0.6 ms in wave V, but only minimal prolongation in wave I and III (Don et al., 1977; Hyde et al., 1976; Kodera, Yamada, Yamane, & Suzuki, 1978; Picton et al., 1981; Stapells & Picton, 1981; Weber & Fujikawa, 1977; Yagi & Kaga, 1979). Clinically, the use of faster stimulus presentation rates allows the clinician to obtain more averages or more conditions within a given period. Picton and coworkers have suggested that the most efficient rates of recording waves I and V of the ABR are between 20 and 40/s and between 80 and 100/s, respectively (Picton et al., 1983; Picton & Maru, 1984). Stapells and Picton investigated the effects of rate (10, 20, and 35/s) on ABR evoked by 110 dB peak SPL, 500-Hz brief tones (Stapells & Picton, 1981). Increases in rate resulted in increases in wave V latency, with

major changes occurring between rates of 10 and 20/s (Stapells & Picton, 1981). Increases in rate up to approximately 25/s have no significant amplitude changes (Davis & Hirsh, 1979; Kodera, Yamada, Yamane, & Suzuki, 1978; Stapells & Picton, 1981). Further increases in rate (to 30-35/s) cause small increases in wave V amplitude (Kodera et al., 1978; Stapells & Picton, 1981). This increase in amplitude at higher rates was suggested to reflect the superimposition of middle latency components on the earlier ABR component (Galambos, Makeig, & Talmachoff, 1981; Stapells & Picton, 1981).

The effect of rate on the MLR

Increasing stimulus rate from 1/s to 15/s has little effect on the amplitude and latency of the MLR (wave Pa) when recorded from normal-hearing adults. However, at rates below 1/s the latency of the response is significantly shorter than that obtained with a stimulus rate of 1/s or higher (Goldstein, Rodman, & Karlovich, 1972; McFarland, Vivion, Wolf, & Goldstein, 1975; Picton et al., 1974). For rates above 15/s, the MLR amplitude decreases and its latency increases (McFarland et al., 1975; Picton et al., 1974). At the rate of 40/s, an exception to the general trend of decreasing amplitude with increasing stimulus rate occurs. This rate produces a steady-state response (SSR) which results in amplitude that is about two to three times greater (in adults) than responses obtained with a 10/s rate (Galambos et al., 1981; Kileny & Shea, 1986; Stapells, Galambos, Costello, & Makeig, 1988; Stapells et al., 1984; Suzuki & Kobayashi, 1984). Steady-state responses are elicited by stimuli presented at a rate sufficiently high to result in an overlapping of the responses to successive stimuli (Regan, 1982; Stapells et al., 1984). This "40-Hz" response was hypothesized to represent the superimposition of previous ABR and MLR peaks, which are

typically 21-25 ms apart (Galambos et al., 1981). Subsequent studies demonstrate that both the magnetic and electrical 40-Hz response can be synthesized by superimposition of the negative-positive waves present in the 10-Hz MLR recorded from adults (Azzena et al., 1995; Hari, Hamalainen, & Joutsiniemi, 1989; Plourde, Stapells, & Picton, 1991; Stapells et al., 1988).

When recording ABR and MLR simultaneously, in order to see the ABR and MLR separately and without any overlapping, as well as without significant decreases in the amplitude of the MLR, a stimulus rate lower than 15/s must be employed (Galambos et al., 1981; McFarland et al., 1975; Picton et al., 1974; Stapells et al., 1984).

In the present thesis study, the ABR and MLR are recorded simultaneously. In order to avoid superimposition of the ABR and MLR and to ensure optimum MLR amplitude, the stimuli are presented at a rate of 10.9/s.

Stimulus Frequency

Stimulus frequency and the ABR

Early researchers recorded responses to tonal stimuli in order to obtain frequency-specific ABR (e.g., Beattie & Boyd, 1985; Davis & Hirsh, 1976; Davis & Hirsh, 1979; Davis et al., 1984; Elberling, 1979a; Elberling, 1979b; Gorga et al., 1984; Jacobson, 1983; Kileny, 1981; Klein, 1983b; Kodera, Marsh, & Suzuki, 1983; Picton et al., 1979; Stapells & Picton, 1981; Suzuki et al., 1977; Suzuki, Kobayashi, & Takagi, 1986; Suzuki et al., 1982; Takagi, Suzuki, & Kobayashi, 1985; Terkildsen, Osterhammel, & Huis in't Veld, 1973; Terkildsen, Osterhammel, & Huis in't Veld, 1975). Stimulus frequency has differential effects on the ABR. Brief high-frequency tones elicit ABRs

similar to those evoked by clicks (Terkildsen et al., 1973; Terkildsen et al., 1975). Initially, researchers encountered difficulties in obtaining responses to 500-Hz tones (Davis & Hirsh, 1976). Subsequent research showed that, with the use of low high-pass filters (50 Hz and below), it is possible to obtain ABRs using 500-Hz tones (e.g., Davis & Hirsh, 1979; Klein, 1983b; Stapells & Picton, 1981; Suzuki et al., 1977; Suzuki & Horiuchi, 1977). ABRs evoked by the 500-Hz tonal stimuli are morphologically different from responses evoked by higher frequency tones which contain equal durations or equal stimulus cycles. For ABR evoked by 500-Hz stimuli, waves I, II, III and IV are absent and wave V is broader and longer in latency (e.g., Beattie & Kennedy, 1992; Jacobson, 1983; Kileny, 1981; Oates, 1996; Oates & Stapells, 1997b; Stapells & Picton, 1981; Stapells et al., 1994). The increase in wave V latency for the low-frequency tones reflects the longer travel time needed to reach the apical region of the cochlea, as well as longer rise time of the stimuli.

Stimulus frequency and the MLR

Many early researchers (e.g., Beiter & Hogan, 1973; Lane, Kupperman, & Goldstein, 1971; McFarland et al., 1975; Skinner & Antinoro, 1971; Thornton et al., 1977; Vivion, Wolf, Goldstein, Hirsch, & MacFarland, 1979) have recorded MLRs to tonal stimuli in order to obtain frequency-specific responses. The stimulus frequency has differential effects on the latency and amplitude of the MLR. Similar to ABR wave V, the inverse relationship between latency and stimulus frequency exists for all stimulus intensities, with the greatest shifts in latency occurring at the lower intensities (Beattie et al., 1984; McFarland et al., 1975; Suzuki et al., 1981; Thornton et al., 1977; Wu & Stapells, submitted). The amplitude of the MLR is larger for responses

evoked by lower frequencies at all intensities (Beattie et al., 1984; McFarland et al., 1975; Oates, 1996; Suzuki et al., 1981; Thornton et al., 1977; Wu & Stapells, submitted), whereas the amplitude of ABR is about equal for responses evoked by 500-4000 Hz stimuli (Takagi et al., 1985).

Stimulus Polarity (Phase)

The polarity of a stimulus is determined by the direction in which the transducer's diaphragm is moving at stimulus onset. Condensation polarity is generated when the stimulus onset is produced by a movement of the transducer diaphragm toward the tympanic membrane, which causes a positive pressure wave. Rarefaction polarity occurs when the transducer diaphragm moves away from the tympanic membrane and a negative pressure wave is generated. Alternating polarity occurs when the phase of the stimulus switches between condensation and rarefaction. Recording responses with alternating polarity reduces stimulus-related electromagnetic artifacts in the average recordings, as well as reducing the cochlear microphonics (CM) and the frequency following response (FFR) artifacts associated with each polarity (Davis, 1976; Terkildsen et al., 1975).

Polarity effects on the ABR

The effects of stimulus polarity on the ABR evoked by clicks have yielded varying results. In normal-hearing subjects, there are studies that report no effect of click polarity (e.g., Beattie & Boyd, 1984; Don, Vermiglio, Ponton, Eggermont, & Matsuda, 1996; Fowler, 1992; Rosenhamer, Lindstrom, & Lundborg, 1978; Terkildsen et al., 1973; Tietze & Pantev, 1986), shorter wave latencies to rarefaction clicks (Ornitz & Walter, 1975; Stockard, Stockard, Westmoreland, & Corfits, 1979), and

shorter wave latencies to condensation clicks (Coutin, Balmaseda, & Miranda, 1987). Don and associates obtained ABR responses to rarefaction and condensation clicks for normal-hearing subjects in quiet and with high-pass noise masking (Don et al., 1996). Their analyses revealed no significant stimulus polarity effects on wave V latency for responses for both the quiet and derived response bands.

Several researchers suggested that changes in polarity cause increases in wave V latency with increased high-frequency hearing losses (Borg & Lofqvist, 1981; Borg & Lofvist, 1982; Coats & Martin, 1977; Schwartz et al., 1990). Schoonhoven, however, demonstrated that there is no consistent polarity effect on derived responses obtained from normal-hearing individuals with simulated high-frequency hearing loss (Schoonhoven, 1992).

When tonal stimuli are used, the polarity of the stimulus affects responses evoked by low-frequency tonal stimuli (Fowler, 1992; Gorga, Kaminski, & Beauchaine, 1991). The latencies of ABR evoked by rarefaction stimuli (for 500- and 1000-Hz tones) are shorter than those evoked by condensation stimuli. No polarity affects are found for ABR evoked by higher frequency tones. These authors suggested that when the ABR is not polarity- dependent, the response is mediated by high-frequency portion of the stimulus, whereas when the evoked response is polarity-dependent, the response is mediated by the low-frequency portion of the stimulus (Fowler, 1992; Gorga et al., 1991). Don and associates argue that the "polarity" effect observed for lower frequencies does not reflect a true polarity effect, as the half-period latency shifts of wave V are not observed in derived bands responses initiated from frequency specific regions of the cochlea (Don et al., 1996).

Polarity effects on the MLR

Extensive literature searches have failed to turn up any MLR papers on this topic.

In order to avoid polarity effects, reduce electromagnetic artifacts and decrease FFR contamination of the ABR/MLR, the alternating onset polarity mode is used in this thesis study.

Effect of Stimulus Envelope

The parameters of the stimulus envelope consist of stimulus rise time, plateau, and fall time. Rise time is the initial portion of a stimulus from its beginning at baseline to maximum amplitude[2]. Fall time is the time from the maximum amplitude to the end of the stimulus at baseline. Plateau is defined as the interval between the rise and the fall time, during which the envelope of the stimulus is at 100% amplitude (Gorga & Neely, 1994; Gorga & Thornton, 1980; Hall, 1992).

Effect of stimulus plateau on the ABR

Gorga and colleagues studied the effect of plateau length (1-512 ms) on the ABR thresholds to 2000-Hz tones (0.5 ms rise/fall) (Gorga et al., 1984). Their results indicate that varying stimulus plateau does not affect ABR thresholds for both normal and hearing-impaired subjects, whereas behavioral thresholds decreased with increases in plateau durations (Gorga et al., 1984). Funasaka and Ito, on the other hand, investigated the effect of plateau durations (5-30 ms) on ABR latency and amplitude using 3000-Hz tones (1-ms rise/fall) (Funasaka & Ito, 1986). Increases in plateau duration caused increases in latency and amplitude of wave V and VI and decreases in amplitude, with no latency changes for wave III (Funasaka & Ito, 1986). Beattie and Boyd analyzed

the effect of plateau duration (25-400 µs) on the latency of ABR evoked by clicks (Beattie & Boyd, 1984). They found that the latency of the ABR is stable until the click plateau reaches 100 µs. Plateaus above 100 µs generated slightly prolonged latencies. This increase in latency was attributed to changes in stimulus spectrum, as the longer the click stimulus, the more energy that is contained in the lower frequencies (Beattie & Boyd, 1984). Hecox and colleagues investigated the effect of plateau durations (0.5-30 ms) of noiseburst stimuli (Hecox, Squires, & Galambos, 1976). Their results indicate increases in wave V latency and decreases in amplitude with increases in plateau durations (Hecox et al., 1976). Thus, increases in plateau durations have no affect on the ABR threshold, but causes increases in latency and decreases in amplitude of ABR wave V.

Effect of stimulus plateau on the MLR

Most studies on the effect of stimulus plateau duration indicate that prolonging plateau duration does not affect the latency or amplitude of the response (Davis & Zerlin, 1966; McCandless & Best, 1966; Onishi & Davis, 1968; Skinner & Jones, 1968; Vivion, Hirsch, Frye-Osier, & Goldstein, 1980). Only Lane and colleagues reported plateau duration to have any significant influence on response characteristics, with wave Nb-Pb amplitude significantly greater for a ~40 ms signal than for a 20-ms signal (Lane et al., 1971).

Effect of stimulus rise time on the ABR

Salt and Thornton investigated the effects of click rise time on the latency of the ABR, with rise/fall times ranging from 170 to 580 µs (Salt & Thornton, 1984). The results indicate that as click rise time increased, so did the latencies of the major components of the ABR.

Brief tones differ from clicks in their rise time and frequency content. There are two ways of specifying rise time: rise times containing constant number of cycles, and rise times lasting a constant time (in ms) regardless of the frequency used. With the constant-number of cycles approach, duration of tones of differing frequency vary, yet energy is held constant. With the constant-time approach, the temporal features of the stimulus are constant; however, its frequency spectrum changes (Stapells et al., 1994). The advantage of the constant rise time is that, after the appropriate traveling wave delays are taken into account, the auditory response should occur at approximately the same time for each frequency (Stapells et al., 1994).

In order to determine what is the optimal rise time settings for recording ABR, Takagi and colleagues compared slow and fast ABRs recorded to tones (500-, 1000-, 2000-, 4000- and 8000-Hz) with constant cycles (2 cycle rise/fall time) to ABRs recorded to tones with constant times in milliseconds (4 ms rise/fall time) (Takagi et al., 1985). Results indicate that wave V latency for both the slow and fast components increases with decreases in stimulus frequency. This occurs with both approaches, with even longer latencies obtained with the constant time condition. When evoked by the constant-time stimulus, the amplitude of the slow component decreases with increasing frequency, while the amplitude of the fast component stays the same. In contrast, when evoked by the constant-cycle stimulus, the amplitude of the fast component decreases with decreases in frequency, while the amplitude of the slow response stays the same. Overall, the amplitude of the ABR (fast+slow) is found to be larger across frequencies for tones with constant cycles *versus* those with constant time. The authors conclude that the constant-cycle approach is preferable for recording ABR since

it provides smaller inter-frequency differences in the amplitude of the overall auditory brainstem response (Takagi et al., 1985).

Davis and colleagues investigated the effect of stimulus plateau on ABR threshold detection in normal- and hearing-impaired subjects (Davis et al., 1984). The 2 cycles rise time, 1 cycle plateau, and 2 cycles fall time ("2-1-2") resulted in a 3-dB better threshold sensitivity for the normal hearing impaired individuals when compared to a 2 cycles rise time, 0 cycle plateau, and 2 cycles fall time ("2-0-2") stimulus (Davis et al., 1984). Thresholds for subjects with steep high-frequency hearing loss were more accurate when the 2-1-2 cycle stimuli were used. Thus, Davis and colleagues recommend the use of the "2-1-2" cycles stimuli for obtaining frequency-specific ABR thresholds (Davis, 1976; Davis et al., 1984). Subsequent studies show that the "2-1-2" cycle tones provides frequency-specific ABR thresholds in both normal and hearing-impaired individuals (e.g., Munnerley et al., 1991; Purdy et al., 1989; Stapells, 1984; Stapells, 1989; Stapells et al., 1995; Stapells et al., 1990).

The rise time of a stimulus affects both the latency and amplitude of the ABR. Most studies have investigated the effect of rise time on the ABR by varying the rise times while keeping the final peak-to-peak equivalent SPL amplitude of the stimulus (i.e., stimulus intensity) the same (e.g., Beattie et al., 1984; Brinkmann & Scherg, 1979; Hecox et al., 1976; Kodera et al., 1977a; Kodera, Hink, Yamada, & Suzuki, 1979; Stapells & Picton, 1981; Suzuki et al., 1977). Because the peak-to-peak equivalent SPL of the stimulus stays constant with increases in rise time, the slope of the rise necessarily varies with increases in rise time. Thus, changes in response amplitude and latency of the evoked response with increases in rise time might reflect rise time and/or

slope effects. Figure 4 schematically presents this "constant-SPL intensity" paradigm.

Kodera and colleagues and Stapells and colleagues evaluated the amplitude and latency of ABR wave V evoked by tonal stimuli at various intensities and rise times (Kodera et al., 1983; Kodera et al., 1977b; Stapells & Picton, 1981). Results indicate that, as rise time increases, wave V latency increases and wave V amplitude decreases for responses to 500- and 2000-Hz stimuli. The increase in latency and decrease in amplitude with increase in rise time are greater for ABR evoked by 500-tones (Kodera et al., 1983; Kodera et al., 1977b; Stapells & Picton, 1981). Overall, the largest amplitude decrease in responses to the 500- to 4000-Hz tonal stimuli occur when rise times exceed 5 ms (Stapells & Picton, 1981). The changes in wave V latency are suggested to be due to specific rise-time effects, as well as increases in the spread of acoustic energy which occurs with the shorter rise times (Kodera et al., 1983; Stapells & Picton, 1981). Shorter rise times evoke responses from more basal regions of the cochlea for same-frequency stimuli. When notched noise masking is applied, the spread of energy to regions other than the nominal frequency of the stimulus is prevented, and the latency of wave V evoked by the shorter rise times increases (Picton et al., 1981; Stapells & Picton, 1981). These results are confirmed by many other studies (e.g., Beattie et al., 1984; Burkard, 1984; Durrant, 1983; Hecox et al., 1976; Jacobson, 1983; Picton et al., 1977; Suzuki et al., 1977).

Brinkmann and Scherg developed the concept of the "virtual trigger time" to explain the stability of the ABR amplitude for responses evoked by rise times up to 5 ms (Brinkmann & Scherg, 1979). The virtual trigger time is described as "the point in the rise time of a stimulus at which the majority of nerve fibers innervating the generators of the

brainstem response are activated" (Stapells et al., 1994). Stapells and Picton reported that the virtual trigger time is a function of rise time, intensity, and frequency of the stimulus (Stapells & Picton, 1981).

Changes in the rise time of the tonal stimuli cause changes in the morphology of the ABR. It is not clear whether the decrease in amplitude and increase in latency of the ABR with increases is rise times are specifically due to (i) stimulus envelope (i.e., rise time, slope), or (ii) spectral splatter effects. In order to determine the effects of rise time on the ABR without the spectral changes which occur with the use of tonal stimuli, investigators used brief noiseburst stimuli to elicit the response (e.g., Barth & Burkard, 1993; Folsom & Aurich, 1987; Hecox & Deegan, 1983; Hecox et al., 1976). As seen in figure 3, the spectral changes which accompany variations in the rise time of the tonal stimuli are essentially absent for the noiseburst stimuli. The noiseburst spectra remain relatively constant despite changes in rise time and duration (Barth & Burkard, 1993; Burkard, 1984; Folsom & Aurich, 1987; Hecox & Deegan, 1983; Hecox et al., 1976). Consequently, any changes in latency and/or amplitude of the response with increases in rise times could be attributed to changes in stimulus envelope (i.e., rise time, slope) rather than due to spectral splatter or lack of cochlear place specificity.

Increases in noiseburst levels produce decreases in ABR peak latency and increases in peak amplitudes (Barth & Burkard, 1993; Burkard, 1991; Folsom & Aurich, 1987). Increases in the noiseburst rise time produce increases in ABR latencies (Barth & Burkard, 1993; Burkard, 1991; Folsom & Aurich, 1987; Hecox & Deegan, 1983; Hecox et al., 1976). The effects of rise time on the amplitude of ABR elicited by noisebursts varies across studies. For human ABR wave V, earlier studies report

little effect of rise time on wave V amplitude (Hecox & Deegan, 1983; Hecox et al., 1976). Later studies, however, report decreases in amplitude with increases in noiseburst rise times (Barth & Burkard, 1993; Folsom & Aurich, 1987). Burkard evaluated the effect of noiseburst rise time on the latency and amplitude of the gerbil ABR. Results indicate that increases in rise time produce increases in wave V latency and decreases of its amplitude (Burkard, 1991).

Both increases in rise time and decreases in intensity cause increases in latency for ABR evoked by noiseburst stimuli (Barth & Burkard, 1993; Burkard, 1991). Burkard and colleagues investigated whether the decrease in amplitude and the increase in latency seen with increasing rise time could be equated to reductions in stimulus intensity (Barth & Burkard, 1993; Burkard, 1991). If correct, the ABR at longer rise times should be similar in amplitude and latency to brainstem responses evoked by lower stimulus intensities. Results from humans (Barth & Burkard, 1993) and gerbils (Burkard, 1991) indicate that latency shifts due to increases in rise time (for a given response amplitude change) are greater than the latency shifts due to reduction in stimulus intensity. Thus, increases in ABR latency with increases in rise time cannot be solely attributed to a reduction in stimulus intensity (Barth & Burkard, 1993; Burkard, 1991). Burkard and colleagues concluded that increases in Wave V latency due to increases in rise time and stimulus intensity may reflect different mechanisms which partially overlap (Barth & Burkard, 1993; Burkard, 1991). Recently, Philips and Burkard investigated the effect of rise time and stimulus intensity on the inferior colliculus potential (ICP) of the chinchillas (Phillips & Burkard, 1999). Similar to the ABR results, the effects of increasing rise time on the ICP latency and amplitude were not equivalent to a simple reduction in the noiseburst intensity. For

both the ABR and the ICP, the latency shift is greater than the amplitude change. The authors conclude that the timing to response initiation is affected by: (i) the duration of the rise time in which the stimulus is sub-threshold, (ii) stimulus envelope, and (iii) a critical integration time, in which the majority of nerve fibers are activated (i.e., virtual trigger time) (Phillips & Burkard, 1999). Similar results were obtained with single-cell recordings in the auditory cortex (Heil, 1997a,b; Biermann and Heil, 2000).

Hecox and Deegan used the high-pass noise/derived response technique to assess the contribution of cochlear place to the effects of rise time on ABR wave V latency evoked by brief noise stimuli (Hecox & Deegan, 1983). They compared the latency shifts across rise times of the nonmasked responses to those obtained for the 500- to 4000-Hz derived responses. Significant increases in wave V latency as a function of rise time were observed for both nonmasked and derived responses. The authors concluded that the latency shifts accompanying increases in rise time cannot be solely attributed to changes in cochlear place (Hecox & Deegan, 1983).

The rise-time results for ABR evoked by tones and by masked and non-masked noisebursts stimuli are similar in trend. As rise time decreases, the amplitude of the ABR evoked by both stimuli increases while its latency decreases. Thus, the effect of rise time on the ABR evoked by tones cannot be solely explained by spectral or cochlear place changes. Rather, they must be due, at least in part, to changes in the stimulus envelope (i.e., rise time, slope).

Effect of stimulus rise time on the MLR

Several early studies investigated the effects of stimulus rise time on the middle latency response (Beiter & Hogan, 1973; Lane et al.,

1971; Skinner & Antinoro, 1971; Skinner & Jones, 1968). However, only limited conclusions can be drawn from these studies due to methodological constraints. The studies are limited in stimulus frequencies (mostly 1000 Hz), stimulus intensity (usually only above 70 dB ppe SPL), and EEG filter setting (restricted to 30-100 Hz) (Beiter & Hogan, 1973; Lane et al., 1971; Skinner & Jones, 1968). Vivion and colleagues investigated the effect of rise time on MLRs elicited by 500-, 1000- and 3000-Hz tones presented at intensities ranging from 35 to 60 dB ppe SPL, albeit with a somewhat restricted EEG bandpass filter setting of 25-175 Hz (Vivion et al., 1980). Increasing the rise time from 3 to 10 ms resulted in small increases in MLR peak latency and small decreases in amplitude for all frequencies and intensities, with the greatest amplitude change occurring for rise times greater than 5 ms (Vivion et al., 1980). These results are similar to earlier results demonstrating decreases in response amplitudes with rise time increases from 250 µs to 25 ms, with the largest decrease occurring between 5 and 10 ms (Beiter & Hogan, 1973; Vivion et al., 1980). When a stimulus with a 50-ms rise/fall time is used to elicit the response, the MLR is not detectable (Beiter & Hogan, 1973).

The effects of rise time on the MLR have not been investigated using noiseburst stimuli. Further research on the effects of rise time and stimulus duration on the MLR is needed.

Similar to the ABR rise time studies, these MLR studies indicate that increases in rise time produce increases in latencies and decreases in amplitude for responses evoked by various tonal stimuli. In addition, increases in rise time above 5 ms result in an amplitude decrease for both the ABR and MLR.

Effective Duration of the Stimulus

Physiologically, the effective duration of the stimulus represents the maximum duration of the stimulus integrated by the evoked potential. The evoked potential can only be as frequency specific as the portion of the tone which contributes to the response. Knowing this maximum duration will further define Brinkmann and Scherg's concept of "virtual trigger time", which represents the point on the rise time when the nerve cells or fibers eliciting the evoked potential are activated (Brinkmann & Scherg, 1979).

In order to determine the effective duration of the stimulus, a "constant-slope" rise-time paradigm has been suggested. In this paradigm, which is schematically described in figure 5, the slope of the stimulus is kept constant while the rise time, and consequently the final peak to peak amplitude of the stimulus, varies. The initial 2 ms of the stimulus with the 8-ms rise time is the same as the first 2 ms of the stimulus with the 4-ms rise time as well as the stimulus with the 2-ms rise time. Thus, if the initial 2 ms of the stimulus determines the response, then further increases in rise time will not produce further increases in response amplitude. Because of the constant slope (across different rise times), the peak-to-peak amplitudes of the stimuli increase with increases in rise time (i.e., the stimulus with an 8-ms rise time is presented at a 6-dB higher intensity than that with a 4-ms rise time).

The premise of the constant-slope rise-time paradigm is that at supra-threshold, the first cycle of the stimulus stimulates the cochlea, initiating a synchronized neuron discharge. The succeeding cycles cause more neuron discharges, and the sum of all these responses are recorded at the scalp. Contributions from later cycles of the stimulus will

continue until the critical or effective duration for the response to the tone is reached (Kodera et al., 1983).

The effective duration of the stimulus for the ABR

Studying responses from cats, Kodera and colleagues reported that increasing the rise time of a tone while keeping the slope constant causes increases in amplitude until a critical duration is reached. Further increases in rise time do not result in further increases in ABR amplitude (Kodera et al., 1983). Longer rise times are necessary to reach this critical duration for lower intensity stimuli, suggesting longer effective durations for lower intensity stimuli. The effective portion of the tonal stimuli for the ABR extended between 4 to 8 ms for responses to 500-Hz tones, and between 2 to 4 ms for responses to 2000-Hz tones. Viewed in terms of number of cycles, these effective durations suggest that the number of stimulus cycles contributing to the response are the first 2 to 4 cycles for the 500-Hz stimuli and the initial 4 to 8 cycles for the 2000-Hz tones (Kodera et al., 1983).

Studying humans, Suzuki and Horiuchi also attempted to determine the effective duration of the stimuli for the ABR using the constant-slope rise- time paradigm (Suzuki & Horiuchi, 1981). In their study, they assessed changes in latency and response threshold to determine the contribution of later stimulus cycles to the tone-evoked ABR. For the 2000-Hz stimuli, rise times between 0.5 and 5 ms evoked ABRs with similar latencies and amplitudes for a series of rise times ending at 76 dB ppe SPL (5-ms rise time). At lower stimulus intensities (starting at 41 dB ppe SPL), the latency of the response increases with increasing rise times up to the 1.5 ms rise time. ABR thresholds were lower for the 0.5 and 1 ms rise time and similar for rise times of 1.5 ms and above. Suzuki and Horiuchi concluded that for the ABR elicited by the

2000-Hz tones, the effective duration of the stimulus is intensity-dependent, with effective durations of 0.5 ms for responses elicited by moderate intensities, and 1.5 ms for responses elicited by low intensities (Suzuki & Horiuchi, 1981). For the 500-Hz stimuli, rise times between 1 and 10 ms were used to evoke the ABR. The amplitude of the response did not increase beyond that of the response to the 3-ms rise time for the intensity series ending at 76 dB ppe SPL (10-ms rise time). The latencies of the ABR to the 500-Hz tones were variable, with general trend of increases in latency with increases in rise times. The response threshold as a function of stimulus intensity was lower for the 1- and 2-ms rise time and similar for rise times of 3 ms and above (Suzuki & Horiuchi, 1981). Suzuki and Horiuchi thus concluded that the effective duration of the stimulus for the ABR elicited by 500-Hz tones is 3 ms for responses elicited by both moderate and low intensities (Suzuki & Horiuchi, 1981). Based on these results, Suzuki and Horiuchi concluded that the initial 3 cycles of the 2000-Hz tone and the first 1.5 cycles of the 500-Hz tone are the essential portions of the stimulus which evoke the human ABR (Suzuki & Horiuchi, 1981).

The results from both studies suggest that the effective duration of the stimulus which elicits the ABR is dependent both upon stimulus frequency and intensity (Kodera et al., 1983; Suzuki & Horiuchi, 1981). The methodology of determining the effective duration of the stimulus, however, differed between the two studies. For moderate-intensity stimuli, Kodera and colleagues determined the effective duration of the stimulus by analyzing amplitude changes, whereas Suzuki and Horiuchi determined the effective duration of the stimulus mainly by analyzing latency changes (Kodera et al., 1983; Suzuki & Horiuchi, 1981). The latency of the ABR, however, is affected differently by increases in rise time compared to increases in intensity. Increases in rise time

increase the latency of the response (e.g., Beattie et al., 1984; Brinkmann & Scherg, 1979; Hecox et al., 1976; Kodera et al., 1977a; Kodera et al., 1979; Stapells & Picton, 1981; Suzuki et al., 1977). In contrast, increases in intensity cause the latency of the response to decrease (e.g., Beattie & Boyd, 1985; Beattie & Kennedy, 1992; Gorga et al., 1988; Kodera et al., 1977a; Picton et al., 1979; Stapells & Picton, 1981; Suzuki et al., 1977; Wu & Stapells, submitted). In the constant-slope rise time paradigm, both rise time and intensity increase simultaneously. Therefore, any changes in latency represent a complex trade-off between rise time and intensity, and may not represent changes due to the effective duration of the stimulus. Kodera and colleagues on the other hand, relied solely on the amplitude of the response to determine the effective duration of the stimulus (Kodera et al., 1983). That study, however, was carried-out in cats and may not apply directly to humans. Thus, in this thesis study, the constant-slope paradigm is employed, and changes in response amplitude used to determine the effective duration of the stimulus.

The effective duration of the stimulus for the MLR

To date, no published studies have evaluated the effective duration of the stimuli for the MLR using the constant-slope rise time paradigm.

When assessing auditory sensitivity using the auditory brainstem and middle latency responses, the primary objective of using the ABR and MLR is to specify, as accurately as possible, an individual's hearing status for different frequencies. Thus, it is essential to select acoustic stimuli which will elicit frequency-specific responses. When selecting the rise time for the stimulus, a compromise must be made

between a longer duration stimulus, which has a more frequency-specific acoustic spectrum, and a shorter duration stimulus, which is necessary for obtaining a synchronized response, but has some spectral splatter. In order to optimize stimulus selection, it is essential to know which portion of the stimulus elicits the response. The effective duration of the stimulus represents the longest portion of a stimulus which still contributes to the response. Increasing the stimulus rise time beyond this effective portion will not improve the responses frequency specificity. Due to the limitations of ABR studies of the effective duration of stimuli, and to the absence of similar MLR studies, further research in humans is needed to determine the effective duration of the ABR and MLR.

The present study is designed to determine the effective duration of the stimulus for the ABR and MLR. In chapter 2, the effective durations of the ABR and MLR evoked by noisebursts, and tonal stimuli (2000- and 500-Hz) are determined. In chapter 3, the effective durations of specific cochlear regions are determined in order to determine whether differences in the effective duration of the stimulus are stimulus- or cochlear-based. Implications and suggestions for future studies are discussed in chapter 4.

Footnotes

1. Pb is P1, which is considered a component of the slow cortical auditory evoked potentials (i.e., not MLR)

2. This is the typical usage and definition of stimulus envelope in the auditory evoked potential/audiology literature. This is different than the definition typically used in the physical/acoustic sciences where rise time is defined = 10% - 90% amplitude (Gorga & Neely, 1994).

FIGURE CAPTIONS

Figure 1. The grand means (n=12) of ABRs and MLRs evoked by 500- and 2000-Hz stimuli at 66 dB ppe SPL.

Figure 2. Presents the ascending auditory pathways (Copied with permission from the Ear-Lab at Boston University, at http://www.earlab.bu.edu).

Figure 3. Electrical spectra of the noisebursts, 2000-, and 500-Hz tonal stimuli with rise times ranging from 0.5 to 8 ms. Stimulus level was kept constant across rise time and frequency.

Figure 4. The "constant-intensity rise-time" paradigm. In this paradigm, stimulus intensity is kept constant with increasing rise time and slope.

Figure 5. The "constant-slope rise-time" paradigm. In this paradigm, stimulus rise-time slope is kept constant with increasing rise time and peak intensity.

Figure 1

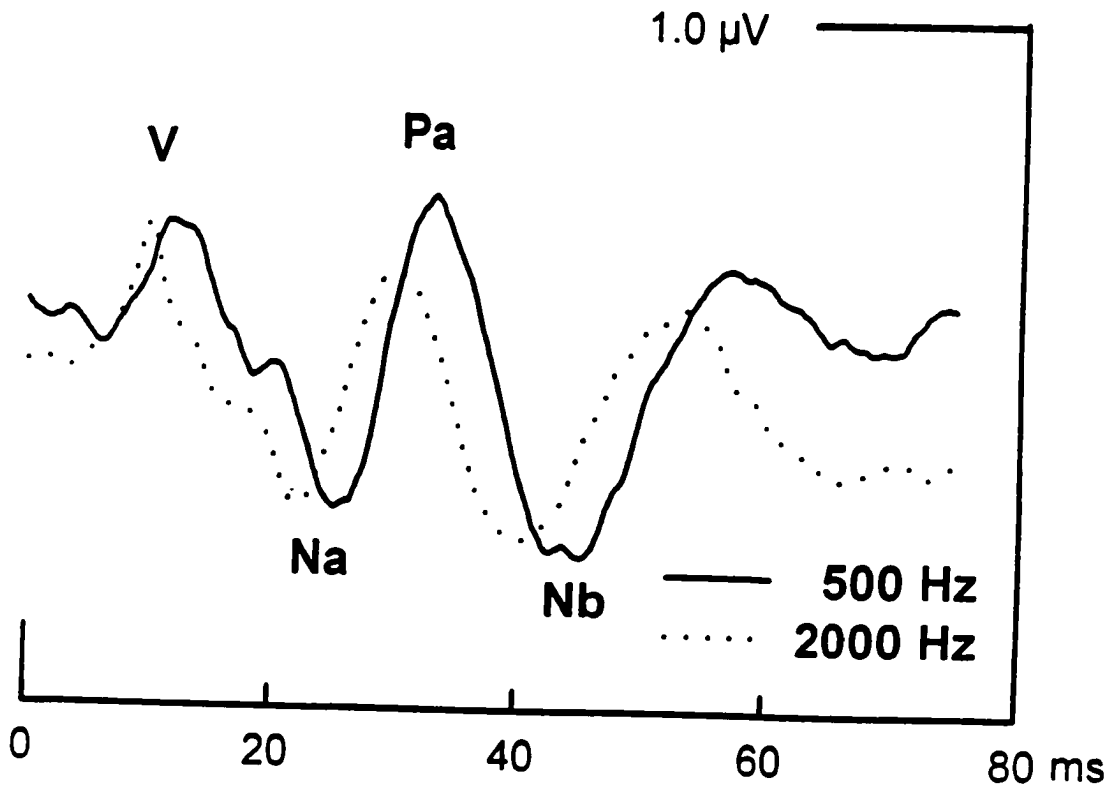
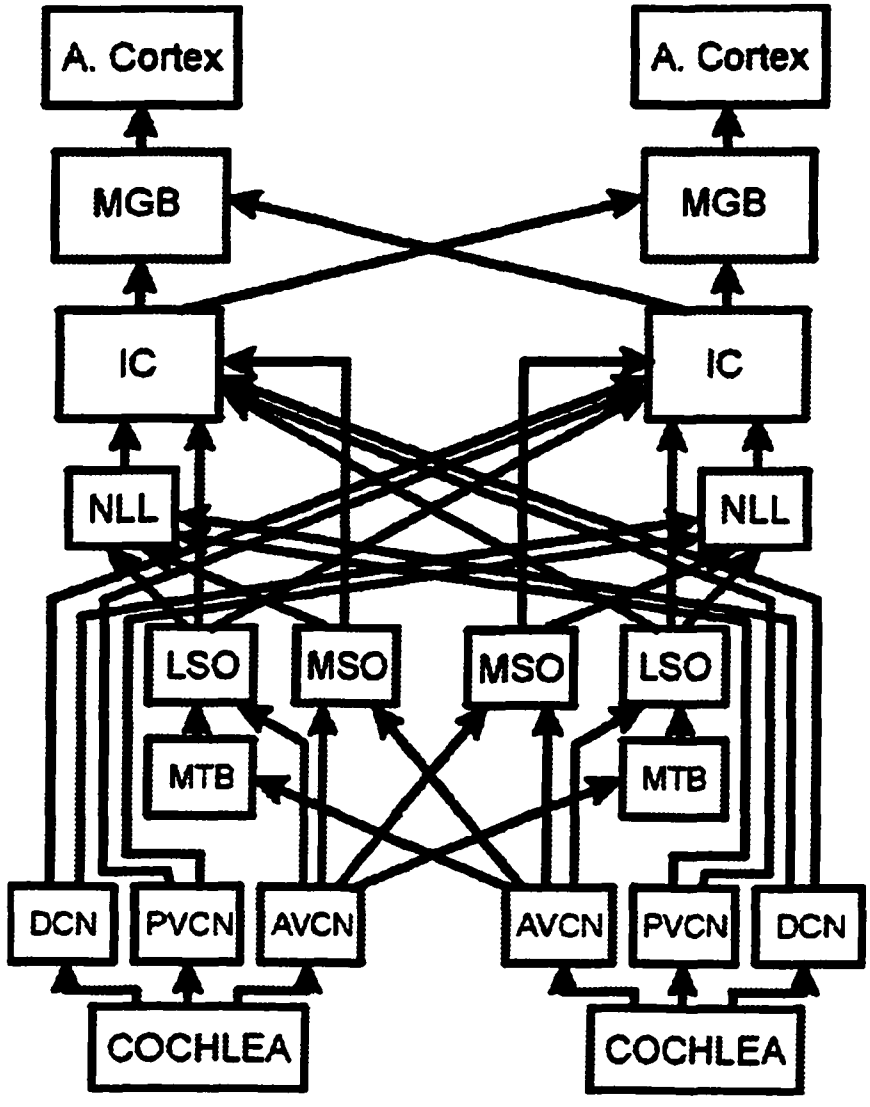


Figure 2



AVCN = anteroventral cochlear nucleus
PVCN = posteroventral cochlear nucleus
DCN = dorsal cochlear nucleus
MTB = medial nucleus of the trapezoid body
LSO = lateral superior olivary complex
MSO = medial superior olivary complex
NLL = nucleus of thelateral lemniscus
IC = inferior colliculus
MGB = medial geniculate body

(Copied with permission from the Ear-Lab at Boston University, at http://earlab.bu.edu)

Figure 3

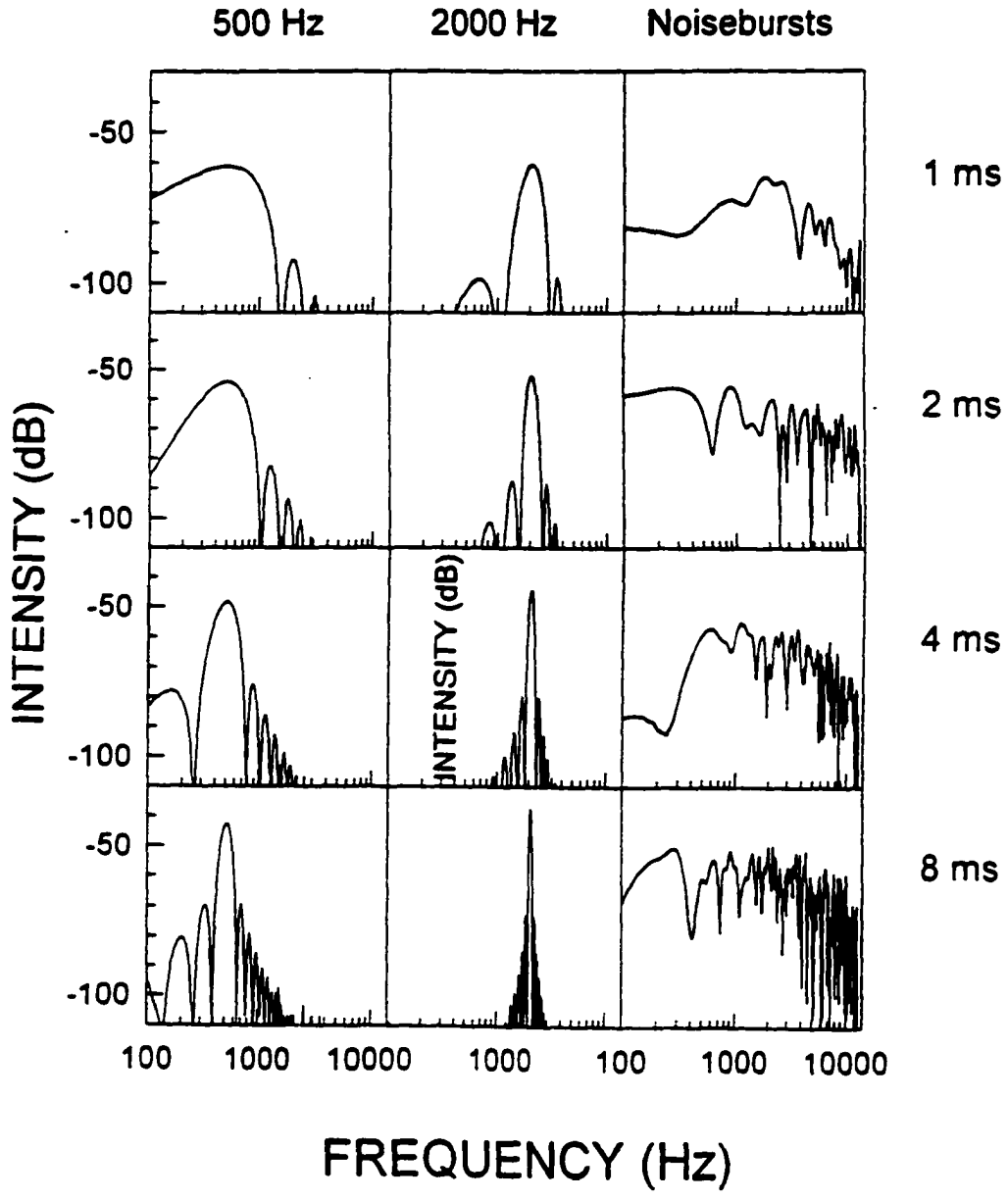
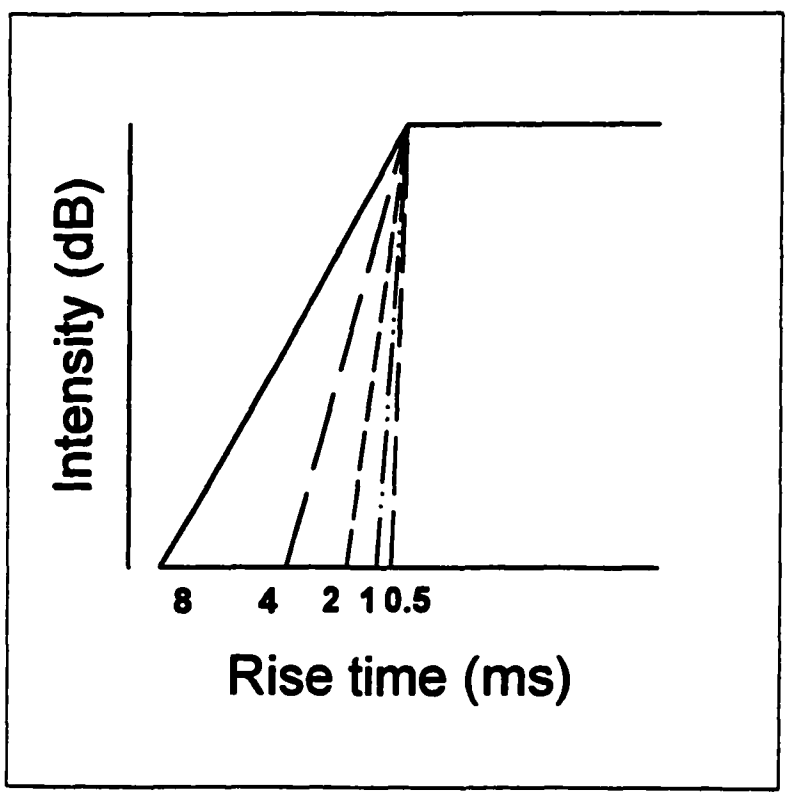


Figure 4



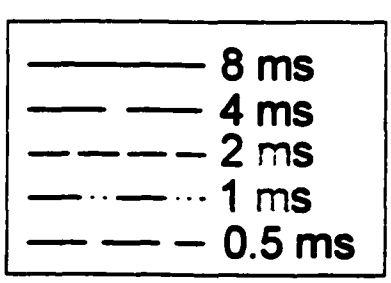
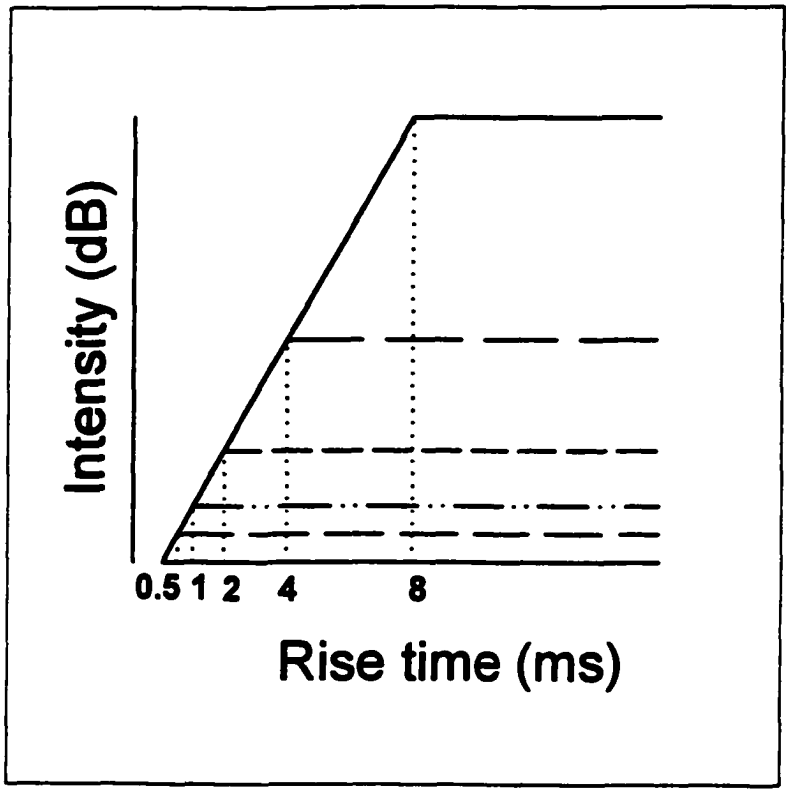
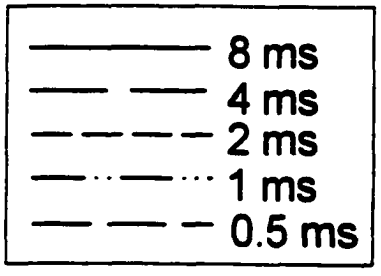


Figure 5





CHAPTER 2: THE EFFECTIVE DURATION OF THE STIMULUS FOR THE AUDITORY BRAINSTEM AND MIDDLE LATENCY RESPONSES

A. ABSTRACT

Objective: The first study of the dissertation was designed to determine the effective duration of the stimulus for ABR and MLR elicited by different stimuli using the "constant-slope" rise-time paradigm. In the "constant-slope" rise-time paradigm, the slope of the rise (rather than the final intensity) for different rise times is kept constant. This results in higher stimulus intensities for the longer rise. The effective duration of the stimulus was reached when the amplitude of the response no longer showed growth even though the intensity of the stimulus continued to increase. In this study, answers to the following questions were sought: (1) What is the effective duration of the stimulus for the auditory brainstem response (ABR) and middle latency response (MLR) evoked by the broadband (noiseburst) stimuli? (2) What is the effective duration of the stimulus for the ABR and MLR evoked by tonal (500- and 2000-Hz) stimuli? (3) Is there a difference in effective durations for the different stimuli (i.e., 2000- and 500-Hz tones, or noisebursts)? (4) Is there a difference between the ABR and MLR in the effective duration of the stimuli?

Design: ABRs and MLRs were recorded from 12 normal-hearing adults. The acoustic stimuli were 500- and 2000-Hz tones, and noiseburst stimuli. The stimuli consisted of linearly-shaped envelopes with rise times ranging from 0.5 ms to 12 ms. With each doubling of rise time, the amplitude of the stimulus doubled, increasing the intensity of the stimulus (in dB ppe SPL) by 6 dB. The intensity of the stimuli ranged from 54 dB ppe SPL for stimuli with 0.5 ms rise time to 80.5 dB ppe SPL for the 12 ms rise time. In this "constant-slope" rise-time paradigm, the slope of the stimulus is kept constant while the rise time and consequently the intensity of the stimulus varies. Thus, the amplitude

of the response increases until a critical duration (i.e., effective duration) is reached where further increases in rise time do not result in further increases in response amplitude.

Results: Results indicate that the effective duration for the ABR and MLR is stimulus dependent, with 500-Hz results exhibiting the longest effective duration (at least 12 ms), the noiseburst results the shortest effective duration (2 ms), and 2000-Hz results falling in between (4 ms). No differences were seen between the ABR and the MLR in the effective durations of the stimuli.

Conclusions: When using the "constant-slope" rise time paradigm, ABR and MLR amplitudes increase with increases in stimulus rise time until a critical duration is reached (i.e., the effective duration). The effective durations for the ABR and MLR are stimulus dependent, with longer effective durations obtained for lower frequency stimuli, suggesting that the effective duration is determined by the region of the cochlea primarily contributing to the response, with contributions from the apical regions of the cochlea requiring longer stimuli, whereas contributions from more basal regions of the cochlea requiring shorter stimuli. Use of the term "onset" response when referring to the ABR or MLR is misleading, because at least the first 4.5 to 8 cycles of a stimulus are involved in eliciting the response. Furthermore, no differences are seen between the ABR and MLR effective durations, indicating that the commonly-held notion that the MLR is less of an "onset" response than the ABR is incorrect.

B. INTRODUCTION

The auditory brainstem (ABR) and middle latency (MLR) responses evoked by tones have often been recommended to assess auditory sensitivity in individuals who are unable to participate in conventional behavioral audiometry (e.g., Kraus & McGee, 1990, 1993; Stapells & Oates, 1997). When assessing auditory sensitivity, the primary objective of using the ABR and MLR is to specify, as accurately as possible, the patient's hearing status for different frequencies. It is, therefore, essential to select acoustic stimuli which will elicit frequency-specific responses. Frequency specificity is a term used to indicate how independent a threshold measure at one frequency is from measures at other frequencies (Stapells et al., 1994).

A practical approach to obtaining frequency-specific responses is to use frequency-specific stimuli (i.e., tones). With the use of ABR and MLR evoked by tones, subjects' thresholds have been successfully identified within 10-20 dB of their behavioral thresholds (e.g., Davis & Hirsh, 1979; Hyde, 1985; Jacobson, 1983; Kavanagh, Harker, & Tyler, 1984; Kileny, 1981; Kileny & Shea, 1986; Kodera, Yamane, Yamada, & Suzuki, 1977; Munnerley, Greville, Purdy, & Keith, 1991; Palaskas, Wilson, & Dobie, 1989; Picton, Ouellette, Hamel, & Smith, 1979; Scherg & Volk, 1983; Sininger, Abdala, & Cone-Wesson, 1997; Stapells, Gravel, & Martin, 1995; Stapells & Picton, 1981; Stapells, Picton, Durieux-Smith, Edwards, & Moran, 1990; Suzuki, Kodera, & Yamada, 1984a; Suzuki, Hirai, & Horiuchi, 1977; Suzuki & Horiuchi, 1981; Wu & Stapells, submitted).

The ABR and MLR are elicited by stimuli of relatively short duration and rise/fall times. These brief stimuli generate the synchronized discharge of the auditory nerve fibers which are required to elicit the far-field brainstem and middle latency responses (Møller, 1993). The shorter the stimulus, the more synchronized is its neural

response (Harris & Dallos, 1979; Kiang, 1965; Smith, 1979), and the larger the amplitude of the ABR and MLR (e.g., Beiter & Hogan, 1973; Hecox, Squires, & Galambos, 1976; Funasaka & Ito, 1986; Kodera et al., 1977; Salt & Thornton, 1984; Skinner & Antinoro, 1971; Stapells & Picton, 1981; Vivion, Hirsch, Frye-Osier, & Goldstein, 1980). With increases in rise time, ABR wave V and MLR wave Pa amplitudes decrease for responses to both tonal and noise stimuli. The major decrease in the ABR's amplitude occurs between rise times of 5 and 8 ms (Stapells & Picton, 1981). Similarly, major decreases in amplitude of the MLR occurs with increases in rise times above 3-5 ms (Beiter & Hogan, 1973; Vivion et al., 1980).

A systematic relationship exists between the duration, rise/fall time, frequency, and intensity of the stimulus and the stimulus spectrum (Burkard, 1984; Davis, 1976; Durrant, 1983). A brief tone contains its maximal energy at its nominal frequency, with side lobes of energy at higher and lower frequencies (Burkard, 1984; Durrant, 1983; Harris, 1978). The acoustic energy at frequencies away from the nominal frequency of the stimulus is known as "spectral splatter" (Durrant, 1983; Harris, 1978). The degree of spectral splatter is determined by the rise time, intensity, and duration of the stimulus. The rise time of the stimulus will determine the amplitudes of the side lobes relative to the amplitude of the main lobe (Burkard, 1984; Durrant, 1983; Pfeiffer, 1974). With increase in total stimulus duration, the main lobe narrows and the relative amplitude of the side lobes decrease (i.e., there is less spectral splatter).

The frequency specificity of the ABR and MLR depends on the spectral characteristics of the eliciting stimulus. In the presence of spectral splatter, the ABR and MLR may be evoked by frequencies other than the stimulus nominal frequency. Because increases in stimulus rise

time decreases spectral splatter and increases frequency specificity (Davis, 1976; Durrant, 1983), the ideal rise time would be the longest possible before response amplitude declines. Therefore, in selecting an optimal rise time for the stimulus, a compromise must be reached between the long-duration stimulus, which provides a more frequency-specific spectrum, and the shorter duration stimulus, which is necessary for obtaining a synchronized response, but has some spectral splatter.

The "effective duration" of the stimulus represents that portion of the stimulus which contributes to the response. Thus, increasing the stimulus rise beyond this effective portion will not change the response and consequently will not improve the response's frequency specificity. In order to determine the effective duration of the stimulus, a "constant-slope" rise-time paradigm may be used. In this paradigm (see Figure 1), the slope of the rise of the stimulus is kept constant while the rise time, and consequently the intensity of the stimulus, increases. Thus, the initial 2 ms of the stimulus with the 8-ms rise time is the same as the first 2 ms of the stimulus with the 4-ms rise time as well as the stimulus with the 2-ms rise time. The underlying premise of the paradigm is that if the initial 2 ms of the stimulus determines the response, then further increases in rise time will not produce further increases in response amplitude (Kodera, Marsh, Suzuki, & Suzuki, 1983; Suzuki & Horiuchi, 1981).

Physiologically, the premise of the constant-slope rise-time paradigm is that at supra-threshold, the first cycle of the stimulus stimulates the cochlea, initiating a synchronized neuron discharge. The succeeding cycles cause more neuron discharges, and the sum of all these responses are recorded at the scalp. Contributions from later cycles of the stimulus will continue until the critical or effective duration for the response to the tone is reached (Kodera et al., 1983).

Kodera and colleagues (Kodera et al., 1983) and Suzuki and Horiuchi (Suzuki & Horiuchi, 1981) used this paradigm to determine the effective duration of the stimulus. Studying cats, Kodera and colleagues reported that increasing the rise time of a tone while keeping the slope of the rise constant caused no significant changes in the amplitude of the ABR after a critical duration was reached (Kodera et al., 1983). This critical duration was 2 to 4 ms for responses to the 2000-Hz tones, and 4 to 8 ms for responses to the 500-Hz tones (Kodera et al., 1983).

Studying humans, Suzuki and Horiuchi (1981) attempted to determine the effective duration using the constant-slope rise-time paradigm (Suzuki & Horiuchi, 1981). In their study, latency changes and response detectability at threshold were used to determine the effective duration of the stimulus. They concluded that the effective duration of the stimulus is 1.5 ms for the ABR evoked by 2000-Hz tones, and 3 ms for the ABR evoked by 500-Hz tones (Suzuki & Horiuchi, 1981).

Kodera and colleagues (Kodera et al., 1983) and Suzuki and Horiuchi (Suzuki & Horiuchi, 1981) determined the effective duration of the stimulus using different measures. Kodera and colleagues (Kodera et al., 1983) analyzed amplitude changes, whereas Suzuki and Horiuchi (Suzuki & Horiuchi, 1981) primarily considered latency changes. The latency of the ABR, however, is affected differentially by increases in rise time and intensity. The ABR latency decreases with increases in stimulus intensity, but increases with increases in rise time (e.g., Kodera et al., 1983; Stapells & Picton, 1981; Suzuki & Horiuchi, 1981). In the constant-slope paradigm, however, both rise time and intensity increase simultaneously. Therefore, any changes in latency represent a complex trade-off between them and may not necessarily represent changes in effective duration. Amplitudes, therefore, are a better measure.

Kodera and colleagues relied solely on the amplitude of the response (Kodera et al., 1983). That study, however, was carried-out in cats and may not apply directly to humans. To date, there are no studies on the effective duration of the stimulus for the MLR.

Due to the limitations of these earlier studies, and to the absence of similar MLR studies of the effective duration of stimuli, further research in humans is needed to determine the effective duration of the stimulus for the ABR and MLR. The present study is designed to determine the effective duration of the stimulus for the ABR and MLR elicited by stimulation of different regions of the cochlea. Responses from the whole cochlea are elicited by gated noiseburst stimuli. Responses from more basal and apical regions of the cochlea are elicited by moderately high- (2000-Hz) and low- (500-Hz) frequency tonal stimuli. Answers to the following questions are sought: (1) What is the effective duration of the stimulus for the brainstem and middle latency responses evoked by noisebursts? (2) What is the effective duration of the stimulus for the ABR and MLR evoked by 500- and 2000-Hz stimuli? (3) Is there a difference in effective durations for the different stimuli (i.e., 2000- and 500-Hz tones, or noisebursts)? And, (4) Is there a difference between the ABR and MLR in the effective duration of the stimuli?

C. METHODS

Subjects

Twelve subjects with normal hearing sensitivity and no history of neurological disorder participated in the study. The age range of the subjects was 18-42 years, with a mean age of 29 years. All subjects met the following criteria: (1) pure-tone audiometric thresholds of 15 dB HL (ANSI, 1989) or better at 250, 500, 2000 and 4000 in both ears; (2) a

normal tympanogram (220-Hz probe tone) with a peak pressure between -100 and +50 daPa; (3) presence of ipsilateral acoustic reflex at 1000 Hz, and (4) no significant neurologic history.

Stimuli

The acoustic stimuli used to elicit the ABR and MLR were 500- and 2000-Hz short-duration tones, as well as short-duration noisebursts, all synthesized (60,000 Hz D/A rate) and presented by a Neuroscan STIM system. The acoustic stimuli were calculated using peak-to-peak equivalent (ppe) sound pressure levels. The stimuli were low-pass filtered at 10,000 Hz to prevent aliasing and attenuated (Coulbourn Instruments S85-08) before being presented to the subject's ear via an ER-3A insert earphone. The subject's test ear was selected randomly.

The stimuli consisted of linearly-shaped envelopes with rise times of 1, 2, 4, 8 and 12 ms for the 500-Hz stimuli, and 0.5, 1, 2, 4, and 8 ms for the noiseburst and 2000-Hz stimuli. The intensity of the stimuli ranged from 80.5 dB ppe SPL for stimuli with the 12-ms rise time to 54 dB ppe SPL for the 0.5-ms rise time. With each doubling of rise time, the amplitude of the stimulus doubled, increasing the intensity of the stimulus (in dB ppe SPL) by 6 dB. All stimuli had a 36-ms fall time and no plateau. The long and gradual fall time was chosen in order to eliminate or reduce any effect of possible offset responses because fall times ranging from 0.5 ms to 10 ms have produced an "off" response (e.g., Brinkmann & Scherg, 1979; Van Campen, Hall, & Grantham, 1997).[1] The noise stimuli were obtained from a burst of white noise which is characterized by being aperiodic and by containing components over a broad frequency range. However, once a restricted noise sample is taken, the sample contains a specific (albeit random) sample of frequencies. Therefore, to ensure the quasi-random characteristics of

the noise stimuli in this study, three different samples of the noiseburst stimuli were used for each rise time. Figure 2(a, b, and c) presents the electrical waveforms of the noisebursts and 2000- and 500-Hz tonal stimuli at the different rise times. Figure 3 presents the electrical spectra of the three stimuli with the different rise times (and fall times equal to the rise times). In both Figure 2 and 3, the constant-slope rise-time paradigm is employed.

Table 1 presents the behavioral thresholds obtained for the three stimuli with *equal* rise and fall times of 1-, 2-, 4-, and 8-ms. Overall, lower thresholds are obtained for the 2000-Hz tonal stimuli. Thresholds for the noiseburst and 500-Hz tonal stimuli are similar. As expected, shorter rise times result in higher thresholds.

All stimuli and the broadband noise were calibrated using a Brüel and Kjaer DB0138 2-cc adaptor and 4152 coupler, 1-inch condenser microphone (type 4144) and 2209 sound level meter. Daily calibration checks were performed for the stimuli with the 8-ms rise time (2000 Hz, 500 Hz, and noiseburst).

The stimuli were presented monaurally at a rate of 10.9/s. This rate was chosen to insure optimum MLR amplitudes (McFarland et al., 1975; Picton et al., 1974) and to avoid superimposition of the ABR and MLR (Galambos, Makeig, & Talmachoff, 1981; Stapells & Picton, 1981; Stapells, Linden, Suffield, Hamel, & Picton, 1984; Suzuki, Hirabayashi, & Kobayashi, 1984b).

ABR and MLR Recordings

Single-channel recordings of the ABR and MLR were obtained using gold-plated cup electrodes placed on the vertex (Cz) and ipsilateral earlobe (A1 or A2) of each subject, with a forehead electrode (Fpz) serving as ground. Interelectrode impedances were less than 3000 Ohms.

The EEG was amplified (gain = 100,000) and analog filtered (10-3000 Hz, 6 dB/octave) before being digitized. The analysis time was 3 ms pre-stimulus and 80 ms post-stimulus. Trials containing amplitudes above ±25 μV were automatically rejected. The averaged responses were digitally filtered offline using a 1000-Hz lowpass filter (12 dB/octave slope, zero phase shift).

Eight replications of 1000 trials each, for a total of 8000 trials, were obtained for each stimulus rise time. A total of 8000 trials were used in order to ensure a response with a good signal-to-noise ratio at all rise times. In order to minimize extraneous muscle movement and maximize patient comfort during the recordings, the data were collected in blocks of 1000 trials. Half of the replications (four replications of 1000 trials) were obtained with a condensation initial onset polarity, and the other half with a rarefaction initial onset polarity. In order to reduce any stimulus-related electrical artifacts, cochlear microphonic (Davis, 1976), and frequency-following response (Davis & Hirsh, 1976; Gerken, Moushegian, Stillman, & Rupert, 1975) present in the single polarity response, the condensation and rarefaction initial onset polarity replications were added offline to produce responses of alternating polarity and were presented via an EAR-3A insert earphone.

To ensure consistency in the recordings between recording sessions, the Grass model 12 EEG amplifiers were calibrated daily. The amplitude of the 50-μV pulse was always within ±2.5 μV of 50 μV.

Procedure

During the recording sessions, the subjects were seated on a recliner in a double-walled sound-attenuated room and were not able to observe the experimenter. Subjects were asked to sit quietly and relax

while reading a book. The subjects were monitored visually and their EEG observed to ensure that they remain in a quiet and relaxed state, but remained awake.

Each subject was paid for attending in four sessions for a total of approximately 20 hours. Each session lasted approximately five hours. The presentation order of stimulus frequencies and rise-time conditions was randomized across subjects.

Data analysis

Decisions regarding the presence or absence of a response were made by combining the ratings of three individuals who were experienced with ABR and MLR waveforms and their measurements.

Each subject's ABR/MLR waveforms were combined to be viewed as waveform sets. Each set represented the subjects's ABR/MLR waveforms for a specific frequency and rise time condition. Each set contained (i) the grand average of 8000 sweeps, (ii) two replications of 4000 sweeps each, and (iii) four replications of 2000 sweeps each.

The rating order of the subjects, frequencies, and rise-time conditions were randomized across raters. Each rater was "blind" as to the stimulus type and envelope (i.e., rise time) as well as to the subject's identity. Each of the raters independently rated the individual ABR/MLR peaks on a scale of "1" to "4" based on visual observation. The peaks rated were ABR wave V, ABR/MLR wave Na, MLR wave Pa, and MLR wave Nb. The rating was based on the grand average response (8000 sweeps), the 2 x 4000 sweeps and the 4x2000 sweeps replications of the response. The score was based on the replicability of the peak in question. The significance of the peak ratings were as follows: a score of "4" indicated a definite response, a score of "3" indicated a probable response present, a score of "2" indicated probably no response

present, and a score of "1" indicated a definite no response. The raters scores for each peak were averaged to obtain a combined score. Peaks with a combined score of ≥2.5 were considered "response present" (Oates & Stapells, 1997a, Oates & Stapells, 1997b; Stapells 1984; Stapells et al., 1990; Wu and Stapells, submitted).

In order to ensure agreement between the three raters, inter-rater agreement was assessed in a pilot study in which the raters rated a set of 50 ABR/MLR waveforms. Using a 4-point scale for rating waves V, Na, Pa and Nb, the raters assigned the same score 50% of the time and were within one rating category 97.5% of the time.

In this study, wave V-Na was selected to represent the ABR and wave Pa-Nb to represent the MLR. Wave Na is the first negativity which is reliably detected after wave V. Physiologically, both wave V and wave Na are likely generated subcortically (Durrant et al., 1994; Hashimoto, 1982; Legatt et al., 1988). Waves Pa and Nb, which represent the MLR, are both generated in cortical regions (Hashimoto, 1982; Kileny et al., 1987; Scherg & von Cramon, 1986; Woods et al., 1987). Peak-to-peak amplitude measures of ABR wave V-Na and MLR wave Pa-Nb for each subject were obtained from each subject's grand average for those peaks judged to contain a response (i.e., having a combined rating of 2.5 or greater). Wave V was defined as the maximum vertex-positive peak occurring between 6 and 20 ms following stimulus onset (Mackersie, Down, & Stapells, 1993; Nousak & Stapells, 1992; Oates, 1996; Stapells & Picton, 1981; Wu and Stapells, submitted). Na was defined as the negativity preceding Pa in the 12-30 ms window following stimulus onset (Oates, 1996; Stapells & Picton, 1981; Wu and Stapells, submitted). Pa was defined as the maximum vertex-positive peak occurring 25-50 ms following stimulus onset(Oates, 1996; Wu and Stapells, submitted). Nb

was defined as the negativity following Pa in the 35-70 ms following stimulus onset.

An estimate of the residual noise level of the waveform was entered as the amplitude for peaks judged as absent (as determined by a mean rating of less than 2.5).[2] In this study, out of 360 possible amplitude measures for ABR wave V-Na and MLR wave Pa-Nb, the residual noise level amplitude was used only once to estimate a wave (Pa-Nb).

Statistical analyses

Peak-to-peak amplitudes and SDR values were analyzed using descriptive statistics and repeated-measures analyses of variance (ANOVAs). Huynh-Feldt epsilon corrections for the degrees of freedom for repeated measures were employed when appropriate (Huynh & Feldt, 1970). Probabilities reported reflect these adjustments. Results of ANOVA were considered statistically significant when $p < .01$. When significant results were found in the ANOVAs, Newman-Keuls *post hoc* tests were performed to determine the pattern of the significant differences. Results of these *post hoc* analyses were considered significant when $p < .05$.

D. RESULTS

Figure 4 displays the grand-mean waveforms (n = 12 subjects) evoked by the noiseburst, 2000- and 500-Hz stimuli at the different rise times. Figure 4a displays the grand-mean waveforms evoked by the noiseburst stimuli with rise times ranging from 0.5 to 8 ms. ABR wave V-Na and MLR wave Pa-Nb are labeled. For these grand-mean waveforms, the amplitudes of ABR wave V-Na to the 1-, 2-, 4- and 8-ms rise-time stimuli are much larger than for the 0.5-ms rise time. The response amplitude increases rapidly until the 2-ms rise time, where the largest

amplitude for wave V-Na evoked by the noiseburst is obtained. Similar to the ABR, the MLR waveforms representing the 1-, 2-, 4- and 8 ms rise times are much larger than the 0.5-ms rise time, but are not different from each other.

Figure 4b displays the grand-mean waveforms evoked by the 2000-Hz tonal stimuli with rise times ranging from 0.5 to 8 ms. For these grand-mean waveforms, the amplitude of ABR wave V-Na increases from the 0.5-ms rise time to the 4-ms rise time, after which further increases in rise time do not result in further amplitude growth. The largest amplitude is obtained with the 4-ms rise time. The responses obtained for MLR wave Pa-Nb evoked by the 2000-Hz tonal stimuli at the various rise times are similar in amplitude. The largest Pa-Nb response is obtained with the 4-ms rise time.

Figure 4c presents the grand-mean waveforms evoked by the 500-Hz tonal stimuli with rise times ranging from 1 to 12 ms. For these grand-mean waveforms, the amplitude of ABR wave V-Na increases from 1- to 12-ms rise times, with the largest amplitude obtained for the 12-ms rise time. Similar to the ABR, MLR wave Pa-Nb increases from the 1-ms to the 12- ms rise time, with the largest amplitude obtained for 12 ms. Unlike the ABR, the major amplitude increase occur initially between the 1 and 4-ms rise time, drops at 8-ms and than increases again at the 12-ms rise time.

Figure 5 presents the means and standard deviations of the amplitudes of ABR V-Na and MLR Pa-Nb evoked by the three stimuli (i.e., noisebursts, 2000-and 500-Hz tones) as a function of rise time. The pattern of amplitude growth is unique for each stimulus. Overall, the noiseburst results show an immediate increase in amplitude, rising until the 2-ms rise time. After 2 ms, further increases in rise time do not result in further increase in response amplitude. For the 2000-Hz

tones, a gradual increase in amplitude occurs until the 4-ms rise time is reached. For the 500-Hz tones, the amplitude of the response increases continuously until the 12-ms rise time.

For ABR wave V-Na evoked by the noiseburst stimuli, a one-way ANOVA indicates a significant rise time main effect [$F(4,44)=11.33$, $\varepsilon=1.000$, $p < .001$]. *Post hoc* testing indicates that the amplitudes of the 1, 2, 4, and 8 ms rise times are significantly larger than those obtained for the 0.5 ms rise time but are not different from each other. These results suggest an effective duration of 1 ms. For MLR wave Pa-Nb, a one-way ANOVA revealed a significant rise-time main effect [$F(4,44)=5.27$, $\varepsilon=.739$, $p < .001$], and Newman-Keuls *post hoc* testing indicates that the amplitudes of the 1-, 2-, 4-, and 8-ms rise times are significantly larger than those of the 0.5-ms rise time and are not different from each other. Again, this suggests a 1-ms effective duration for the MLR evoked by noisebursts.

Two-way repeated measures ANOVAS were calculated to determine whether there is a difference between the amplitude growth of wave V-Na and compared to wave Pa-Nb. Results indicate that there is no wave effect [$F(1,11)=.474$, $p = .505$] and no rise x wave interaction [$F(4,44)=.813$, $p = .524$]. These results do not support the suggestion that the amplitude growth pattern of ABR wave V-Na is different than the amplitude growth pattern obtained for MLR wave Pa-Nb for noisebursts.

For ABR wave V-Na evoked by the 2000-Hz stimuli, the results of a one-way ANOVA demonstrate a significant rise-time effect [$F(4,44)=5.067$, $\varepsilon=1.000$, $p = .002$]. *Post hoc* testing indicates that the amplitudes of the 4- and 8-ms rise times are significantly larger than the amplitude responses of the 0.5- and 1-ms rise times. These results suggest that the effective duration of the stimulus for wave V-Na evoked by the 2000 Hz stimulus is 4 ms. The MLR Pa-Nb results show a maximum amplitude at

4 ms, however, the results of a one-way ANOVA indicates no significant effect of rise time [$F(4,44)=.765$, $\varepsilon=1.000$, $p = .553$].

Results of a two-way repeated measures ANOVA on the 2000-Hz results indicate a trend toward a greater effect of rise-time on V-Na compared to Pa-Nb, however, this trend did not reach significance [$F(4,44)=2.507$, $p = .055$]. These results suggest that the null hypothesis can be rejected only with guarded confidence, and that there is no significant difference between the amplitude growth pattern of the ABR *versus* that of the MLR for 2000-Hz tones.

For ABR wave V-Na evoked by the 500-Hz stimuli, results of a one-way ANOVA demonstrate a significant rise-time effect [$F(4,44)=7.043$, $\varepsilon=1.000$, $p < .001$]. *Post hoc* testing indicates that the amplitudes of the 8- and 12- ms rise times are significantly larger than the amplitude of responses of the 1-, 2- and 4- ms rise times, but are not different from each other. These findings suggest an effective duration of the stimulus for the 500-Hz stimulus of at least 8 ms. For MLR wave Pa-Nb evoked by the 500-Hz stimuli, a one-way ANOVA revealed only a trend for an increase in amplitude with increases in rise time [$F(4,44)=2.609$, $\varepsilon=1.000$, $p = .048$].

Two-way repeated measures ANOVA indicate that there is no significant difference between V-Na and Pa-Nb [$F(1,11)=.620$, $p = .447$] but that there is a significant effect of rise-time [$F(4,44)=8.05$, $\varepsilon=.956$ $p < .001$]. Newman-Keuls *post hoc* analysis revealed that the amplitude of the 12-ms rise time was significantly larger than the amplitude of the shorter rise times. These results suggest that the effective duration of the stimulus for the 500-Hz stimulus is at least 12 ms, with no significant difference between the ABR and the MLR. Because the amplitude of the response continues to grow up to and

including 12-ms rise time, it is possible that amplitude continues to increase for rise times greater than 12 ms.

The data obtained in this study suggest that the effective duration for wave V-Na and wave Pa-Nb range essentially between 1 and 2 ms for the noiseburst stimuli, 4 to 8 ms for the 2000-Hz stimuli, and at least 12 ms for the 500-Hz stimuli. In addition, the data obtained in this study does not support the hypothesis that the amplitude growth pattern of MLR wave Pa-Nb is different than the amplitude growth pattern obtained for ABR wave V-Na.

Another method to determine the effective duration of a stimulus for the ABR or MLR is by determining the rise time resulting in the largest amplitude for each stimulus for each subject. For responses evoked by noisebursts, most subjects obtained the largest amplitude response at the 2-ms rise time for both the ABR and MLR. For responses evoked by the 2000-Hz stimulus, the 8- and 4-ms rise times generated the largest amplitudes for the ABR and MLR, respectively. For the 500-Hz tones, the largest amplitudes are obtained using the 12-ms rise time. Two-way repeated measures ANOVAS indicate that there is a significant main effect for stimulus [$F(2,22)=31.186$, $\varepsilon=1.000$, $p < .001$]. Newman-Keuls *post hoc* analysis revealed that the rise time evoking the maximum amplitude by the 500-Hz stimulus is significantly longer than those for the 2000-Hz tones and the noisebursts. No significant difference between waves V-Na and Pa-Nb [$F(1,11)=.372$, $p = .554$] and no significant stimulus and wave interaction [$F(2,22)=2.1757$, $p = .137$] were obtained. Again, these data do not provide any evidence that the amplitude growth patterns of ABR wave V-Na differs from the amplitude growth patterns of MLR wave Pa-Nb across the three stimuli. These results are similar to the mean amplitude results (see Figure 5), with the noiseburst stimuli showing the shortest effective duration, 500-Hz tones showing the

longest effective duration, and 2000-Hz tones having effective durations in between. As with the mean amplitude response results, there are no significant differences between wave V-Na and wave Pa-Nb for the three stimuli.

E. DISCUSSION

The results of this study indicate that, using the "constant-slope" rise-time paradigm, ABR and MLR amplitudes increase with increases in stimulus rise time until an integration duration is reached. This integration duration is the "effective duration" of the stimulus. Further increases in stimulus amplitude do not result in substantial changes in amplitude. The effective duration of the stimulus for the ABR and MLR elicited by broadband noiseburst stimuli is approximately 1 to 2 ms. The effective duration of the ABR and MLR evoked by 2000-Hz tonal stimuli is between 4 to 8 ms, and the effective duration of the ABR and MLR evoked by the 500-Hz tonal stimuli is at least 8 to 12 ms. The effective duration of the stimulus for both the ABR and MLR is thus stimulus dependent.

The effective durations obtained in this study for the ABR evoked by 500- and 2000-Hz tonal stimuli are similar to, albeit somewhat longer than, the effective durations obtained by Kodera and colleagues for the cat ABR (Kodera et al., 1983). The absolute differences in effective durations are probably due to the physiological differences between the two species' auditory systems (e.g., Fullerton, Levine, Hosford-Dunn, & Kiang, 1987). The effective durations of at least 8-12 ms for ABR evoked by the 500-Hz tones and 4 ms for ABR evoked by the 2000-Hz tones obtained in this study appear to be substantially longer than the effective durations of 3 and 1.5 ms for the 500- and 2000-Hz stimuli previously obtained by Suzuki and Horiuchi (1981). However, Suzuki and

Horiuchi determined the effective duration of the stimulus by analyzing changes in latency and response detectability at threshold, rather than by changes in response amplitude (Suzuki & Horiuchi, 1981). Because in the constant-slope rise-time paradigm both rise time and stimulus intensity increase simultaneously, changes in latency represent a complex trade-off between these two variables, not simply differences in effective duration.

To determine whether the differences in the effective durations obtained may be due to differences in threshold, behavioral and electrophysiological thresholds for the three stimuli may be compared. The behavioral thresholds for both the 500-Hz and the noiseburst stimuli are 35 dB ppe SPL for the 1-ms rise/fall time, which is 10 dB higher than the 25 dB ppe SPL behavioral threshold obtained for the 2000-Hz stimuli (see Table 1). If the effective durations of the stimuli simply reflect the behavioral audibility of the stimuli, then the 500-Hz and noiseburst stimuli should have similar effective durations, but they do not. The ABR and MLR thresholds for 500- and 2000-Hz stimuli reported by Wu and Stapells are less than 43 dB ppe SPL for both stimuli and waves (Wu & Stapells, submitted). If the effective durations only depended on electrophysiological audibility, then the 2000- and 500-Hz stimuli should have similar effective durations. The effective durations obtained in this study do not follow these patterns, and the stimulus intensities of 54 (the lowest intensity for the noiseburst and 2000-Hz stimuli) and 60 dB ppe SPL (the lowest intensity for the 500-Hz stimulus) are sufficiently above threshold for the shorter rise times to elicit an ABR and MLR (as can be seen in Figure 4).

With increasing stimulus intensity, the ABR and MLR reach a saturation point, beyond which further increases in intensity do not yield further increases in response amplitude (e.g., Hecox & Galambos,

1974; Jewett & Williston, 1971). Studies have shown that, provided the stimulus is below approximately 100 dB ppe SPL, ABR and MLR response amplitude increases when intensity increases (ABR: Eggermont & Don, 1980; Gorga et al., 1988; Picton et al., 1981; Stapells & Picton, 1981; Starr & Don, 1988; MLR: Mendel & Goldstein, 1969; Thornton et al., 1977). For the moderate intensities used in this study (54 to 80.5 dB ppe SPL), saturation should not, therefore, be an issue. Thus, the absence of amplitude growth with increasing intensity beyond the "effective duration of the stimulus" cannot be attributed to saturation.

Some researchers have suggested that because the ABR is highly dependent on neural synchrony, it requires an abrupt stimulus onset (e.g., Gorga, Beauchaine, Reiland, Worthington, & Javel, 1984; Kraus, McGee, & Stein, 1994), whereas some have suggested that the MLR is less dependent on neural synchrony and therefore may be elicited by longer stimuli (e.g., Kileny & Shea, 1986; Kodera, Hink, Yamada, & Suzuki, 1979; Kraus & McGee, 1990; Kraus et al., 1994; McFarland, Vivion, & Goldstein, 1977; Thornton, Mendel, & Anderson, 1977). In contrast, this study does not support the suggestion that the effective durations of the stimuli for the MLR are different from those for the ABR, as it finds no significant differences between the effective durations of the ABR and MLR. Thus, the commonly-held notion that the MLR is less of an "onset" response than the ABR is incorrect.

Kodera and colleagues suggested that the effective duration of the stimulus is intensity dependent, resulting in longer effective durations for lower intensities (Kodera et al., 1983). In the present study, only one intensity range (54 dB ppe SPL at 0.5 ms to 80.5 dB ppe SPL at 12 ms) was studied. Thus, at or close to threshold, the effective duration of the stimuli might be even longer than indicated by the present study, suggesting that the optimum stimulus for obtaining more frequency-

specific auditory thresholds might have longer rise times than those in current clinical practice.

In terms of number of cycles, the effective durations obtained in this study reveal that the number of stimulus cycles contributing to the response for the different stimuli is similar, albeit longer for responses evoked by the 2000-Hz stimuli. *At least* four and a half cycles are required before responses to 500-Hz tones reach their maximum amplitude; responses to the 2000-Hz tones reach their maximum amplitude after eight cycles. The use of the term "onset" response when referring to the ABR or MLR is therefore misleading, because at least the first four and a half to eight cycles of the stimulus are effective in eliciting the response.

In practical terms, the stimuli typically recommended for clinical assessment of auditory sensitivity using the ABR have rise and fall times of 2 cycles each and a plateau duration of 1 cycle (i.e., the "2-1-2" cycles tone) (e.g., Davis, Hirsh, Popelka, & Formby, 1984; Stapells & Oates, 1997). The present study suggests that the ABR and MLR can integrate longer stimuli portions and thus, when frequency specificity is of a major concern, stimuli rise time could be extended up to the effective duration of the stimuli (i.e., 12 ms for the 500-Hz stimulus, 4 ms for the 2000-Hz stimulus, and 2 ms for the noiseburst stimulus). Further research is needed to determine whether thresholds obtained with these longer rise times correlate well with pure-tone behavioral thresholds in normal- and hearing-impaired subjects.

The shorter effective durations for higher frequency stimuli obtained in this study may be related to the trends shown in psychoacoustic studies that temporal integration times are shorter for high-frequency tones (e.g., Campbell & Counter, 1969; Plop & Bowman, 1959; Watson & Engel, 1969). This trend has also been reported by

electrophysiological studies of the cortical event-related potential N1 (Alain, Woods, & Covarrubias, 1997). Thus, the differences in effective durations as a function of frequency suggest that the frequency differences in temporal integration originate from processes at or before the level of the midbrain (i.e., the inferior colliculus level - the highest generator of ABR wave V, (Durrant et al., 1994; Hashimoto, 1982; Legatt et al., 1988).

It is possible that the difference in the effective durations between the 500- and 2000-Hz stimuli indicates the effective duration of the stimulus for the ABR and MLR is determined by outputs from the region of the cochlea primarily contributing to the response, rather than some stimulus-based difference. That is, responses originating from apical regions of the cochlea require longer stimuli than responses originating from the basal regions. In the present study, the effective duration of 1 to 2 ms obtained for the noiseburst stimuli is shorter than the effective durations obtained for the 2000- (4 to 8 ms) and 500-Hz (at least 8 to 12 ms) tonal stimuli. The effective duration of the noiseburst may, therefore, be primarily influenced by the high-frequency components of the stimulus stimulating the basal regions of the cochlea.

As suggested above, the differences in effective durations for the low- and high-frequency stimuli obtained in this study might be attributable to cochlear place-specific effects. However, at the moderate intensities used in this study, the frequency specificity of the response might be poor due to spectral splatter (Durrant, 1983), resulting in contributions from more basal regions of the cochlea in response to the low-frequency stimuli (e.g., Kiang & Moxon, 1974; Kiang et al., 1967; Özdamar & Dallos, 1976). Alternatively, the differences in the effective durations of the tonal stimuli might reflect stimulus-

specific effects such as periodicity and phase locking (Anderson, Rose, Hind, & Brugge, 1970; Hind, 1972; Kiang, 1965; Rose, Brugge, Anderson, & Hind, 1967). In order to separate these issues, the ABR and MLR could be generated by an aperiodic stimuli which generate place-specific responses. The noiseburst stimuli are aperiodic but stimulate the whole cochlea. However, using the high-pass noise/derived response technique (Don & Eggermont, 1978; Don et al., 1979; Elberling, 1974; Parker & Thornton, 1978a; Parker & Thornton, 1978b; Teas et al., 1962) to limit the noiseburst responses to specific cochlear regions, aperiodic place-specific responses can be obtained. In the next chapter (Chapter 3), the effective durations of the derived responses representing one-octave-wide regions of the cochlea centered at 500-, 1000-, and 2000-Hz evoked by noiseburst stimuli will be determined.

Footnotes

1. A pilot study using a 36-ms fall time demonstrated that responses evoked by a 36-ms fall time are very small in amplitude and are not likely to interfere with responses evoked by the rise of the stimulus (see appendix G).

2. For peaks judged as having no response, the conventional approach of assigning a zero amplitude to the response has not been used because Oates and Stapells suggested that the use of zero amplitude values (0 μV) might violate the assumptions of the ANOVA regarding normal distributions and heterogeneity of variance (Oates and Stapells, 1997b). Instead, peaks rated as "no response" were assigned the residual noise amplitude level of that recording. This residual noise level was determined by calculation of the standard deviation of the (±) response. The (±) response, calculated by subtracting one replication (4000 trials) from another, divided by two, represents an estimate of the "residual noise" in the overall average (8000 trials) waveform (Schimmel, 1967; Picton et al., 1984). The standard deviation of the (±) response, calculated over the 80 ms post-stimulus window, is equivalent to the RMS noise level of the average (Picton et al., 1984; Picton et al., 1994). In the present study, only one instance of "no response" occurred for an MLR peak.

TABLES

Table 1

Behavioral thresholds (dB ppe SPL) for 1 to 8 ms equal rise and fall times for the 500-, 2000-Hz and noiseburst stimuli

Rise	500-Hz		2000-Hz		Noisebursts	
	Mean	SD	Mean	SD	Mean	SD
1-ms	34.9	3.2	25.3	2.8	35.2	2.7
2-ms	32.3	4.1	22.3	2.9	30.7	4.1
4-ms	30.8	3.7	19.2	4.3	29.6	3.4
8-ms	27.8	3.4	16.7	5.3	27	3.1

N=9 subjects

FIGURE CAPTIONS

Figure 1. The "constant-slope rise-time" paradigm. In this paradigm, the stimulus slopes are kept constant with increasing rise times and peak intensity.

Figure 2. Acoustic waveforms of the three stimuli (a. noisebursts, b. 2000-Hz tones, and c. 500-Hz tones) with rise times ranging from 0.5 to 12 ms and fall time of 36 ms.

Figure 3. Acoustic spectra for the three stimuli for rise times ranging from 0.5 to 8 ms for the noiseburst and 2000-Hz stimuli and rise times from 1 to 12 ms for the 500-Hz stimuli. Stimulus level increased by 6 dB with each increase in rise time to represent the constant-slope rise-time paradigm. Stimulus envelope for these analysis consisted of equal rise/fall times and no plateau.

Figure 4. The grand mean waveforms (n = 12 subjects) evoked by the 3 stimuli (a. noisebursts, b. 2000-Hz tones, and c. 500-Hz tones) with rise times ranging from 0.5 to 12 ms. These evoked potentials are the average of a total of 96,000 trials (8000 trials per subject).

Figure 5. The means and standard deviations of the amplitudes of ABR V-Na and MLR Pa-Nb evoked by the three stimuli (i.e., noisebursts, 2000- and 500-Hz tones) as a function of rise time.

Figure 1

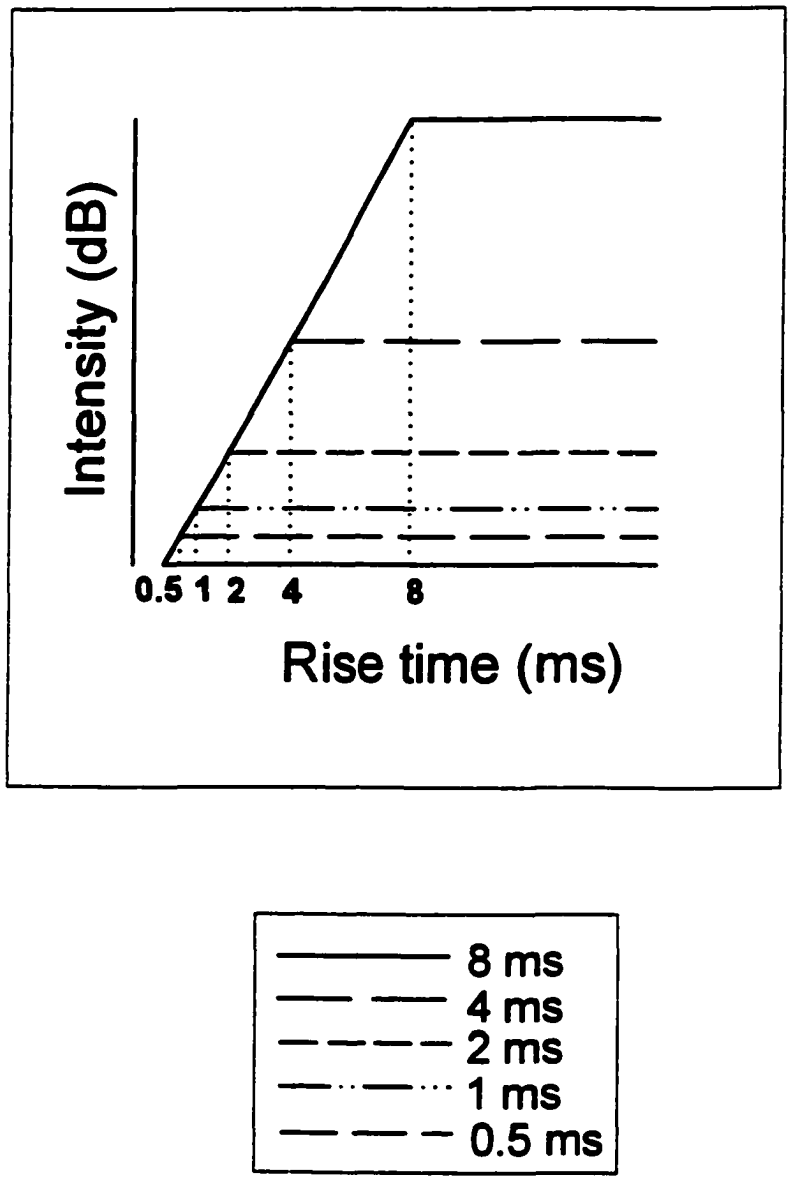


Figure 2a

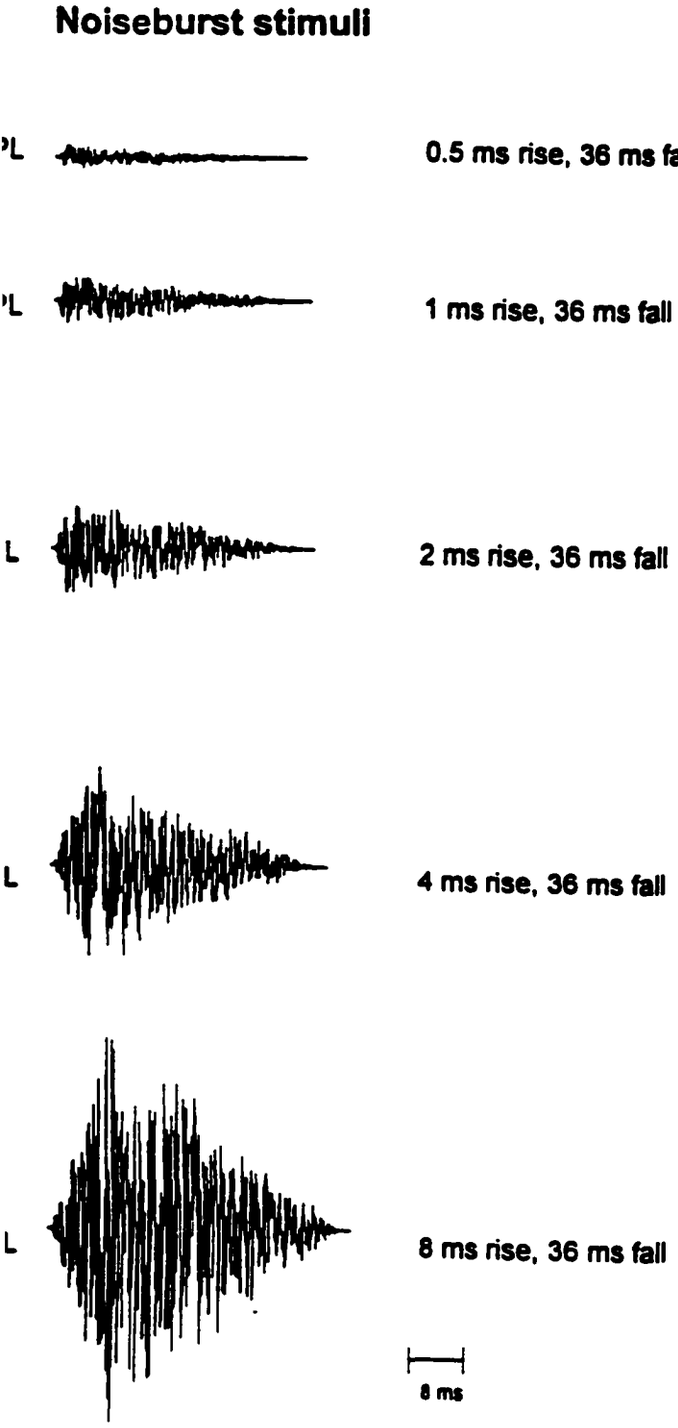


Figure 2c

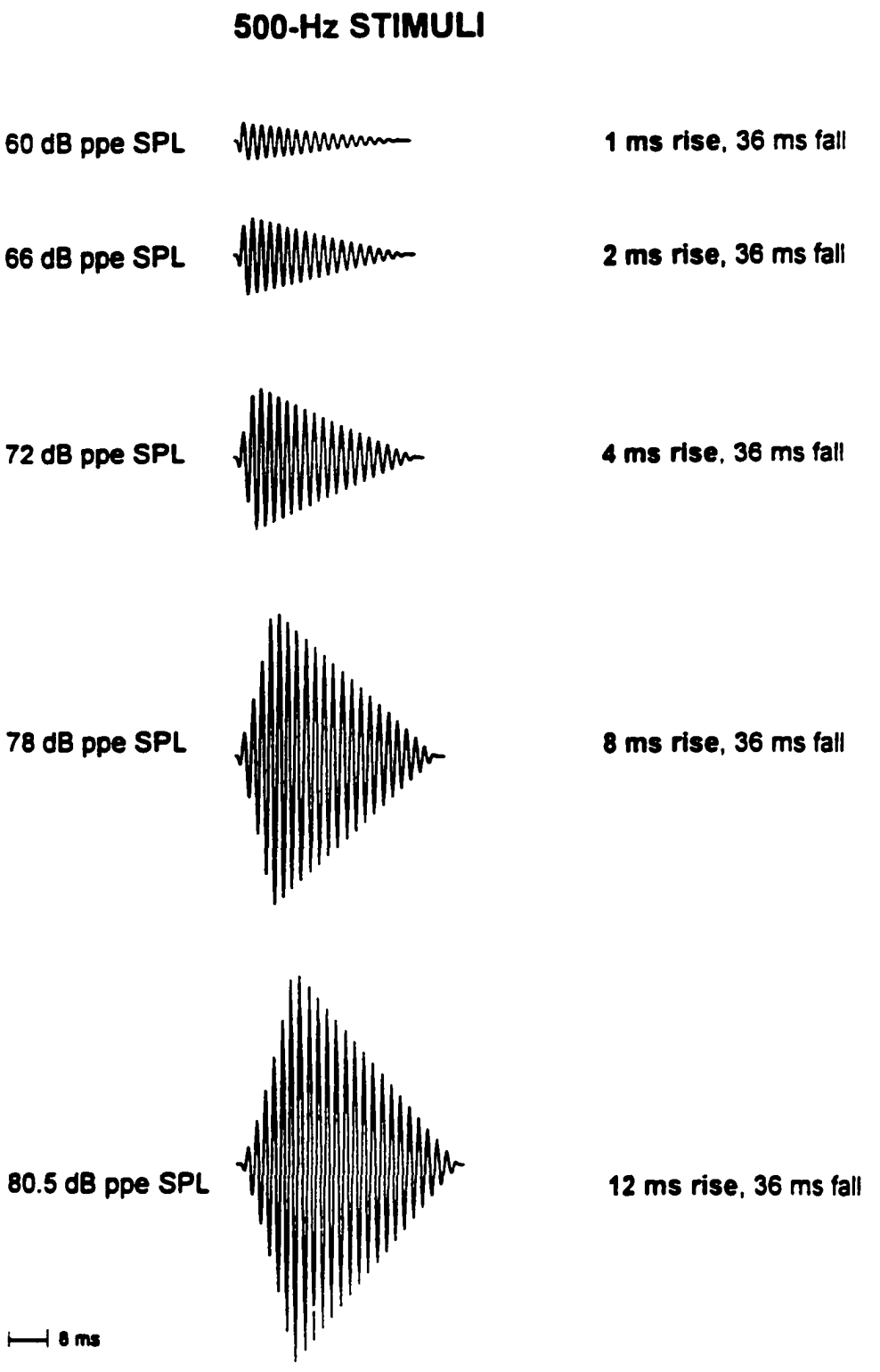


Figure 3

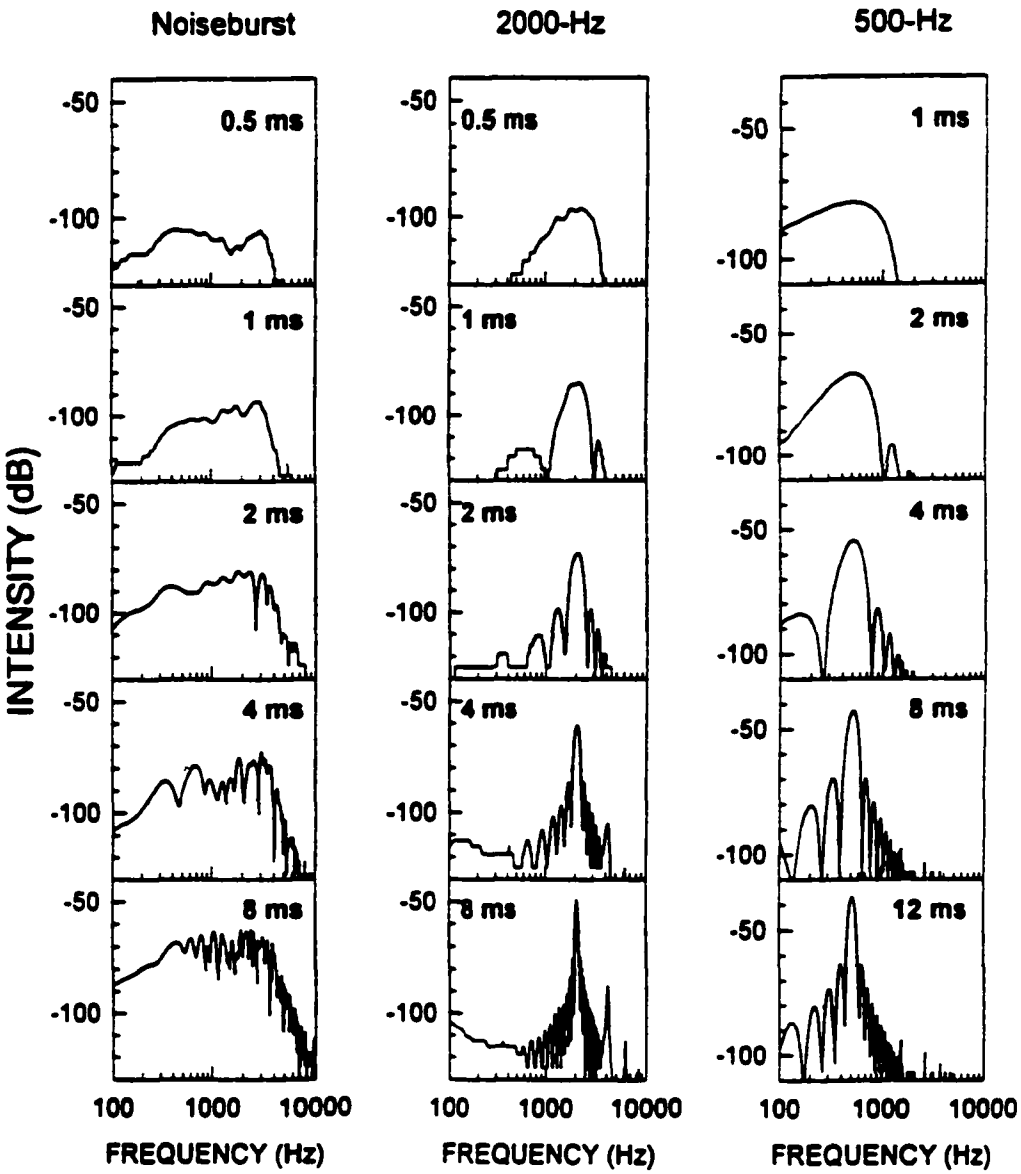


Figure 4a

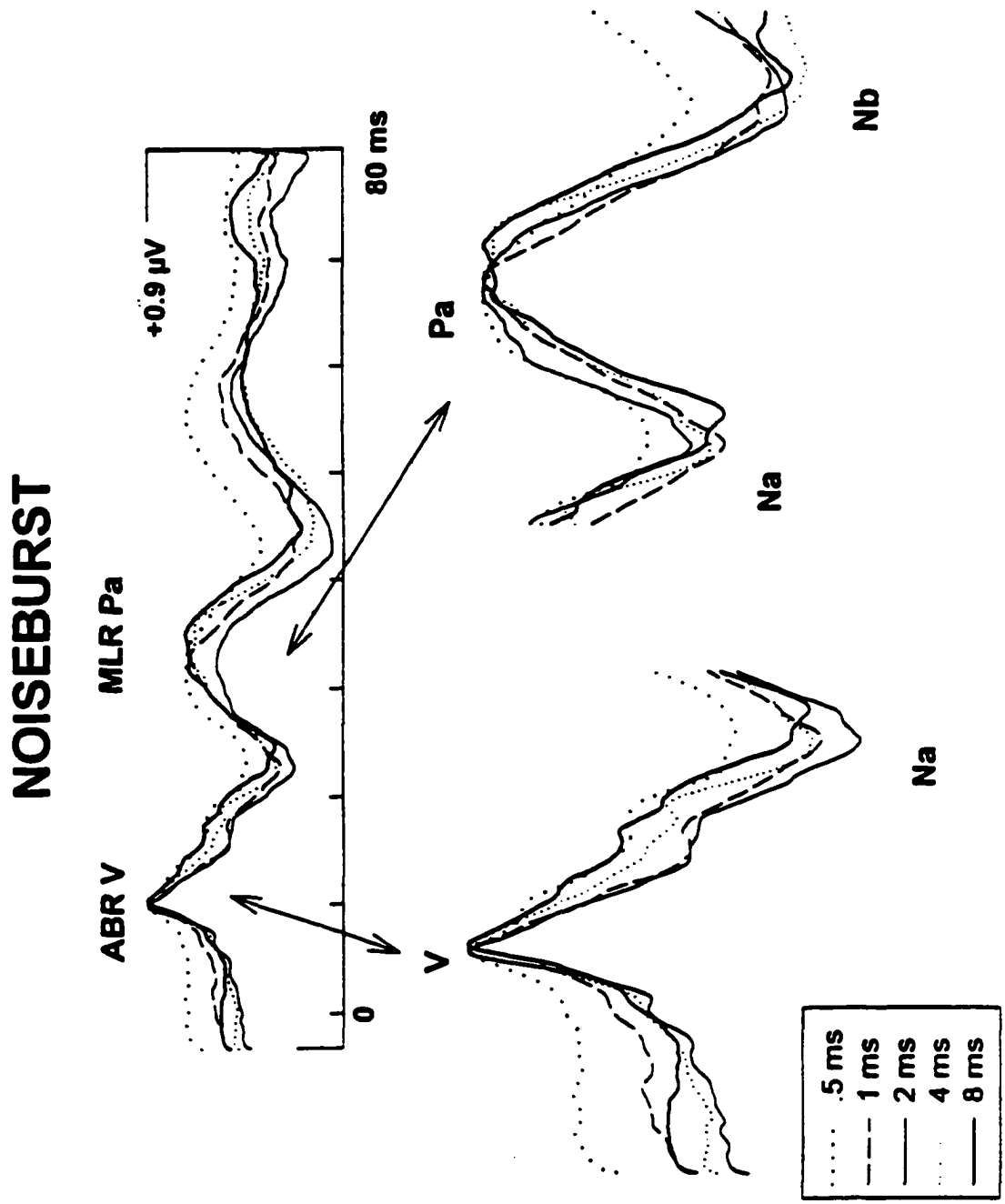


Figure 4b

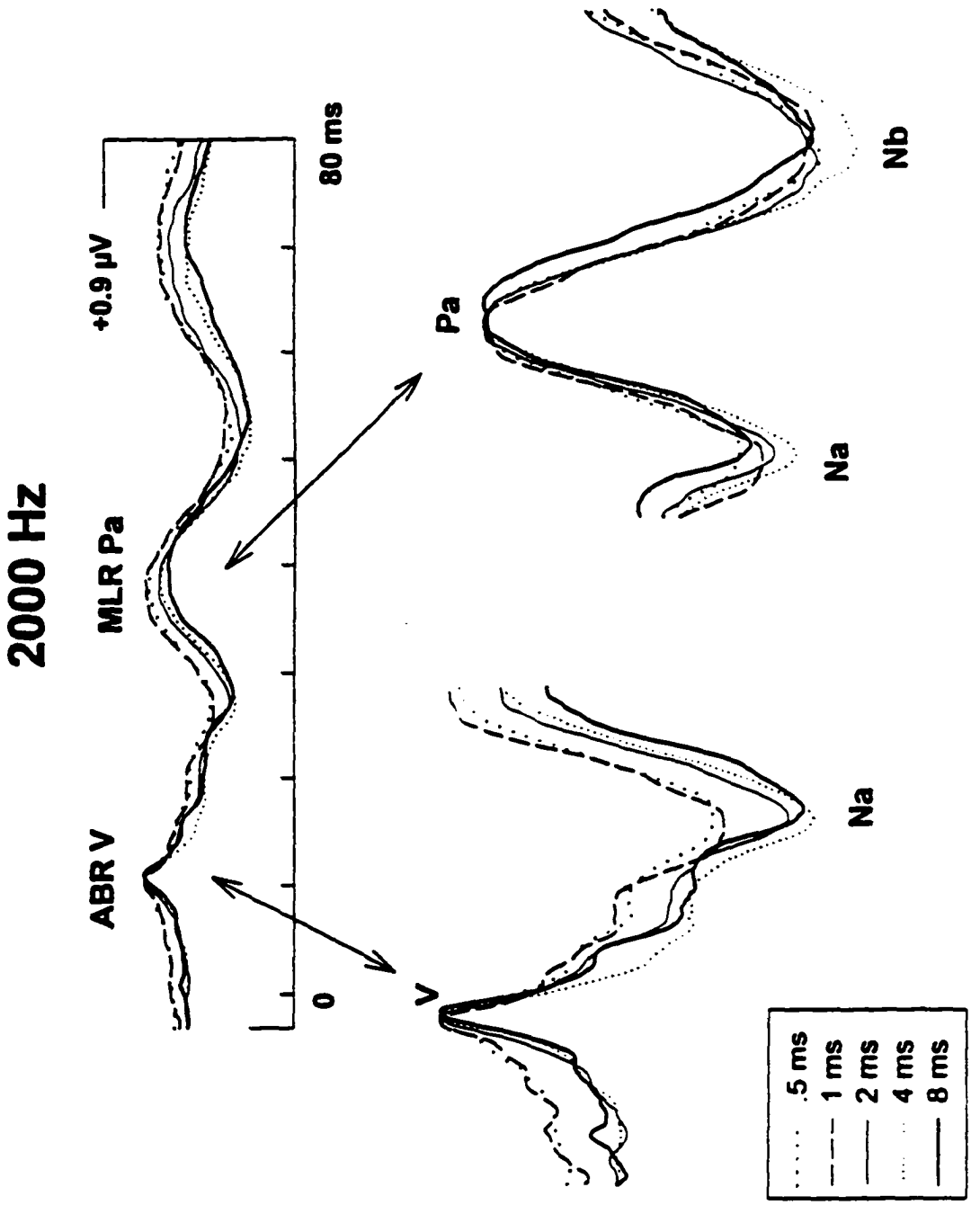


Figure 4c

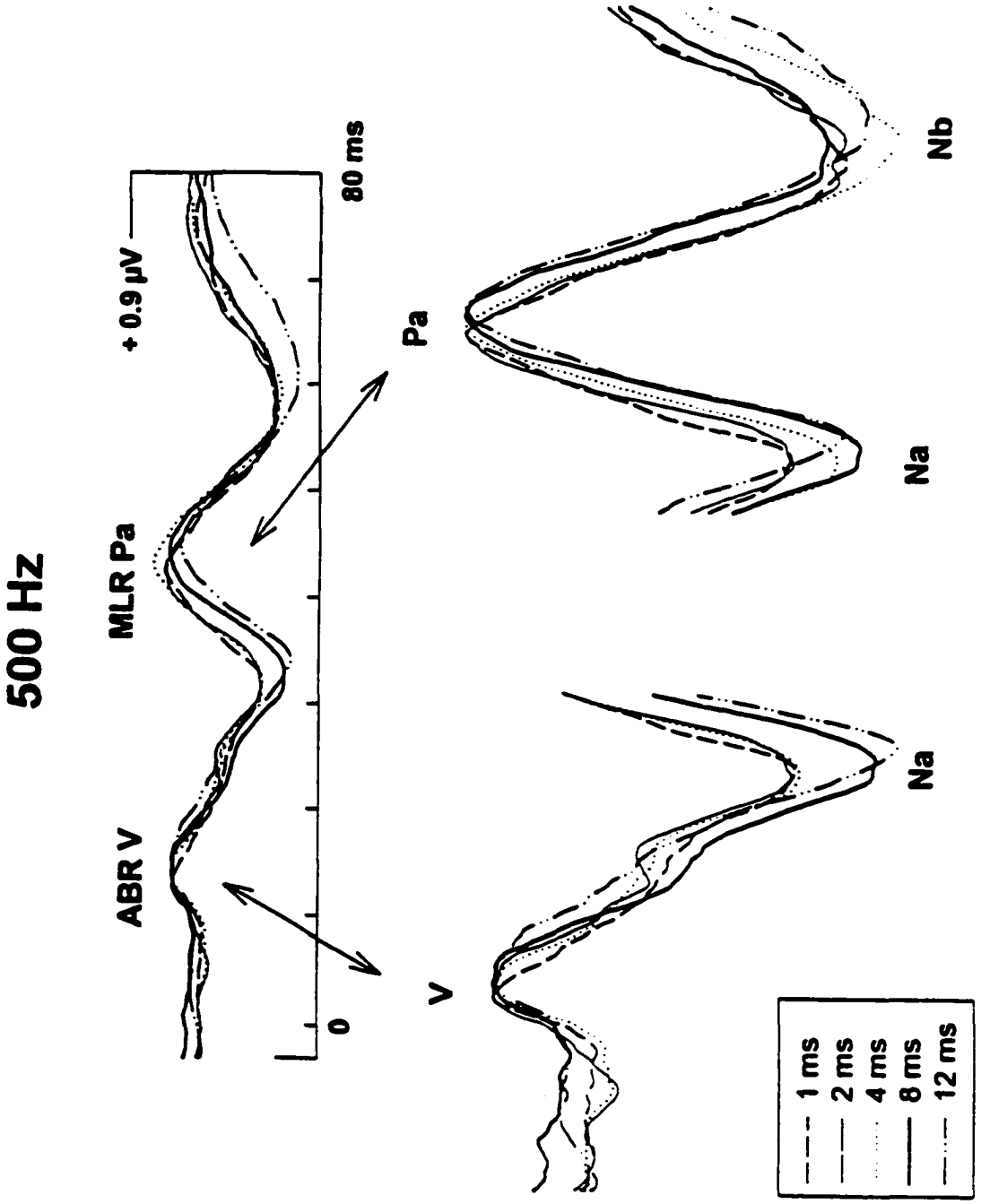
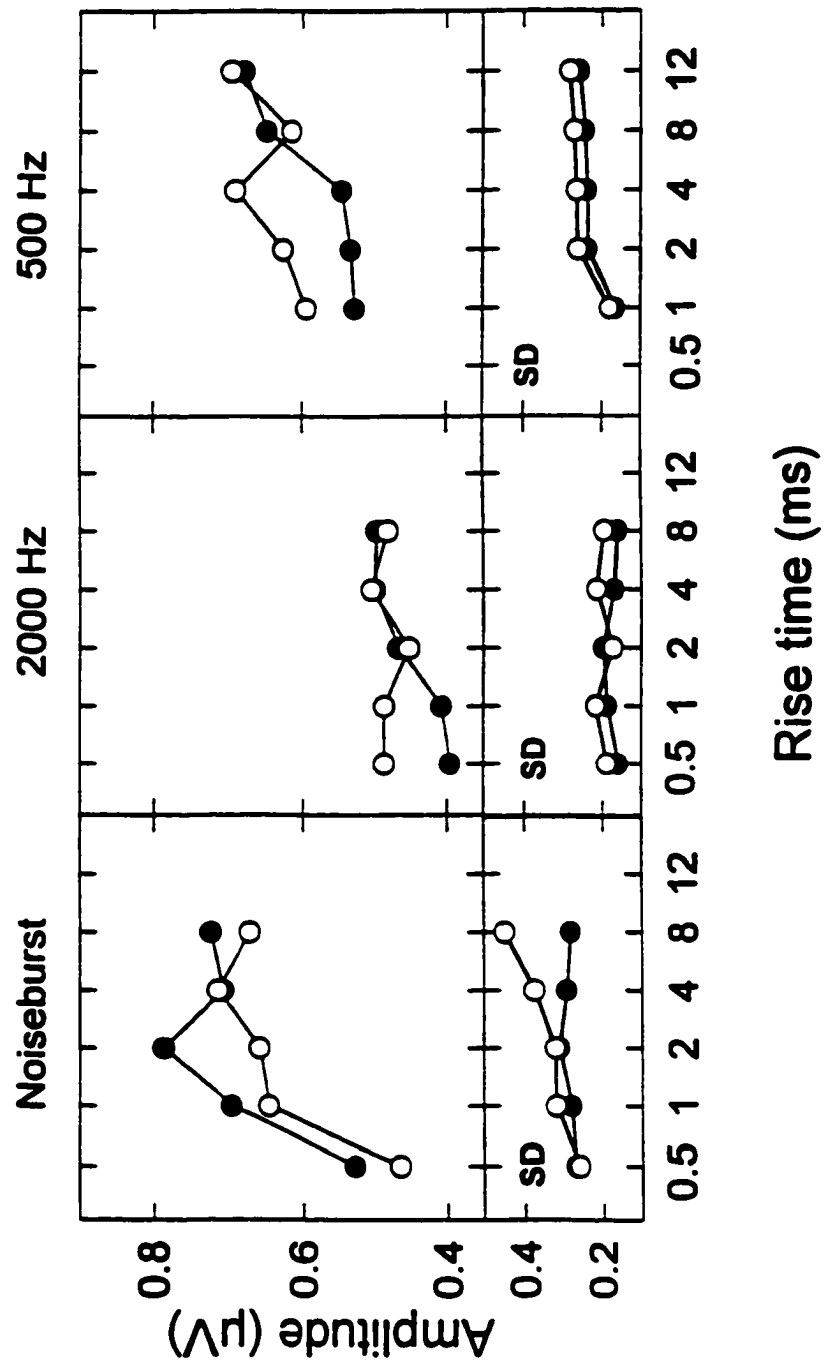


Figure 5



CHAPTER 3: COCHLEAR PLACE DETERMINANTS OF THE EFFECTIVE DURATION OF THE STIMULUS FOR THE AUDITORY BRAINSTEM AND MIDDLE LATENCY RESPONSES

A. ABSTRACT

Objective: Our previous study determined that the effective durations for the ABR and MLR evoked by tones are stimuli dependent, with 500-Hz exhibiting longer effective duration (~12 ms) than the 2000-Hz tone (~4 ms) (Chapter 2). The present study examines whether these differences in effective durations reflect stimulus differences or differences in processing for different cochlear places. ABRs and MLRs to brief noisebursts were recorded, and narrowband derived responses obtained, using the high-pass (HP) noise masking subtraction technique. The aperiodic nature of the noiseburst stimuli allowed the determination of the effective durations of the stimuli for differing cochlear places without the possible confounding differences between tonal stimuli of differing frequencies. As in the first study, the effective duration of the stimulus for the ABR and MLR were determined using the "constant-slope" rise-time paradigm.

Design: ABRs and MLRs to brief noisebursts were recorded, and narrowband derived responses obtained, using the high-pass (HP) noise masking subtraction technique. The one-octave-wide narrowband derived responses obtained were centered at 500-, 1000- and 2000 Hz. The noiseburst stimuli consisted of linearly-shaped envelopes with rise times ranging from 0.5 ms to 8 ms. The intensity of the stimuli ranged from 54 dB ppe SPL for stimuli with 0.5 ms rise time to 78 dB ppe SPL for stimuli with 8 ms rise time. With each doubling of rise time, the amplitude of the stimulus doubled, increasing the intensity of the stimulus by 6 dB. In this "constant-slope" rise-time paradigm, the brainstem and middle latency responses increase until a critical duration (i.e., the effective duration) is reached, where further increases in rise time do not result in further increases in response

amplitude. The noiseburst stimuli along with the narrowband derived responses provided effective durations of the stimuli for different cochlear places without the confounding differences of tonal stimuli of differing frequencies.

Results: Results indicate that the effective duration of the stimulus for the ABR and MLR is dependent on cochlear place, with the 500-Hz derived response exhibiting the longest effective duration (8 ms), the 2000-Hz derived response exhibiting the shortest effective duration (2 ms), and the 1000-Hz results falling in between (4 ms). As with our previous study, no differences were seen between the effective duration of the stimulus for the ABR compared to the MLR.

Conclusions: The effective duration of the stimulus for both the ABR and MLR is cochlear place dependent rather than specifically stimulus-based, with responses originating from stimulation of apical regions of the cochlea integrating longer portions of the stimuli. The effective durations of the ABR are not different from those for the MLR, suggesting that the time it takes tc achieve maximum output is determined by more peripheral processing (e.g., cochlear and VIII nerve), and not by where in the brain the response is generated.

B. INTRODUCTION

In the previous chapter, the effective durations of the tonal stimuli for the auditory brainstem and middle latency responses were determined using the "constant-slope" rise time paradigm. In this paradigm, the slope of the rise of the stimulus is kept constant while the rise time, and consequently the intensity of the stimulus, increases. The underlying premise of the paradigm is that if only the initial 2 ms of the stimulus determines the response, then further increases in rise time will not produce further increases in amplitude (Kodera et al., 1983; Lichtenstein, 2001; Suzuki & Horiuchi, 1981). Physiologically, the first cycle of the stimulus stimulates the cochlea, initiating a synchronized neural discharge. The succeeding cycles cause more neural discharges, and the sum of all these responses are recorded at the scalp. Contributions from later cycles of the stimulus will continue until the critical or effective duration for the response to the tone is reached (Kodera et al., 1983). Further information regarding the constant-slope rise time has been presented in greater detail in the study of Chapter 2. Results of that study indicate that for the ABR and MLR evoked by noisebursts and by 500- and 2000-Hz tonal stimuli, the effective duration for the ABR and MLR appears to be stimulus dependent, with the 500-Hz brief-tone results exhibiting the longest effective duration (~12 ms), the noiseburst results the shortest effective duration (~2 ms), and the 2000-Hz results in between (~4 ms). Interestingly, no differences were seen between the effective durations of the stimuli for the ABR and MLR.

The differences in effective durations of the tonal stimuli might be due to stimulus-specific effects such as (1) periodicity and phase locking (Anderson et al., 1970; Hind, 1972; Kiang et al., 1965; Rose et al., 1967), and/or (2) spectral changes caused by increases in the rise

time and intensity of the tonal stimuli (Durrant, 1983; Kiang & Moxon, 1974; Kiang et al., 1967; Özdamar & Dallos, 1976). Alternatively, the differences in effective durations might be strictly due to differences in processing at different places along the basilar membrane.

In order to determine the effective durations of the stimulus without the confounding stimulus characteristics of the tonal stimuli, a combination of broadband aperiodic noise stimuli combined with place-limiting masking noise may be used to evoke the ABR and MLR. Noiseburst stimuli contain a broad frequency spectrum with approximately equal energy across the frequencies regardless of stimulus envelope. The spectra of noiseburst stimuli, unlike tonal stimuli, remain relatively constant despite changes in rise time and duration (Barth & Burkard, 1993; Burkard, 1984; Folsom & Aurich, 1987; Hecox & Deegan, 1983; Hecox et al., 1976). Thus, any changes in response amplitude seen with increases in rise time and intensity could be attributed to rise time rather than spectral changes. Further, the ABR and MLR evoked by noisebursts will be time-locked to the overall stimulus envelope, but due to the random phases of the different frequencies in the noisebursts, the neural response is less likely to reflect any specific phase of the stimuli. Thus, unlike ABR and MLR evoked by tonal stimuli, ABR and MLR evoked by noisebursts should not reflect stimulus periodicity or phase.

Noiseburst stimuli are aperiodic, but do not provide cochlear place-specific responses. In order to determine the effective duration of the stimuli for the ABR and MLR to stimulation of specific cochlear places, the high-pass noise derived response technique (HP/DR) may be used. In this technique, the evoked potential recorded in the presence of HP noise at one cutoff frequency is subtracted from response recorded in the presence of HP noise with a higher cutoff frequency, leaving a

"derived response" approximately to the frequencies between the two cutoff frequencies (Don & Eggermont, 1978; Parker & Thornton, 1978a; Parker & Thornton, 1978b; Teas et al., 1962). Recently, Stapells and So demonstrated that the center frequencies (CFs) of the derived bands for ABR wave V are close to the lower high-pass cutoff frequency involved in the subtractions (Stapells & So, 1999).

The aim of the present study is to determine the effective duration of the stimulus for the auditory brainstem and middle latency responses originating from restricted cochlear regions without the confounding phase or spectral differences seen with the tonal stimuli.

C. METHODS

Information regarding subject criteria, the generation, presentation and calibration of the stimuli, and the recording of the evoked potentials employed in the study have been presented in full detail in Chapter 2 and will be presented only briefly below.

Subjects

The ABR and MLR were recorded from 12 normal-hearing subjects who had no history of neurological disorder. Subjects' ages ranged from 18 to 42 years (mean age 29 years).

Stimuli

The acoustic stimuli used to elicit the ABR and MLR were short-duration noisebursts, all synthesized by the STIM portion of a Neuroscan system using a digital-to-analog (D/A) rate of 60,000 Hz (10,000 Hz anti-imaging filter). The stimuli are attenuated (Coulbourn Instruments S85-08) before being presented to the subject's ear via an ER-3A insert earphone. The subject's test ear was selected randomly.

The noiseburst stimuli consisted of linearly-shaped envelopes with rise times of 0.5, 1, 2, 4, and 8 ms, and a fall time of 36-ms, with no plateau. The long and gradual fall time was chosen in order to eliminate or reduce any effect of possible offset responses since fall times ranging from 0.5 ms to 10 ms have produced an "off" response (e.g., Brinkmann & Scherg, 1979; Van Campen et al., 1997). The intensity of the stimuli ranged from 78 dB ppe SPL for the 8-ms rise time stimuli to 54 dB ppe SPL for the stimuli with the 0.5-ms rise time. The quasi-random characteristics of the brief noiseburst stimuli was ensured by using three different stimulus samples for each rise time. Figure 1 presents sample acoustic spectra of the noise stimuli with rise/fall times ranging from 1 to 8 ms (with fall times equal to the rise times). Figure 2 presents the acoustic waveforms of the noiseburst stimuli with rise times ranging from 1 to 8 ms, and a 36-ms fall time. To ensure optimum MLR amplitudes (McFarland et al., 1975; Picton et al., 1974) and avoid superimposition of the ABR and MLR (Galambos et al., 1981; Stapells et al., 1984; Stapells & Picton, 1981; Suzuki et al., 1984b), the stimuli were presented monaurally at a rate of 10.9/s.

ABR and MLR Recordings

Single-channel recordings of the ABR and MLR were obtained using gold-plated cup electrodes placed on the vertex (Cz) and ipsilateral earlobe (A1 or A2), with a forehead electrode (Fpz) serving as ground. Interelectrode impedances were less than 3000 Ohms. The EEG was amplified (gain = 100,000) and analog filtered (10-3000 Hz, 6 dB/octave) before being digitized. The analysis time was 3 ms pre-stimulus and 80 ms post-stimulus. Trials containing amplitudes above ±25 μV were automatically rejected. The averaged responses were digitally filtered offline using a 1000-Hz lowpass filter (12 dB/octave slope, zero phase

shift). Eight replications of 1000 trials each, for a total of 8000 trials, were obtained for each stimulus rise time. A total of 8000 trials were used in order to ensure a response with a good signal-to-noise ratio at all rise times. In order to minimize extraneous muscle movement and maximize patient comfort during the recordings, the data were collected in blocks of 1000 trials. Half of the replications (four replications of 1000 trials) were obtained with a condensation initial onset polarity, and the other half with a rarefaction initial onset polarity. In order to reduce any stimulus-related electrical artifacts, cochlear microphonic (Davis, 1976), and frequency-following response (Davis & Hirsh, 1976; Gerken et al., 1975) present in the single polarity response, the condensation and rarefaction replications were added offline to produce responses of "alternating" polarity. Following digital filtering, average waveforms representing the overall average of 8000 sweeps were calculated, as were two replications of 4000 sweeps each and four replications of 2000 sweeps each.

Broadband and HP noise masking

The broadband masking noise was generated by a white-noise generator and fed to a dual-channel filter (Wavetek, model 852) with both channels set to high pass and connected in series (96 dB/octave slope). After filtering, the noise was attenuated (Coulbourn S85-08) and the output was fed to another attenuator/mixer where the noise masker was mixed with the stimulus (when indicated), then fed to a passive attenuator and then to the EAR-3A insert earphone.

The intensity of masking noise required to mask the ABR and MLR for the 78 dB ppe SPL 8-ms-rise/36-ms-fall time of the 500- and 2000-Hz tonal and noiseburst stimuli was determined for each subject. The mean broadband noise (BBN) masking intensity needed to mask the ABR and MLR

was 86 dB SPL (range: 84 to 88 dB SPL). The BBN was subsequently filtered using high-pass filter settings of 4000, 2000, 1000 and 500 Hz.

Derived responses

Octave-wide derived responses were obtained by subtracting individual recordings of the response in HP noise at one cutoff frequency from the response to the same stimulus and rise time recorded in HP noise at a higher cutoff frequency. The HP/DR subtraction technique resulted in three separate derived responses (500-, 1000- and 2000-Hz octave-wide derived responses) for each rise time (0.5- to 8 ms). The lower frequency of the two HP cutoff frequencies used in the subtraction process was considered the center frequency of the derived band (Don et al., 1979; Eggermont & Don, 1980; Kramer, 1992; Nousak & Stapells, 1992; Oates & Stapells, 1997b; Picton et al., 1981; Stapells, 1984; Stapells & So, 1999).

Procedures

All testing was performed in a double-walled sound-attenuated room (Industrial Acoustics Corporation). Subjects were seated in a recliner, resting or reading quietly during testing. The subjects were monitored visually and their EEG observed to ensure that they remained in a quiet and relaxed state, but remained awake. The presentation order of stimulus rise-time and HP noise conditions was randomized across subjects.

The stimuli and white noise were calibrated daily using a Brüel and Kjaer DB0138 2-cc adaptor and 4152 coupler, 1-inch condenser microphone (type 4144), and 2209 sound level meter.

Data analyses

Detailed description of the criteria used to identify the responses as well as the response measurements taken are provided in detail in the previous study (Chapter 2) and therefore are only summarized here.

Decisions regarding the presence or absence of a response were made by combining the ratings of three individuals experienced with ABR and MLR waveforms and their measurements. Each subject's ABR/MLR waveforms were combined to be viewed as waveform sets. Each set represented the subjects's ABR/MLR waveforms for a specific derived response center frequency and rise-time condition. The rating order of subjects, derived response frequencies, and rise-time conditions were randomized across raters. Each rater scored the ABR/MLR independently of the other raters.

Peak-to-peak amplitude measures of ABR wave V-Na and MLR wave Pa-Nb for each subject were obtained from that subject's grand average for those peaks judged to contain a response (Oates & Stapells, 1997a; Oates & Stapells, 1997b; Stapells, 1984; Stapells, Picton, Durieux-Smith, Edwards, & Moran, 1990; Wu & Stapells, submitted).

For responses judged as absent, the residual noise level of the waveform was entered as the amplitude for peaks judged as having no response.[1] In this study, out of 180 possible amplitude measures for both the ABR wave V-Na and MLR wave Pa-Nb, the residual noise level was used for 25 measures of ABR wave V-Na amplitude and 39 measures of MLR wave Pa-Nb amplitude (further details of the rating process are provided in Chapter 2).

Statistical analyses

Peak-to-peak amplitudes values were analyzed using descriptive statistics and repeated-measures analyses of variance (ANOVAs). Huynh-Feldt epsilon degrees of freedom corrections for repeated measures were applied when appropriate (Huynh & Feldt, 1970). Probabilities reported reflect these adjustments. Results of the ANOVAs were considered statistically significant when $p < .01$. When significant results were found in the ANOVAs, Newman-Keuls *post hoc* tests were performed to determine the pattern of the significant differences. Results of these *post hoc* analyses were considered significant when $p < .05$.

D. RESULTS

Figure 3a, 3b, and 3c displays the grand-mean waveforms (n = 12 subjects) of the 2000-, 1000- and 500-Hz one-octave-wide derived responses evoked by the noiseburst stimuli with rise times ranging from 0.5 to 8 ms, respectively. The amplitude of ABR wave V-Na in the 2000-Hz derived response increases from the 0.5 ms rise time to the 1-ms rise time. Further increases in rise time do not appear to yield further increases in response amplitude. The amplitude of MLR wave Pa-Nb increases rapidly until the 2-ms rise time, where its largest amplitude is obtained. The amplitudes of ABR wave V-Na and MLR wave Pa-Nb for the 1000-Hz derived responses increase from the 0.5-ms rise time to the 4-ms rise time, after which further increases in rise time do not appear to result in further amplitude growth. The results obtained from the grand-mean waveforms of the one-octave-wide 500-Hz derived response indicate that ABR wave V-Na amplitudes increase from 0.5- to 8-ms rise times, and that the amplitudes of MLR wave Pa-Nb increase until the 4-ms rise time.

The grand-mean waveforms suggest that the effective duration of the stimulus for the ABR and MLR is dependent on the cochlear region activated, with the 500-Hz derived response exhibiting the longest amplitude growth (~4 to 8 ms), the 2000-Hz derived response exhibiting the shortest amplitude growth (~1 to 2 ms), and the 1000-Hz results falling in between (~4 ms)(see figure 3).

Figure 4 presents the mean (and standard deviation) amplitudes of ABR V-Na and MLR Pa-Nb for the 2000-, 1000- and 500-Hz derived responses as a function of rise time. The pattern of amplitude growth is unique for each cochlear place representing the different frequencies. The 2000-Hz place-specific ABR and MLR show an immediate increase in amplitude until the 1- and 2-ms rise time, respectively. For the 1000-Hz place-specific ABR and MLR, a gradual increase occurs until the 2- and 4-ms rise time, respectively, and for the 500-Hz place-specific results, the amplitudes of both the ABR and MLR increase continuously until at least the 8-ms rise time (figure 3).

Three-way repeated measures ANOVA were calculated for the amplitudes of the 2000-, 1000-, and 500-Hz one-octave-wide derived responses as a function of rise time. The results of these ANOVAs, displayed in Table 1, reveal a significant cochlear place x rise interaction, indicating different amplitude growth patterns with increases in rise time from the three cochlear place regions. Newman-Keuls *post hoc* analysis of results obtained from the 500-Hz cochlear region reveals amplitude increases until the longest rise time tested (i.e., 8 ms), with response amplitude obtained with the 8-ms rise time significantly longer than those obtained with the 2-ms rise time ($p=.031$). The results obtained for the 1000-Hz cochlear region show increases until the 4-ms rise time. Statistically, however, only the increase in amplitude from the 0.5-ms rise time to the 1-, 2-, 4-, and

8-ms rise times are significant ($p < .01$). The amplitudes obtained from the 2000-Hz cochlear region increase until the 2-ms rise time. Newman-Keuls *post hoc* analysis reveal that the 2-ms rise time is statistically different from the 0.5-ms rise ($p = .037$). A non-significant trend for wave x rise time exists ($p = .02$), suggesting a possibility of differences between the amplitude growth between the ABR and MLR which do not differ for frequency. When the amplitudes of the ABR across the 500-, 1000- and 2000-Hz cochlear regions are averaged, the resultant ABR amplitude continues to grow slowly for the 0.5 ms until the 8-ms rise time (amplitudes of 0.18, 0.25, 0.29, 0.30 and .32 μV). The averaged MLR amplitudes does not increase after the 4 ms rise-time (amplitudes of 0.15, 0.25, 0.33, 0.37 and .36 μV). These amplitudes suggest that the effective duration of stimuli for the MLR could be *shorter* than that of the ABR. This trend was not found in the previous effective duration study (Chapter 2) and is not supported by any other ABR/MLR studies. This non-significant trend might reflect greater difficulty in identifying the MLR (39 absent cases) *versus* the ABR (25 absent cases)(see Table 1).

Another method of assessing the effective duration of the stimuli for the ABR and MLR obtained from specific cochlear regions is to determine the rise time resulting in the largest amplitude response for each cochlear region for each subject (Chapter 2). For the one-octave-wide 2000-Hz derived response, most subjects obtained the largest amplitude at the 1- and 2-ms rise times for both the ABR and MLR. For the 1000-Hz derived response, the largest amplitudes were obtained with the 2- and 4-ms rise for the ABR and MLR, respectively. For the 500-Hz derived response, the largest amplitudes were obtained using the 8-ms rise time for the ABR and MLR. However, because the amplitude of the response continued to grow up to the last rise time tested (i.e., 8 ms),

it is possible that the amplitude of the response would have continued to increase for rise times greater than 8 ms. These results are consistent with the amplitude results, indicating that the effective duration of stimuli for ABR and MLR generated from the 500-Hz cochlear place region is longer in duration than those obtained from the 1000- and 2000-Hz regions.

E. DISCUSSION

The results of this study indicate that the effective duration of the stimuli for ABR and MLR generated from a one-octave-wide region of the cochlea with a center frequency of 2000 Hz is about 1-3 ms, for the 1000-Hz cochlear region about 2-4 ms, and for the 500-Hz region about 4-8 ms (or greater). The effective durations of the stimuli for both the ABR and MLR are thus cochlear place dependent, with responses from the apical regions of the cochlea integrating longer portions of the stimuli than those evoked from the more basal regions of the cochlea.

In this study, the effective durations of the stimuli for ABR and MLR were determined by using noiseburst stimuli. The use of the noiseburst stimuli ensures that the resultant effective durations are less likely to be due to stimulus-specific effects such as periodicity, spectral splatter or phase locking, which might have an effect on responses evoked by tonal stimuli. The use of the high pass noise/derived response technique (Don & Eggermont, 1978; Don et al., 1979; Elberling, 1974; Parker & Thornton, 1978a; Parker & Thornton, 1978b; Teas et al., 1962) to limit the evoked potentials to specific cochlear regions further ensures frequency and place-specific responses without the confounding effects of spectral splatter (Durrant, 1983) or spread of cochlear excitation which occur when the intensity or rise time of tonal stimuli are changed (Beattie & Kennedy, 1992; Burkard &

Hecox, 1983; Jacobson, 1983; Klein, 1983b; Picton et al., 1979; Stapells & Picton, 1981).

The patterns of results obtained from the one-octave-wide 2000-, 1000- and 500-Hz cochlear regions cannot be explained by differences in stimulus characteristics such as stimulus intensity, spectrum or phase, as the ABR and MLR from each region are all evoked by the same stimuli presented at the same intensities and masked with the same masking noise, with the only difference being the masker HP cutoff frequency. The results are not due to differences in the stimulus audibility between the different cochlear regions, as ABR and MLR thresholds for 500- and 2000-Hz stimuli are at least 15 dB below the lowest intensity (54 dB ppe SPL) used in this study (Wu & Stapells, submitted). Furthermore, ABR and MLR thresholds for 500- and 2000-Hz tones are within 10 dB of each other (Wu & Stapells, submitted). The differences in effective duration of the stimuli also do not reflect response amplitude saturation because, at the moderate intensities used in this study (54 to 78 dB ppe SPL), ABR or MLR amplitude saturation does not occur (Gorga et al., 1988; Mendel & Goldstein, 1969b; Picton et al., 1981; Stapells & Picton, 1981; Starr & Don, 1988; Thornton et al., 1977). Thus, the results obtained appear to reflect differences in processing at different cochlear places, and cannot be explained by effects specific to the stimuli.

The longer effective durations obtained for responses elicited from the more apical regions of the cochlea are similar in trend to previous effective-duration studies of ABR and MLR evoked by tonal stimuli (Kodera et al., 1983; Suzuki & Horiuchi, 1981; Chapter 2, present volume). In the preceding chapter, the effective durations of the stimulus for the ABR and MLR evoked by 500- and 2000-Hz *tonal* stimuli were determined to be stimulus dependent, with effective

durations of approximately 4 and 12 ms, respectively (Chapter 2). In the present study, the effective durations of approximately 2 ms and at least 8 ms obtained for ABR and MLR elicited by the stimulation of one-octave-wide cochlear places representing 2000- and 500-Hz cochlear regions are similar in trend, albeit shorter, to those obtained for the 2000- and 500-Hz tonal stimuli. Any differences between the effective durations of the 2000- and 500-Hz tonal stimuli and the one-octave-wide cochlear places representing the 2000- and 500-Hz cochlear regions evoked by the noisebursts might be due to place-specific effects. At the moderate intensities used, responses elicited by the tonal stimuli could have been partially mediated by regions of the cochlea away from the nominal frequency of the stimuli due to both the upward spread of cochlear excitation and/or the effects of spectral splatter (Beattie & Kennedy, 1992; Burkard & Hecox, 1983; Jacobson, 1983; Klein, 1983b; Picton et al., 1979; Stapells & Picton, 1981). In contrast, the present study's derived responses obtained using noisebursts and masking are unlikely to reflect changes in place because the responses are restricted to one-octave-wide regions of the cochlea (Don & Eggermont, 1978; Don et al., 1979; Elberling, 1974; Parker & Thornton, 1978a; Parker & Thornton, 1978b; Stapells et al., 1994; Teas et al., 1962). Alternatively, the differences in the effective durations obtained might be due to stimulus-specific effects such as periodicity and phase. Phase locking occurs at frequencies below 5000 Hz when the VIIIth nerve fibers are time locked to one phase of the stimulating waveform, discharging only at that particular stimulus phase. Period histograms of fibers activated by frequencies below 5000 Hz indicate spikes are evoked in only one-half of the cycle continuously (Pickles, 1988, p. 90; Rose, Hind, Anderson, & Brugge, 1971). Thus, when the ABR and MLR are evoked by tonal stimuli below 5000 Hz, such as in the preceding chapter,

the impulses in the auditory nerve fibers are time locked to the stimulus and occur preferentially at a particular phase of the stimulus (Anderson et al., 1970; Hind, 1972).

In the present study, on the other hand, the ABR and MLR are not affected by phase because of the way the auditory fibers respond to broadband noise stimuli. Even though, the cochlear output in response to the stimuli is periodic, due to the filter characteristic of the basilar membrane, the noiseburst stimuli can excite neurons with multiple CFs simultaneously. The auditory neurons' response to noisebursts reflect the sum of responses to the tonal stimuli with each specific nerve fiber being evoked by wavelets of the noise stimulus within its frequency characteristics (de Boer & de Jongh, 1978; Evans, 1977). Consequently, even though responses evoked by the noiseburst stimuli are time locked to the cycles within the stimuli, the overall response is not phase dependent as stimulus phase is random across each frequency (de Boer, 1980; de Boer & de Jongh, 1978). Thus, in the present study, the responses evoked from the 500- and 2000-Hz one-octave-wide region of the cochlea most likely do not reflect stimulus periodicity or phase.

It has been suggested that the ABR requires an abrupt stimulus onset (e.g., Gorga et al., 1984; Kraus et al., 1994), whereas the MLR can be elicited using longer stimuli (e.g., Kileny & Shea, 1986; Kodera et al., 1979; Kraus, 1990; Kraus et al., 1994; McFarland et al., 1977; Thornton et al., 1977). The effective durations of 1 to 8 ms obtained in this study and the effective durations of 4 to 12 ms obtained for the ABR and MLR evoked by tones in the previous study (see Chapter 2) indicate that both the ABR and MLR are not strictly immediate onset responses. Furthermore, in both studies, the effective durations of the stimuli for the MLR are not significantly different from those for the

ABR. Thus, the commonly-held notion that the MLR is less of an "onset" response than the ABR (Kraus, 1990; Kraus et al., 1994) is incorrect.

The longer effective durations obtained for responses elicited from the more apical regions of the cochlea for the ABR and MLR (Chapter 2; Kodera et al., 1983; Suzuki & Horiuchi, 1981) are similar to behavioral (Plop & Bowman, 1959; Watson & Engel, 1969), primary auditory cortex single neurons recording (Heil, 1997a,b; Heil and Irving, 1997), auditory evoked magnetic field recordings (Biermann and Heil, 2000) and cortical event-related potential studies of temporal integration studies (Alain et al., 1997).

Behaviorally, temporal integration is defined as the time necessary to process timing information as the duration of the stimulus is increased up to a critical length of time (Gelfand, 1990, p. 332). Behavioral psychophysical studies suggest that temporal integration times are significantly shorter for high-frequency tones for the detection of threshold, (Campbell & Counter, 1969; Plop & Bowman, 1959; Watson & Engel, 1969). Alain and colleagues determined the temporal integration of the N1 and P2 cortical event-related potentials (Alain et al., 1997). The temporal integration of N1 and P2 was defined as the minimal stimulus duration that produces a response of maximal amplitude. Even though different temporal integration times were seen for N1 and P2 as well as for the different N1 sub-components, the N1 and P2 results indicate consistently longer integration times for lower frequency signals (Alain et al., 1997). Heil, analyzed the number and timing of spikes discharged by single neurons in primary auditory cortex of cats to the onsets of characteristic frequency tones (Heil, 1997a,b). Stimulus envelope was altered by varying intensity, frequency, and rise time. Results indicated that stimulus rise time had major effects on the spike count-level functions. Functions obtained with long rise

times were often monotonic whereas those obtained with shorter rise times were highly non-monotonic, accounting for less sharp tuning at longer rise times. More importantly, transmission delay decreases with increasing stimulus frequency were observed. This decrease in transmission delays is consistent with frequency dependent delays in the cochlea. In order to verify this suggested peripheral origin, Heil and Irving compared the responses of the auditory nerve fibers to those of the primary auditory cortex (Heil and Irving, 1997). Results indicate that the latency-acceleration functions as well as the first-spike timing of the auditory nerve fibers are similar to those of the primary auditory cortex. Heil and Irving thus concluded that the single neuron characteristics observed at the auditory cortex, reflect peripheral processes probably at the synapses between the inner hair cells and the auditory nerve fibers (Heil and Irving, 1997). In a more recent study (2000), Biermann and Heil demonstrated that stimulus-response characteristics for N100m and P50m evoked magnetic fields in humans are similar to single neuron recordings from cats. The authors concluded that the parallels between the response timing of the single cortical neurons and of auditory evoked magnetic fields provide a strong link between single neuron and population activity (Biermann and Heil, 2000).

The results of the studies reviewed above as well as the present study's results, suggest that differences in cortical ERP and behavioral temporal integration across frequency likely begin at lower levels of the auditory system - lower than the brainstem region generating ABR wave V and likely at the level of the cochlea and VIIIth nerve.

The longer effective durations obtained for responses elicited from the more apical regions of the cochlea for the ABR and MLR are consistent with Brinkmann and Scherg's concept of the "virtual trigger time". The virtual trigger time describes the point on the rise time of

a stimulus when the majority of nerve fibers innervating the generators of the evoked potentials are activated (Brinkmann & Scherg, 1979). The virtual trigger time is a function of rise time and intensity as well as a function of frequency with lower frequencies having longer virtual trigger times (Stapells & Picton, 1981; Stapells et al., 1994). Stapells and Picton suggested that the longer trigger time for lower frequencies is due to phase locking which could delay the time of major nerve fiber activation by one or more stimulus cycle (Stapells & Picton, 1981). The effective durations obtained in this study suggest that the longer "trigger" times for lower frequencies may be due to cochlear place- rather than stimulus-specific effects.

The results of the studies of Heil and colleagues studies on responses of single auditory cortical neurons in cats and of evoked magnetic fields (N100 and P50) in humans, indicate that the neural and the evoked magnetic fields response to stimulus onset is determined by a dynamic interaction of stimulus rise time, and slope (rapidity of signal change), and not by changes of sound pressure levels (SPL) alone (Biermann and Heil, 2000; Heil, 1997a, b; Heil & Irving, 1998). Biermann and Heil reject any "fixed amplitude" model such as Brinkmann and Scherg's "virtual trigger time" concept to explain the stability of the ABR amplitude for responses evoked by rise times up to 5 ms (Brinkmann & Scherg, 1979). They showed that the stimulus amplitudes at which the N100 or P50 peak amplitudes are triggered are not constant even for a given frequency, but vary systematically with rise time, level, and rise function (Biermann and Heil, 2000). In the constant-slope rise-time paradigm used in this study, the slope of the stimulus remained constant while the rise time, level and frequency varied. It then becomes possible to determine the effective duration of the stimulus for the ABR and MLR without the confounding effects of stimulus

slope. Without the confounding factor of slope, the finding of longer effective durations for responses elicited from the more apical regions of the cochlea for the ABR and MLR do not contradict Brinkmann and Scherg's concept of the "virtual trigger time". Further studies are needed to determine wether the effective duration of the stimulus will vary with varied slopes.

The frequency-related differences in the rise time required to reach the effective durations of the stimulus might be in part due to traveling wave delays which occur in cochlea. Traveling wave delay is frequency dependent and consists of cochlear transport time and cochlear filter build-up time (Don et al., 1998; John & Picton, 2000). Cochlear transport time depends mainly on the passive properties of the basilar membrane. The delay is in the millisecond range, increasing exponentially with increasing distance along the basilar membrane, with larger delays observed for the lower frequencies (Don et al., 1998; John & Picton, 2000; Ruggero, 1994). Filter build-up time is the additional time needed for the acoustic energy to pass through the active filtering process of the basilar membrane (Don et al., 1998; John & Picton, 2000). The increase is due to the cochlear amplifier, which sharpens the tuning of the BM and shifts the place of resonance for a particular stimulus frequency to a more apical location (Don et al., 1998). This increase in time is dependent on filter sharpness, stimulus intensity, and the CF of the BM location (Don et al., 1998; John & Picton, 2000; Ruggero, 1992b). The filter build-up time is usually measured by the number of stimulus cycles necessary to reach a maximum amplitude response. According to Don and colleagues, the filter build-up time for the 2000 Hz one-octave-wide region is approximately one cycle longer than the filter build-up time for the 500-Hz one-octave-wide region, but shorter by approximately 2.5 cycles for the 6000-Hz one-octave-wide region (Don

et al., 1998). When the effective durations of the one-octave-wide cochlear places representing 2000, 1000, and 500 Hz obtained in this study are converted to the number of periods necessary to reach the effective duration of the stimulus for each stimulus frequency, the results obtained suggest 4-8 cycles for 2000-Hz, 2-4 cycles for 1000-Hz and 2-4 cycles (or more) for the 500-Hz cochlear regions. When the effective durations of the 500- and 2000-Hz tonal stimuli obtained in the preceding study (Chapter 2) were converted to the number of periods necessary to reach the effective duration of the stimulus for each stimulus frequency, the results suggest 8 cycles for the 2000-Hz stimulus and at least 4.5 cycles for the 500-Hz stimulus. Similar to the hypotheses concerning filter build-up time (Don et al., 1998), the effective duration of the stimulus for responses elicited from more basal regions of the cochlea requires a larger number of stimulus cycles. The effective duration results of this study and the preceding may thus reflect cochlear filter build-up time.

In summary, this study demonstrates that the effective durations of the ABR and MLR vary as a function of the cochlear region activated, rather than as a function of the wave evoked (i.e., ABR or MLR) with responses from the apical regions of the cochlea integrating longer portions of the stimuli. These findings are consistent with previous research on virtual trigger and cochlear filter build-up times. The effective durations of the stimuli for the ABR and MLR for specific cochlear regions are determined by cochlear and eighth nerve processes, which occur well before the midbrain level, where the generators of wave V are located.

FOOTNOTES

1. For peaks judged as having no response, the approach of assigning a zero amplitude (0 μV) to the response has not been used as it might violate the assumptions of the ANOVA regarding normal distributions and heterogeneity of variance (Oates and Stapells, 1997b). Instead, when judged as absent, that peak was assigned the amplitude of the residual noise of that recording. This residual noise level was determined by calculation of the standard deviation of the (±) response. The (±) response, calculated by subtracting one replication (4000 trials) from another, then divided by two, represents an estimate of the "residual noise" in the overall average waveform (Schimmel, 1967; Picton et al., 1983, 1984). The standard deviation of the (±) response, calculated over the 80-ms post-stimulus window, is equivalent to the RMS noise level of the average (Picton et al., 1984; Picton et al., 1994). In the present study, out of 360 peak measurements, 64 peaks were judged as having no response.

Table 1.

Three-way repeated measures ANOVA calculated for the 2000-, 1000-, and 500-Hz one-octave derived response

Source of Variance	Effect df	Effect MS	Error df	Error MS	F	P
Cochlear Place	2	0.01	22	0.01	0.43	0.65[1]
Wave	1	0.05	11	0.03	1.49	0.25[1]
Rise	4	0.41	44	0.02	22.80	0.00*[1]
Cochlear place x Wave	2	0.05	22	0.02	2.67	0.09
Cochlear place x Rise	8	0.07	88	0.02	4.62	0.00*
Wave x Rise	4	0.02	44	0.01	3.37	0.02
Cochlear Place x Wave x Rise	8	0.01	88	0.01	0.74	0.65

[1]Probabilities reflect Huynh & Feldt epsilon corrections of degrees of freedom for repeated measures

*p<.01

FIGURE CAPTIONS

Figure 1. The acoustic spectra of the noiseburst stimuli with rise times ranging from 0.5 to 8 ms. In contrast to stimuli of the actual study, the stimuli shown in this figure had envelopes consisting of equal rise/fall times and no plateau. The left side presents the acoustic spectra for the constant intensity paradigm. In this paradigm, the stimuli are all presented at the same intensity. The right side presents the acoustic spectra for the constant-slope paradigm. In this paradigm, the intensity of the stimulus doubles (i.e., increases in 6-dB steps) with each doubling of rise time.

Figure 2. Electrical waveforms for the noiseburst stimuli with rise times ranging from 0.5 to 8 ms, and a fall time of 36 ms. The intensity of the stimulus doubles with each doubling of rise time, representing the constant-slope paradigm.

Figure 3. The grand-mean ABR and MLR waveforms (n = 12 subjects) of the derived responses for 1-octave-wide cochlear regions centered on (a) 2000 Hz, (b) 1000 Hz, and (c) 500 Hz. These evoked potentials are the grand-mean average of a total of 96,000 trials (8000 trials per subject).

Figure 4. Amplitude means and standard deviations of the derived responses for 1-octave-wide cochlear region centered at 2000, 1000, and 500 Hz as a function of rise time.

Figure 1

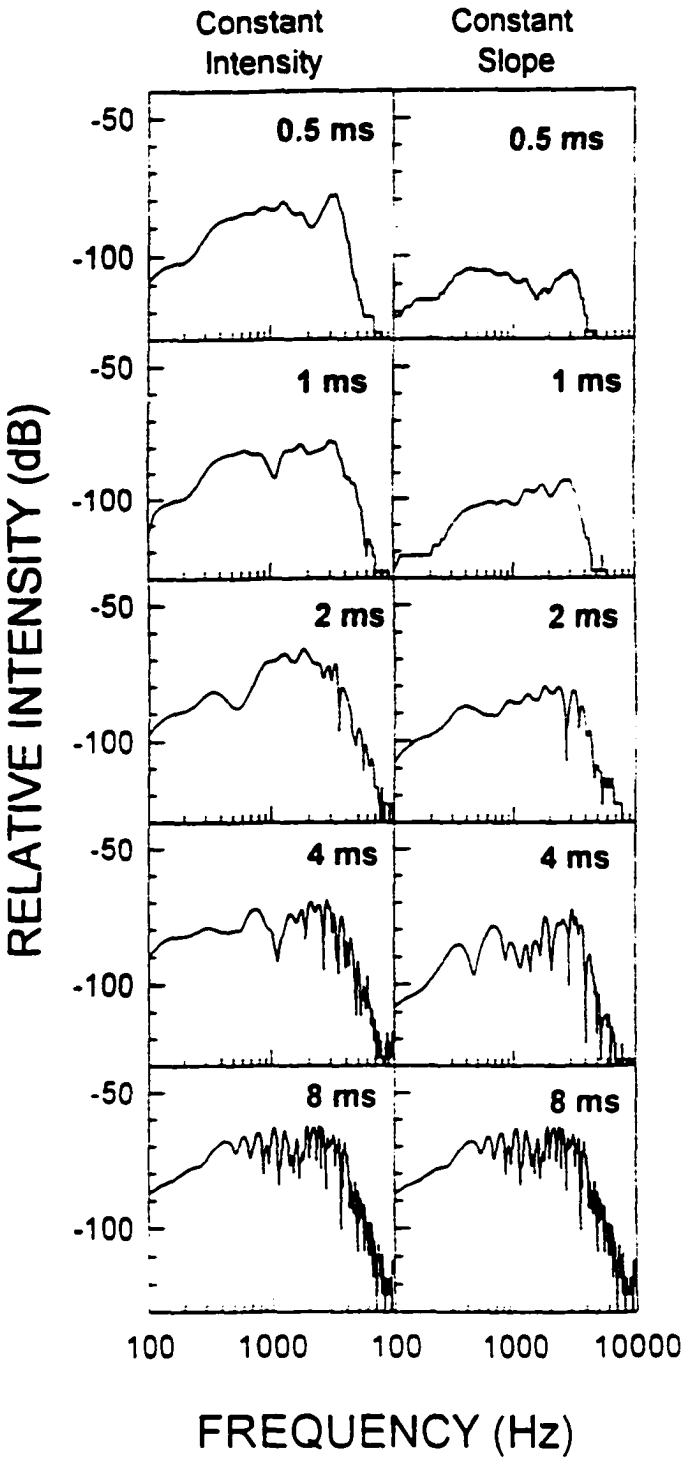


Figure 3a

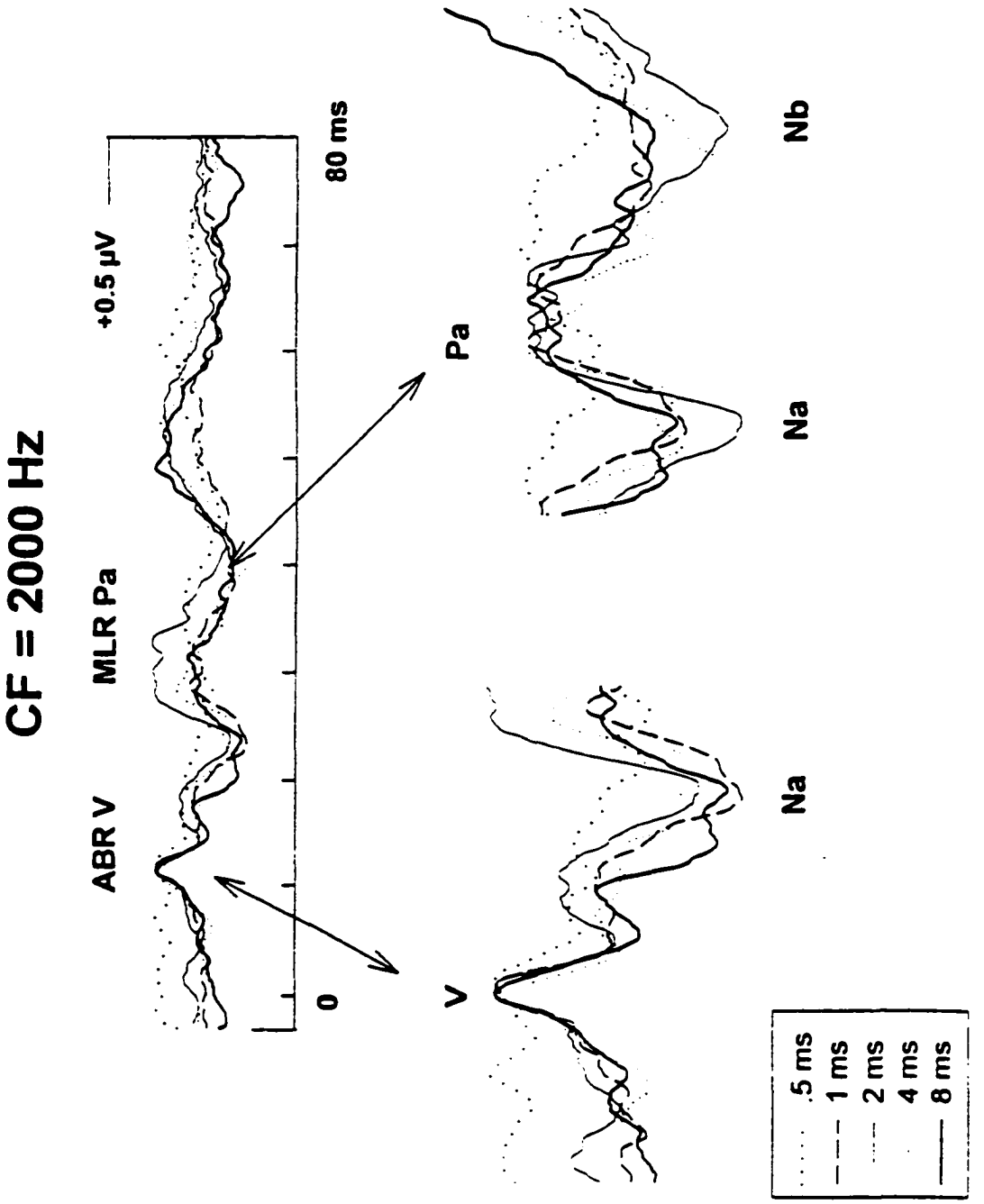


Figure 3b

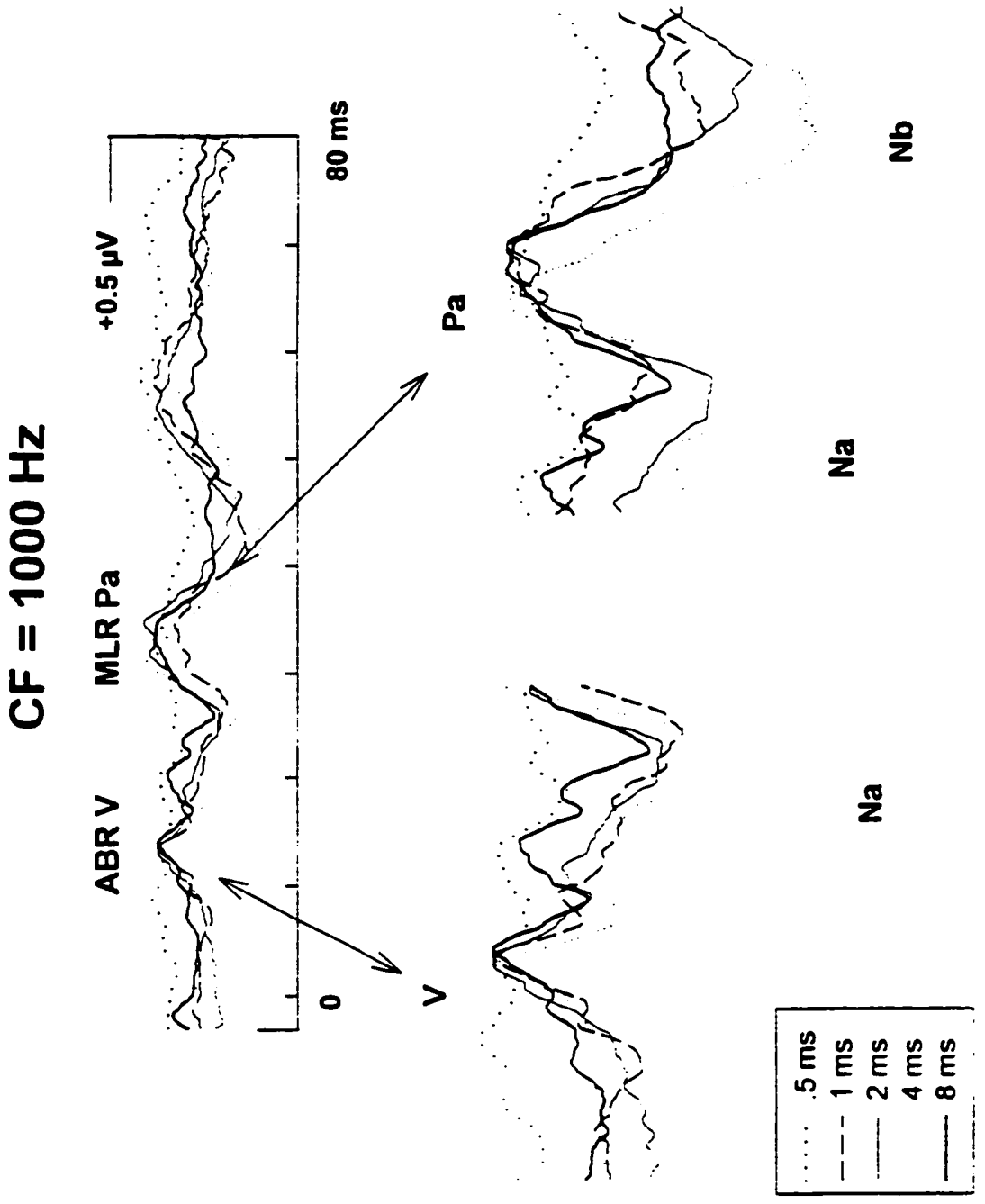


Figure 3c

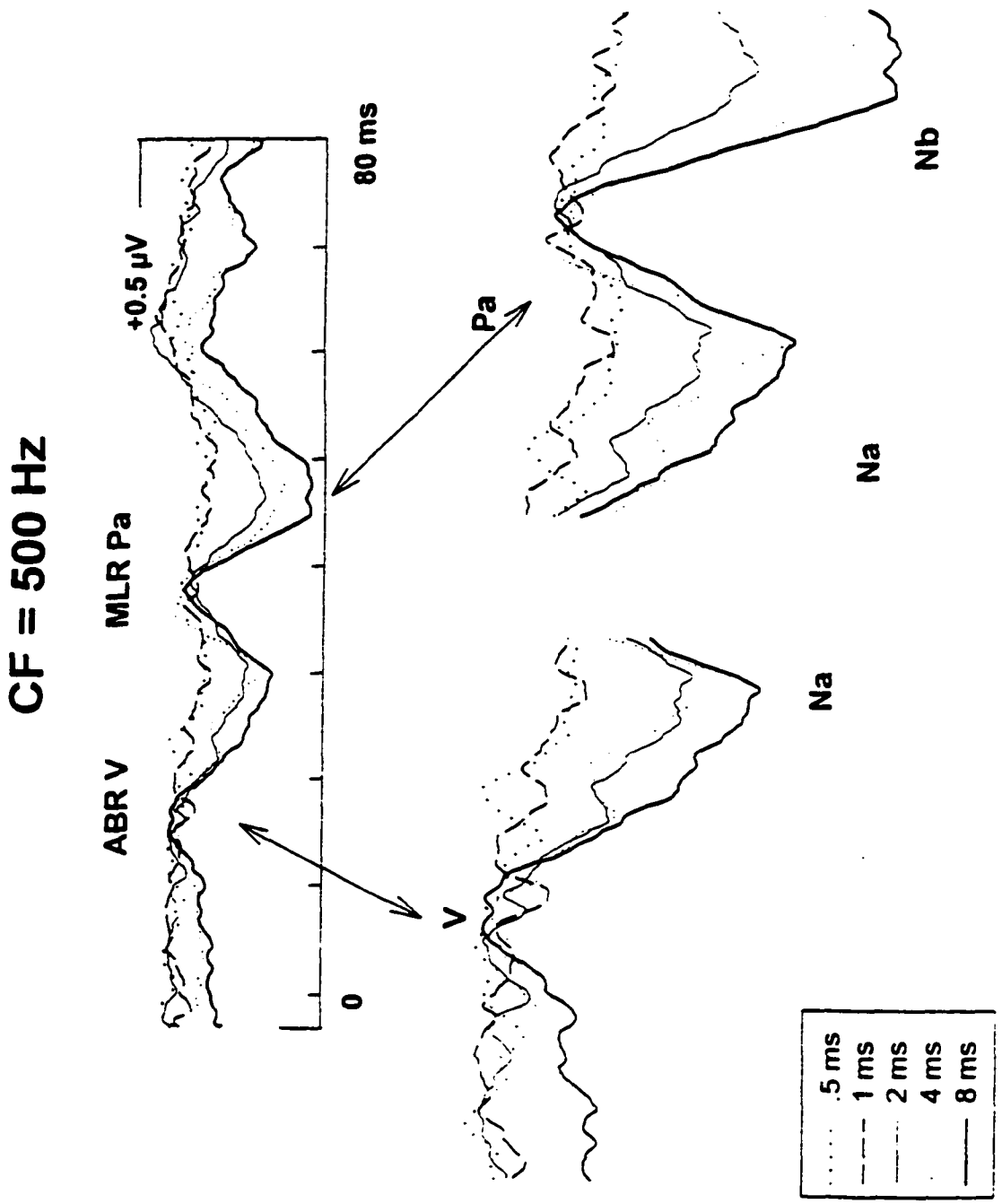
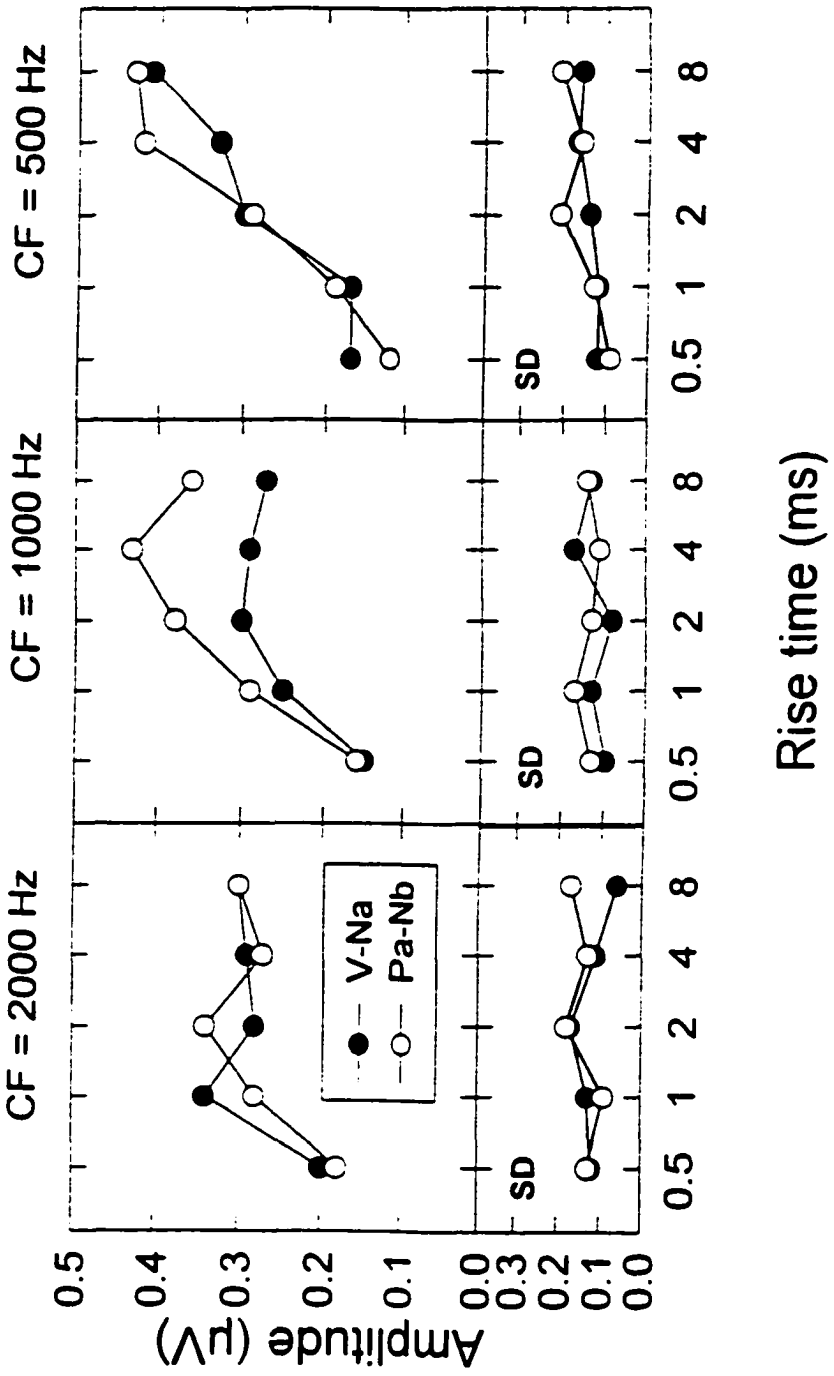


Figure 4



CHAPTER 4: SUMMARY AND IMPLICATIONS

When using the "constant-slope" rise time paradigm, ABR and MLR amplitudes increase with increases in stimulus rise time until a critical duration is reached (i.e, the "effective" duration). Results from the first study (Chapter 2) indicate that the effective duration of the stimulus for the ABR and MLR is stimulus dependent, with 500-Hz results exhibiting the longest effective duration (~12 ms), the noiseburst results the shortest effective duration (~2 ms), and 2000-Hz results falling in between (~4 ms). Results from the second study (Chapter 3) further suggest that the pattern of results of the first study are not stimulus specific -- rather, they reflect differences in processing at different cochlear places. That is, the effective duration of the stimulus for the ABR and MLR are cochlear place dependent. Further studies with longer rise times are needed to determine the effective duration of ABR and MLR evoked by 500-Hz tones (and for responses evoked from the 500-Hz one-octave-wide cochlear region), because, in both studies, response amplitudes continued to grow at the longest rise-time tested. The differences in the effective durations of responses to the 500- and 2000-Hz stimuli and between the effective durations obtained for the one octave-wide 500- and 2000-Hz cochlear regions elicited by the noiseburst stimuli, indicate that the effective duration of the stimulus for the ABR and MLR is primarily a cochlear place phenomenon, with responses from the apical regions of the cochlea integrating longer portions of the stimuli. The longer effective durations obtained for the tonal stimuli compared to responses from the 2000- and 500-Hz one-octave-wide cochlear regions (derived using noise masking) suggest that the effective duration of the tonal stimuli might be further affected by stimulus-specific effects such as periodicity and phase, or by acoustic and place specificity.

The frequency-related differences in the effective duration of the stimulus might be in part due to traveling wave delays which occur in the cochlea. The traveling wave delay is frequency dependent and consists of cochlear transport time and cochlear filter build-up time (Don, et al., 1998; John & Picton, 2000). According to Don and colleagues, the filter build-up time for the 2000-Hz one-octave-wide region is approximately one cycle longer than the filter build-up time for the 500-Hz one-octave-wide region, but shorter by approximately 2.5 cycles for the 6000-Hz one-octave-wide region (Don et al., 1998). When the effective durations of the 500- and 2000-Hz tonal stimuli (Chapter 2) are converted to the number of stimulus cycles necessary to reach the effective duration of the stimulus for each stimulus frequency, the results suggested 8 cycles for the 2000-Hz stimulus and 4.5 cycles for the 500-Hz stimulus. Similar results were obtained by Kodera and colleagues, albeit in cats (Kodera et al., 1983). When the effective durations of the one-octave-wide cochlear places representing 2000, 1000, and 500 Hz (Chapter 3) are converted to the number of stimulus cycles necessary to reach the effective duration of the stimulus, the results suggest 4-8 cycles for 2000-Hz, 2-4 cycles for 1000-Hz, and 2-4 cycles for the 500-Hz cochlear regions. Similar to cochlear filter build-up time (Don et al., 1998), the number of stimulus cycles necessary to reach the effective duration of the stimulus are higher for responses elicited from the more basal regions of the cochlea suggesting that the effective duration of the stimulus may partially reflect cochlear filter build-up time delays, which differ for differing cochlear place.

In the current studies (Chapters 2 and 3), the effective duration of the stimulus for the ABR and MLR ranged from 1 to 12 ms, indicating that the use of the term "onset" response when referring to the ABR or

MLR is misleading, as at least the first 2 to as many as 8 cycles of the stimulus are effective in eliciting the response. Furthermore, these results do not support the commonly-held notion that the MLR is *less* of an "onset" response than the ABR. In both studies, no differences in the effective durations of the stimuli between the ABR and MLR were observed. The lack of differences in the effective durations of the ABR and MLR indicate that the effective durations vary as a function of cochlear region rather than as a function of the wave evoked (i.e., ABR or MLR), suggesting that the effective durations of the stimuli/specific cochlear regions are determined prior to (or at) the midbrain level, the region generating ABR wave V.

In clinical practice, the stimuli typically used for the assessment of auditory sensitivity using the ABR have rise and fall times of 2 cycles each and a plateau duration of 1 cycle (i.e., the "2-1-2" cycles tone) (e.g., Davis, Hirsh, Popelka, & Formby, 1984; Stapells & Oates, 1997). The present study suggests that the ABR and MLR can integrate longer stimulus portions and thus, when frequency specificity is of a major concern, stimulus rise time could be extended up to the effective duration of the stimuli (i.e., 12 ms for the 500-Hz stimulus, 4 ms for the 2000-Hz stimulus, and 2 ms for the noiseburst stimulus). Further research is needed to determine wether thresholds obtained with these longer rise time correlate well with pure-tone behavioral thresholds.

Biermann and Heil (2000) found that stimulus onset is determined by a dynamic interaction of stimulus rise time and slope. Therefore, unlike, the current belief that rise function is irrelevant and rise times are only important as to how they affect spectral splatter (Hyde, 1997), they recommend stimulus selection for AEP testing to include careful rise time and slope selection (Biermann and Heil, 2000). The

present study supports the notion that further research is needed to determine the optimum rise time and slope functions for AEP thresholds testing.

In the present studies, the effective durations of the stimulus were determined for an intensity series which started at 54 dB ppe SPL and ended at 80.5 dB ppe SPL. Studying responses from cats, Kodera and colleagues reported that longer rise times are necessary to reach the effective duration of the stimulus when stimulus intensity is lowered (Kodera et al., 1983). Studying humans, Suzuki and Horiuchi suggested that the effective duration of the stimulus is intensity dependent, with longer effective durations elicited by lower intensities (Suzuki & Horiuchi, 1981). Further studies are needed in order to determine the effective duration at or close to threshold, as the extent of this increase is currently unknown. If longer effective durations are required for lower intensities, then the optimum stimulus for obtaining more frequency-specific auditory thresholds might be longer than those suggested from this study. Suzuki and Horiuchi and Kodera and colleagues also suggested that the effective duration of the stimulus is shorter for effective durations elicited by high intensities (Kodera et al., 1983; Suzuki & Horiuchi, 1981). Further studies are needed in order to determine the effective duration at higher intensity levels, as the extent of this decrease is currently unknown.

The effective duration of the stimulus has been studied in this and previous studies in normal-hearing humans (Suzuki & Horiuchi, 1981) and cats (Kodera et al., 1983). To date, no published studies have evaluated the effective duration of the stimuli for the ABR and MLR in hearing-impaired individuals. The effective durations obtained from the normal functioning cochlea (Chapters 2 and 3) suggest that the effective duration of the ABR and MLR are determined prior to the wave V

generators, likely at the cochlea or VIIIth nerve levels. Ruggero demonstrated that loss of outer hair cells results in shorter cochlear response times (Ruggero, 1994). Earlier, Eggermont showed that cochlear hearing loss causes shorter neural (VIIIth nerve compound action potential) response times and shorter cochlear filter response times (Eggermont, 1979). Recently, Don and colleagues found that, with cochlear hearing loss, the number of periods to obtain maximum response amplitude decreased as a function of hearing loss, especially for low-CF derived bands (Don et al., 1998). Thus, the effective duration of the stimulus for the ABR and MLR in the presence of hearing loss might differ from the effective durations which have been obtained for normal-hearing individuals. Further studies are thus needed to determine the effective durations of the stimulus for the ABR and MLR for cochlear hearing-impaired individuals.

APPENDIX A: CHAPTER 2 - PEAK-TO-PEAK AMPLITUDE MEASURES OF WAVES V-Na AND Pa-Nb

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

Noiseburst Stimuli

V-Na

Subject	Rise .5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.36	0.54	0.46	0.42	0.41
subj 2	0.84	1.00	0.91	0.88	0.78
subj 3	0.58	0.68	1.01	0.85	0.98
subj 4	0.50	0.80	0.86	0.67	0.74
subj 5	0.56	0.79	0.91	0.66	0.89
subj 6	0.54	0.76	0.93	0.75	0.63
subj 7	0.51	0.50	0.73	0.62	0.62
subj 8	1.27	1.34	1.54	1.49	1.39
subj 9	0.56	0.61	0.50	0.56	0.61
subj 10	0.08	0.22	0.39	0.40	0.25
subj 11	0.47	0.47	0.60	0.43	0.73
subj 12	0.47	0.68	0.61	0.80	0.69
mean	0.56	0.69	0.79	0.71	0.73
SD	0.28	0.28	0.31	0.29	0.28

Pa-Nb

Subject	Rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.32	0.34	0.39	0.36	0.33
subj 2	0.55	0.94	0.81	1.19	1.08
subj 3	0.24	0.43	0.34	0.25	0.36
subj 4	0.65	0.61	0.93	0.90	0.60
subj 5	0.13	0.51	0.48	0.70	0.27
subj 6	0.42	0.47	0.45	0.57	0.67
subj 7	0.89	1.15	0.99	1.20	1.03
subj 8	0.70	1.21	1.24	1.11	1.44
subj 9	0.50	0.61	0.89	0.66	0.87
subj 10	0.44	0.61	0.48	0.40	0.14
subj 11	0.73	0.78	0.80	1.10	1.22
subj 12	0.07	0.12	0.14	0.17	0.09
mean	0.46	0.65	0.66	0.72	0.67
SD	0.26	0.32	0.32	0.38	0.45

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

2000-Hz Stimuli

V-Na

Subject	Rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.32	0.26	0.24	0.31	0.4
subj 2	0.50	0.36	0.54	0.55	0.61
subj 3	0.29	0.52	0.45	0.65	0.62
subj 4	0.49	0.60	0.56	0.65	0.62
subj 5	0.45	0.44	0.39	0.41	0.54
subj 6	0.28	0.26	0.48	0.49	0.29
subj 7	0.48	0.56	0.62	0.60	0.68
subj 8	0.74	0.76	0.88	0.82	0.72
subj 9	0.39	0.20	0.32	0.39	0.30
subj 10	0.12	0.1	0.10	0.21	0.27
subj 11	0.43	0.41	0.46	0.42	0.41
subj 12	0.26	0.42	0.55	0.47	0.48
mean	0.39	0.41	0.47	0.50	0.50
SD	0.16	0.19	0.20	0.17	0.16

Pa-Nb

Subject	Rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.36	0.14	0.27	0.35	0.24
subj 2	0.54	0.69	0.63	0.71	0.62
subj 3	0.34	0.27	0.35	0.23	0.22
subj 4	0.68	0.71	0.62	0.70	0.67
subj 5	0.27	0.28	0.28	0.37	0.37
subj 6	0.42	0.52	0.33	0.45	0.61
subj 7	0.78	0.61	0.64	0.65	0.57
subj 8	0.57	0.67	0.69	0.88	0.79
subj 9	0.60	0.55	0.38	0.61	0.34
subj 10	0.25	0.26	0.29	0.16	0.28
subj 11	0.73	0.79	0.63	0.54	0.67
subj 12	0.28	0.33	0.31	0.38	0.06
mean	0.48	0.49	0.45	0.50	0.45
SD	0.19	0.22	0.17	0.21	0.24

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

500-Hz Stimuli

V-Na

Subject	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms	Rise 12ms
subj 1	0.45	0.30	0.25	0.38	0.42
subj 2	0.78	0.87	0.84	1.01	0.97
subj 3	0.46	0.50	0.65	0.64	0.65
subj 4	0.41	0.33	0.43	0.54	0.59
subj 5	0.46	0.41	0.36	0.68	0.73
subj 6	0.43	0.45	0.52	0.50	0.50
subj 7	0.65	0.45	0.33	0.44	0.69
subj 8	0.89	1.06	1.08	1.21	1.34
subj 9	0.33	0.43	0.47	0.47	0.42
subj 10	0.48	0.66	0.51	0.52	0.75
subj 11	0.48	0.28	0.38	0.64	0.56
subj 12	0.48	0.63	0.70	0.78	0.55
mean	0.52	0.53	0.54	0.65	0.68
SD	0.16	0.24	0.24	0.24	0.26

Pa-Nb

Subject	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms	Rise 12ms
subj 1	0.40	0.41	0.41	0.48	0.54
subj 2	0.91	0.99	1.12	1.15	1.01
subj 3	0.31	0.38	0.46	0.33	0.34
subj 4	0.59	0.65	0.61	0.65	0.60
subj 5	0.38	0.33	0.42	0.25	0.32
subj 6	0.69	0.61	0.59	0.49	0.62
subj 7	0.62	0.87	0.83	0.81	1.07
subj 8	0.72	0.55	0.93	0.84	0.78
subj 9	0.51	0.45	0.67	0.59	0.68
subj 10	0.71	0.77	0.67	0.56	0.58
subj 11	0.79	1.14	1.18	0.94	1.26
subj 12	0.50	0.38	0.43	0.30	0.58
mean	0.56	0.63	0.70	0.61	0.70
SD	0.18	0.26	0.27	0.27	0.28

APPENDIX B: CHAPTER 3 - PEAK-TO-PEAK AMPLITUDE MEASURES OF WAVES V-Na AND Pa-Nb

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

One-octave-wide 2000-Hz derived response

V-Na

Subject	rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.11	0.14	0.14	0.19	0.36
subj 2	0.38	0.50	0.48	0.48	0.27
subj 3	0.08	0.25	0.46	0.36	0.34
subj 4	0.23	0.44	0.44	0.24	0.36
subj 5	0.15	0.29	0.11	0.26	0.28
subj 6	0.22	0.20	0.08	0.29	0.30
subj 7	0.32	0.53	0.24	0.32	0.29
subj 8	0.33	0.48	0.45	0.38	0.29
subj 9	0.07	0.26	0.46	0.25	0.21
subj 10	0.05	0.26	0.06	0.08	0.33
subj 11	0.30	0.36	0.14	0.18	0.19
subj 12	0.21	0.28	0.29	0.40	0.39
mean	0.20	0.33	0.27	0.29	0.30
SD	0.12	0.13	0.17	0.11	0.06

Pa-Nb

Subject	Rise0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.23	0.19	0.18	0.11	0.25
subj 2	0.40	0.35	0.46	0.46	0.26
subj 3	0.13	0.28	0.23	0.24	0.16
subj 4	0.08	0.35	0.25	0.26	0.16
subj 5	0.07	0.23	0.47	0.24	0.12
subj 6	0.07	0.25	0.24	0.26	0.07
subj 7	0.24	0.18	0.40	0.33	0.49
subj 8	0.06	0.47	0.59	0.44	0.54
subj 9	0.31	0.18	0.65	0.34	0.57
subj 10	0.05	0.29	0.06	0.08	0.42
subj 11	0.37	0.33	0.29	0.35	0.21
subj 12	0.20	0.09	0.21	0.07	0.29
mean	0.18	0.28	0.33	0.26	0.30
SD	0.13	0.09	0.18	0.13	0.17

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

One-octave-wide 1000-Hz derived response

V-Na

Subject	rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.19	0.17	0.17	0.12	0.13
subj 2	0.05	0.39	0.38	0.57	0.45
subj 3	0.15	0.06	0.42	0.45	0.09
subj 4	0.19	0.2	0.29	0.23	0.29
subj 5	0.31	0.07	0.34	0.25	0.24
subj 6	0.07	0.21	0.19	0.05	0.07
subj 7	0.27	0.32	0.24	0.29	0.24
subj 8	0.08	0.50	0.35	0.66	0.43
subj 9	0.06	0.36	0.37	0.18	0.40
subj 10	0.06	0.22	0.30	0.20	0.34
subj 11	0.11	0.26	0.35	0.27	0.25
subj 12	0.28	0.36	0.22	0.24	0.31
mean	0.15	0.26	0.30	0.29	0.27
SD	0.09	0.13	0.08	0.18	0.12

Pa-Nb

Subject	Rise0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.29	0.27	0.27	0.27	0.25
subj 2	0.05	0.48	0.42	0.56	0.66
subj 3	0.28	0.15	0.25	0.41	0.35
subj 4	0.37	0.41	0.66	0.55	0.41
subj 5	0.06	0.07	0.28	0.50	0.36
subj 6	0.07	0.15	0.27	0.31	0.31
subj 7	0.32	0.45	0.45	0.43	0.37
subj 8	0.08	0.19	0.37	0.53	0.55
subj 9	0.06	0.34	0.21	0.28	0.39
subj 10	0.06	0.09	0.46	0.47	0.33
subj 11	0.07	0.56	0.37	0.54	0.11
subj 12	0.07	0.25	0.53	0.33	0.28
mean	0.15	0.28	0.38	0.43	0.36
SD	0.13	0.16	0.13	0.11	0.14

Peak-to-peak amplitude measures (in μV) for Waves V-Na and Pa-Nb

One-octave-wide 500-Hz derived response

V-Na

Subject	rise 0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.06	0.06	0.18	0.20	0.34
subj 2	0.30	0.32	0.49	0.65	0.69
subj 3	0.32	0.05	0.37	0.61	0.47
subj 4	0.38	0.09	0.34	0.38	0.34
subj 5	0.23	0.27	0.32	0.26	0.34
subj 6	0.25	0.08	0.20	0.15	0.32
subj 7	0.08	0.08	0.27	0.17	0.45
subj 8	0.09	0.07	0.61	0.48	0.74
subj 9	0.17	0.06	0.26	0.38	0.22
subj 10	0.07	0.20	0.08	0.14	0.26
subj 11	0.06	0.32	0.23	0.26	0.40
subj 12	0.08	0.38	0.25	0.32	0.32
mean	0.17	0.16	0.30	0.33	0.41
SD	0.12	0.12	0.14	0.17	0.16

Pa-Nb

Subject	Rise0.5ms	Rise 1ms	Rise 2ms	Rise 4ms	Rise 8ms
subj 1	0.06	0.06	0.32	0.31	0.26
subj 2	0.06	0.39	0.56	0.71	0.86
subj 3	0.05	0.05	0.11	0.19	0.32
subj 4	0.28	0.09	0.59	0.25	0.62
subj 5	0.25	0.05	0.07	0.42	0.24
subj 6	0.07	0.31	0.07	0.29	0.47
subj 7	0.11	0.31	0.39	0.57	0.42
subj 8	0.09	0.21	0.28	0.64	0.34
subj 9	0.07	0.37	0.36	0.31	0.23
subj 10	0.07	0.24	0.08	0.43	0.41
subj 11	0.29	0.07	0.60	0.54	0.71
subj 12	0.07	0.10	0.05	0.37	0.22
mean	0.12	0.19	0.30	0.42	0.42
SD	0.09	0.13	0.21	0.16	0.21

APPENDIX C: CHAPTER 2 - ANOVA TABLES

Two-way repeated measures ANOVA

Wave (V-Na, Pa-Nb) x Rise-time (0.5-8 ms)

Noiseburst Stimuli

DESIGN: 2 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-WAVE(2) x 2-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (qampall.sta) 1-WAVE, 2-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	1	.106803	11	.172142	.620439	.447525
2	4*	.061560*	44*	.007643*	8.054143*	.000058*
12	4	.030539	44	.011891	2.568317	.051060

One-way repeated measures ANOVA

Wave: V-Na

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none

STAT. GENERAL MANOVA	Summary of all Effects; design: (qnamp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4*	.114958*	44*	.010147*	11.32983*	.000002*

Wave: Pa-Nb

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none

STAT. GENERAL MANOVA	Summary of all Effects; design: (qnamp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4*	.115396*	44*	.021904*	5.268250*	.001482*

#Probabilities do not reflect Huynh-Feldt p-levels

Two-way repeated measures ANOVA
Wave (V-Na, Pa-Nb) x Rise-time (0.5-8 ms)

2000-Hz Stimuli

DESIGN: 2 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-WAVE(2) x 2-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (qampall.sta) 1-WAVE, 2-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	1	.014741	11	.053770	.274146	.610950
2	4	.013511	44	.005818	2.322291	.071498
12	4	.020855	44	.008319	2.507083	.055519

One way ANOVAs:

PEAK: V-Na

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (q2amp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4*	.027735*	44*	.005474*	5.066595*	.001905*

PEAK: Pa-Nb

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (q2amp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4	.006632	44	.008663	.765554	.553399

#Probabilities do not reflect Huynh-Feldt p-levels

Two-way repeated measures ANOVA

Wave (V-Na, Pa-Nb) x Rise-time (0.5-8 ms)

500-Hz Stimuli

DESIGN: 2 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-WAVE(2) x 2-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (qampall.sta) 1-WAVE, 2-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	1	.106803	11	.172142	.620439	.447525
2	4*	.061560*	44*	.007643*	8.054143*	.000058*
12	4	.030539	44	.011891	2.568317	.051060

One way ANOVAs:

PEAK: V-Na

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (q5amp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4*	.065344*	44*	.009278*	7.043065*	.000179*

PEAK: Pa-Nb

DESIGN: 1 - way ANOVA, fixed effects
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (q5amp.sta) 1-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	4*	.026754*	44*	.010256*	2.608639*	.048323*

#Probabilities do not reflect Huynh-Feldt p-levels

APPENDIX D: CHAPTER 3 - ANOVA TABLES

Three-way repeated measures ANOVA

Center Frequency (CF) x Wave x Rise-time

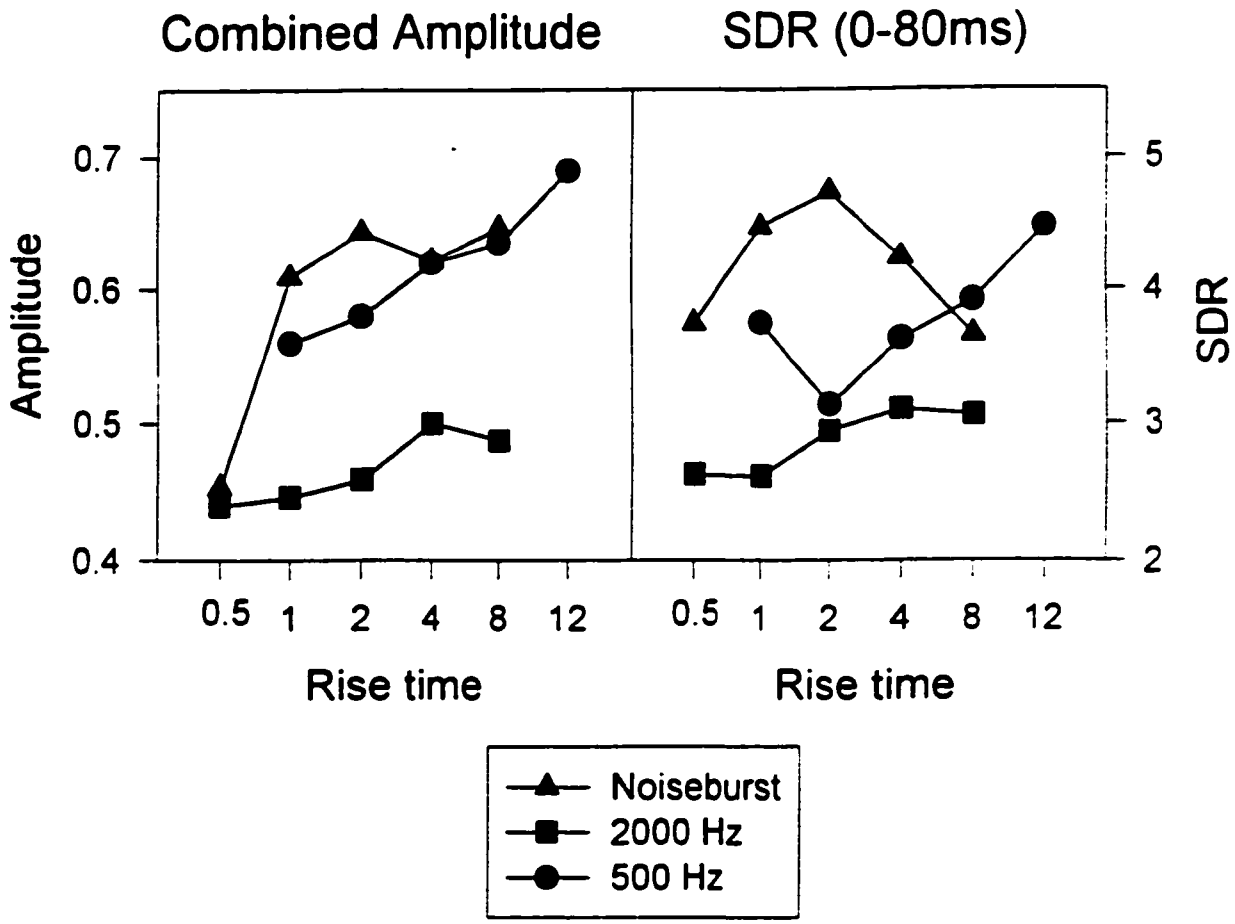
3 way ANOVA
DEPENDENT: 1 variable (Repeated Measure)
BETWEEN: none
WITHIN: 1-CF(3) x 2-WAVE(2) x 3-RISE(5)

STAT. GENERAL MANOVA	Summary of all Effects; design: (derived.sta) 1-STIM, 2-WAVE, 3-RISE					
Effect	df Effect	MS Effect	df Error	MS Error	F	p-level#
1	2	.005369	22	.012411	.43260	.654221
2	1	.046672	11	.031295	1.49134	.247537
3	4*	.411396*	44*	.018051*	22.79134*	.000000*
12	2	.047049	22	.017629	2.66882	.091681
13	8*	.072447*	88*	.015662*	4.62570*	.000097*
23	4*	.025291*	44*	.007514*	3.36559*	.017326*
123	8	.010251	88	.013739	.74607	.650717

#Probabilities do not reflect Huynh-Feldt p-levels

APPENDIX E: CHAPTER 2 - SDR RESULTS

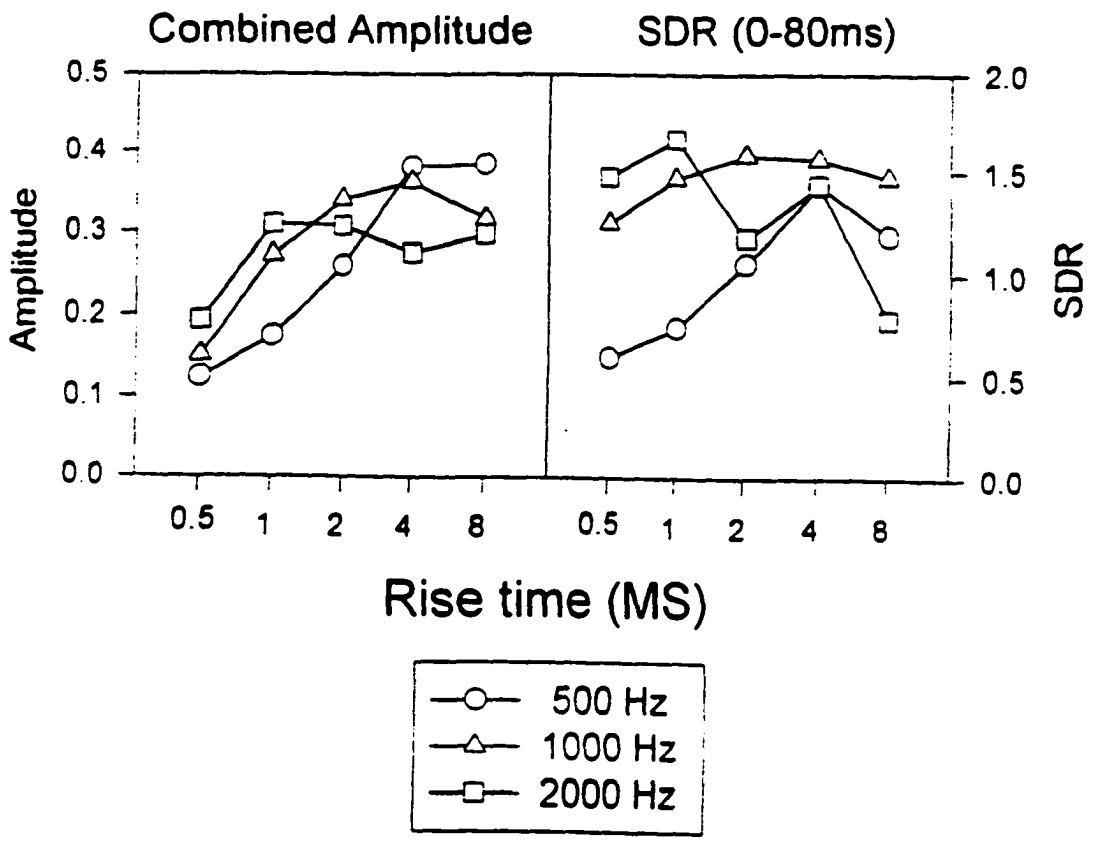
As an alternative measure to determine the effective duration of the stimulus of the ABR and MLR evoked responses, the "Standard Deviation Ratio (SDR)" was also employed. The SDR is defined as "the ratio of the root-mean-square amplitude of the signal divided by the root-mean-square of the (±) reference" (Picton et al., 1983, 1984). The SDR is one measure suggested as an objective measure of the signal-to-noise ratio of an evoked potential, and thus response presence, of the ABR or MLR (Picton et al., 1994; Picton et al., 1984; Picton et al., 1983; Valdes-Sosa et al., 1987). The SDR was calculated over the 80-ms post-stimulus window for all subjects, rise times, and derived responses. The analyses in study 1 depended on human observers judging visually whether a response is present or absent. In order to validate the results using an objective method, the standard deviation ratio (SDR) was calculated for the 0-80 ms post stimulus window. The SDR figure presents the mean SDR results, plotted as a function of rise time for each stimulus. Also plotted for comparison are the mean combined amplitudes of waves V-Na and Pa-Nb, as the preceding analysis had indicated no difference between these two waves. For the noiseburst stimulus, the SDR results exhibit an immediate increase until the 2-ms rise time, after which further increases in rise time do not increase the SDR value. For the 2000-Hz stimulus, a gradual increase in amplitude occurs until the 4-ms rise time, after which the SDR does not change. For the 500-Hz stimulus, SDR increases from the 2-ms rise time until the 12-ms rise time. Overall, these objectively obtained SDR results are similar to the observer-determined amplitude results for the two waves combined, further indicating the validity of the obtained results.



Mean SDR results for the 0-80 ms recording window for the three stimuli are plotted as a function of rise time (right). The averaged mean amplitudes of waves V-Na and Pa-Nb for the three stimuli are plotted for comparison (left).

APPENDIX F: CHAPTER 3 - SDR RESULTS

As in the previous study (appendix E), an alternative measure to determine the effective duration of the stimulus of the ABR and MLR evoked responses, the "Standard Deviation Ratio (SDR)" was also employed in study 2. As in study 1, the SDR was calculated over the 80-ms post-stimulus window for all subjects, rise times, and derived responses. As, in study 1, the analyses in study 2 depended on human observers judging visually whether a response is present or absent. In order to validate the results using an objective method, the standard deviation ratio (SDR) was calculated for the 0-80 ms post stimulus window. The SDR figure below, presents the mean SDR results, plotted as a function of rise time, for each derived response. Also plotted for comparison are the combined amplitude results for waves V-Na and Pa-Nb. Amplitude for V-Na and Pa-Nb have been combined because the preceding analyses indicate no significant differences between results for these two waves. For the 2000-Hz one-octave-wide derived response, the SDR results exhibit an immediate increase up until the 1-ms rise time, after which further increases in rise time do not increase the SDR value. For the 1000-Hz stimulus, a gradual increase in amplitude occurs until the 2-ms rise time, after which the SDR does not change. For the 500-Hz stimulus, SDR increases until the 4-ms rise time. Overall, these objectively obtained SDR results are similar to the observer-determined combined amplitude results, further indicating the validity of the preceding results.



Mean SDR results for the 0-80 ms recording window for the 1-octave-wide cochlear region centered at 2000, 1000, and 500 Hz are plotted as a function of rise time (right). In order to compare the SDR results, which represent the total recording window, to an amplitude measure representing the total recording window, the ABR and MLR amplitudes are combined.

APPENDIX G: THE "OFF RESPONSE

In this study, a long and gradual fall time of 36 ms was used in order to eliminate or reduce any offset responses. The 36-ms fall time was used since shorter fall times (0.5 ms to 10 ms) have produced an "off" response (e.g., Brinkmann & Scherg, 1979; Van Campen et al., 1997).

A pilot study was carried out to determine the response, if any, that a 36-ms fall time evokes. Two normal-hearing adult participated in this study. Recordings to an 81 dB ppe SPL 500-Hz tone with a 12-ms rise time, a 100-ms plateau, and a 36-ms fall time, were obtained. The 12-ms rise time at 500-Hz was chosen for this pilot study because it contains the steepest rise-time slope and highest level used in this study. Two recordings (4500 trials each) were collected using a stimulus rate of 3/s and analysis window of 300 ms. The EEG was amplified (gain = 100,000), and analog filtered on line with a 10-1000 Hz passband (6dB/octave). Single-trial EEG epochs were filtered digitally offline using a 20-Hz high-pass filter (12 dB/octave) and a 400-Hz low-pass filter (24 dB/octave slope).

Figure 1a presents the electrical waveform of the stimulus for this pilot study. The evoked potentials waves are presented in figure 1b. The beginning of the rise time is marked with an arrow. As would be expected, clearly identifiable ABR wave V, MLR waves Na, Pa and Nb, and cortical auditory evoked potential (CAEP) waves P1 and N1 are seen in the initial 100 ms of the response. The beginning of the fall time is marked with a double arrow (i.e., starting at 112 ms). In order to determine if a replicable ABR or MLR to the "fall" portion of the stimulus occurred, the 80 ms of the response following the beginning of the fall time are "zoomed" in figure 3c. In this portion of the response, ABR wave V and MLR waves Na or Pa are not detectable. At 65

ms from the beginning of the fall time, however, CAEP wave P1 is detectable.

The amplitude of the cortical responses decrease with decreasing interstimulus intervals (e.g., Picton et al., 1977). Thus, at the rate used in the thesis studies (10.9/s) and without the stimulus plateau, the CAEP results obtained in this pilot study indicate that there will be no significant CAEP off response. Overlap of any CAEP "off" response to the response to a subsequent stimulus will likely not have an effect on waves V, Na, Pa and Nb.

This pilot study demonstrated that responses evoked by the 36-ms fall time are very small in amplitude and will not interfere with responses evoked by the rise of the stimulus. Thus, in the proposed study, a 36-ms fall time was used for all stimuli.

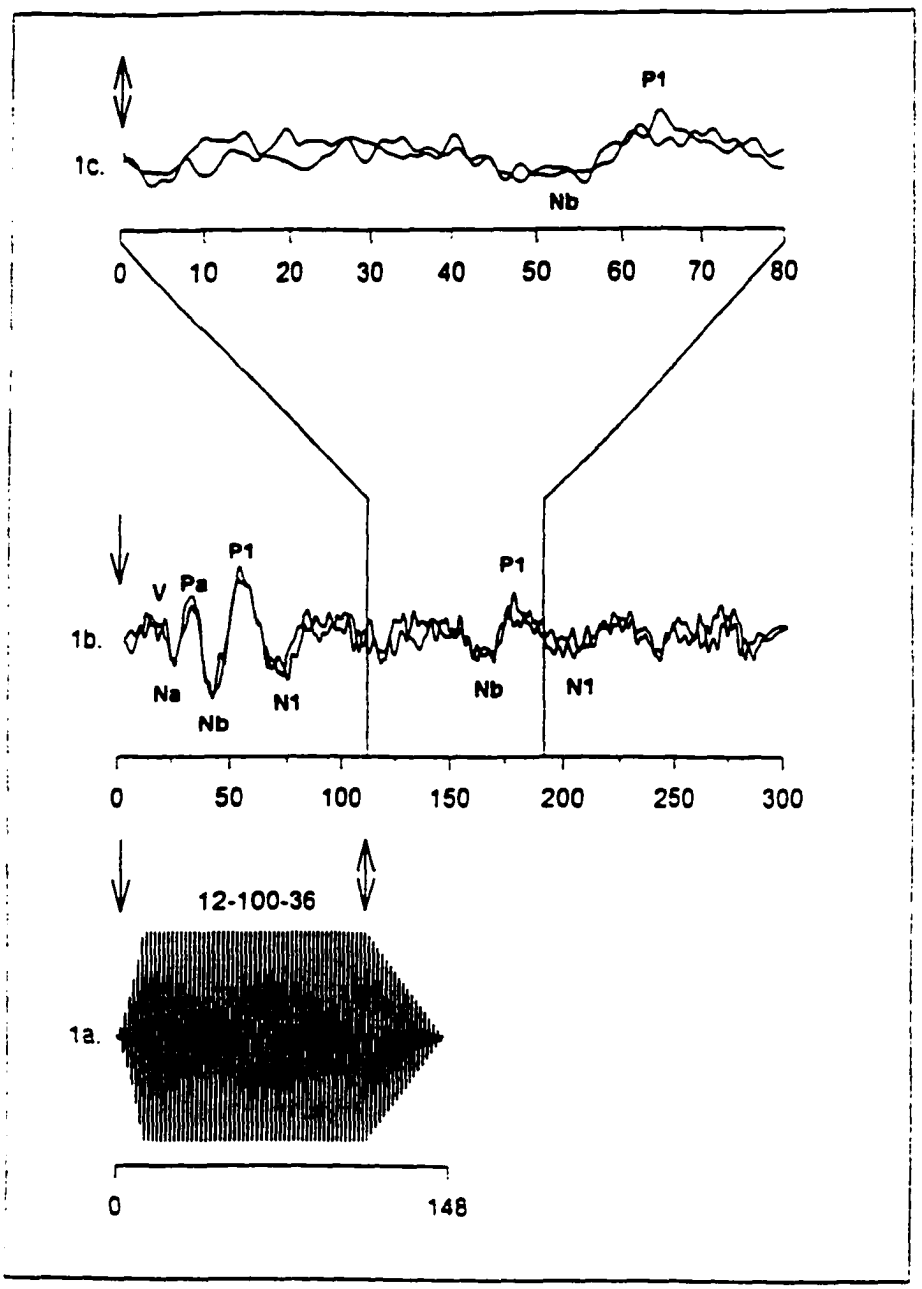


Figure 1: The onset and offset response for a 500-Hz tone stimulus with a 12-ms rise time, 100-ms plateau, and a 36-ms fall time. The beginning of the rise time is marked with an arrow. The beginning of the fall time is marked with a double arrow. **1a** presents the acoustic waveform of the stimulus. **1b** presents the AEP. **1c** presents the first 80 ms of the response following the beginning of the fall time

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