STUDIES OF THE AUDITORY STEADY-STATE RESPONSES

by

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We accept this thesis as conforming
to the required standard

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Date April 26, 2002
Scalp-recorded auditory steady-state responses (ASSRs) to multiple stimuli may be useful in objectively estimating hearing thresholds of individuals who are unable to reliably respond behaviourally, such as infants. Primary objectives of the present thesis are: (1) to identify the anatomical location of neurons responsible for generating ASSRs; (2) to determine cochlear place specificity of the multiple-ASSR method; (3) to evaluate the benefit of using the multiple-ASSR method in estimating hearing thresholds, as compared to single-stimulus methods; and (4) to determine the accuracy of using multiple-ASSRs to estimate hearing thresholds in subjects with normal or impaired hearing. Results show that the entire auditory system contributes to the generation of ASSRs to modulated stimuli. Cortical neurons are more responsive at lower modulation frequencies (e.g., \(<40\) Hz), whereas brainstem structures primarily generate ASSRs to higher modulation frequencies (e.g., \(80\) Hz). ASSRs to multiple amplitude-modulated tones (modulated between 77-105 Hz) reflect activation of approximately 1-octave-wide cochlear regions around each carrier frequency. This is similar to results reported for the auditory brainstem response method. As compared to presenting stimuli separately, simultaneously presenting multiple (i.e., at least 4 per ear) amplitude-modulated tones to evoke the ASSR can considerably reduce the time needed to estimate hearing thresholds for octave frequencies between 500 and 4000 Hz. Furthermore, multiple-ASSR thresholds are not different than thresholds for ASSRs to stimuli presented separately. For individuals with normal or impaired hearing, multiple-ASSR thresholds are approximately 5-15 decibels higher than behavioural thresholds, on average. Furthermore, multiple-ASSRs can accurately estimate the behavioural audiogram configurations (threshold by frequency) in subjects with various types of hearing impairments. Collectively, results from the present thesis indicate that the multiple-ASSR method is useful for evaluating hearing thresholds and provides advantages over the conventional objective audiometric methods.
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Subjects

Stimulation & Recordings

Procedure

Thresholds Evaluation

Evoked Potential Analyses

Results

Thresholds
Chapter 5: ASSR Thresholds of Adults with Sensorineural Hearing Impairments

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ASSR Stimuli

Procedure

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<td>ABR</td>
<td>auditory brainstem response</td>
</tr>
<tr>
<td>AEP</td>
<td>auditory evoked potential</td>
</tr>
<tr>
<td>AM</td>
<td>amplitude-modulated</td>
</tr>
<tr>
<td>ANOVA</td>
<td>analysis of variance</td>
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<tr>
<td>ASSF</td>
<td>auditory steady-state field</td>
</tr>
<tr>
<td>ASSR</td>
<td>auditory steady-state response</td>
</tr>
<tr>
<td>BESA</td>
<td>Brains Electrical Source Analysis</td>
</tr>
<tr>
<td>BW&lt;sub&gt;6dB&lt;/sub&gt;</td>
<td>bandwidth at 6 dB down from maximal amplitude</td>
</tr>
<tr>
<td>CAEP</td>
<td>cortical auditory evoked potential</td>
</tr>
<tr>
<td>CF</td>
<td>centre frequency</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>dB</td>
<td>decibel</td>
</tr>
<tr>
<td>dB HL</td>
<td>decibels hearing level</td>
</tr>
<tr>
<td>dB nHL</td>
<td>decibels normal hearing level</td>
</tr>
<tr>
<td>dB SL</td>
<td>decibels sensation level</td>
</tr>
<tr>
<td>dB SPL</td>
<td>decibels sound pressure level</td>
</tr>
<tr>
<td>df</td>
<td>degrees of freedom</td>
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<tr>
<td>DM</td>
<td>dichotic multiple</td>
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<tr>
<td>DR</td>
<td>derived-band response</td>
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<tr>
<td>EEG</td>
<td>electroencephalography or electroencephalographic</td>
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<tr>
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<tr>
<td>ERP</td>
<td>evoked response potential</td>
</tr>
<tr>
<td>F</td>
<td>Fisher's F ratio</td>
</tr>
<tr>
<td>fc</td>
<td>carrier frequency</td>
</tr>
<tr>
<td>FFT</td>
<td>fast Fourier transform</td>
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<tr>
<td>fm</td>
<td>modulation frequency</td>
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<tr>
<td>HPN</td>
<td>high-pass noise</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>kHz</td>
<td>kiloHertz (1000 Hz)</td>
</tr>
<tr>
<td>L</td>
<td>latency</td>
</tr>
<tr>
<td>LE</td>
<td>left ear</td>
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<tr>
<td>MEG</td>
<td>magnetoencephalography</td>
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<td>MLF</td>
<td>middle-latency field</td>
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<td>MLR</td>
<td>middle-latency response</td>
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<tr>
<td>MM</td>
<td>monotic multiple</td>
</tr>
<tr>
<td>ms</td>
<td>millisecond</td>
</tr>
<tr>
<td>MS</td>
<td>monotic single</td>
</tr>
<tr>
<td>μV</td>
<td>microvolt</td>
</tr>
<tr>
<td>nV</td>
<td>nanovolt</td>
</tr>
<tr>
<td>p</td>
<td>probability</td>
</tr>
<tr>
<td>Q6dB</td>
<td>product quotient at 6 dB down from maximal amplitude</td>
</tr>
<tr>
<td>r</td>
<td>Pearson's product-moment correlation</td>
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<tr>
<td>RE</td>
<td>right ear</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
</tr>
<tr>
<td>SSEP</td>
<td>steady-state evoked potential</td>
</tr>
<tr>
<td>$z$</td>
<td>standard score</td>
</tr>
<tr>
<td>$Z_B$</td>
<td>standard score for behavioural threshold</td>
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<tr>
<td>$Z_R$</td>
<td>standard score for auditory steady-state response threshold</td>
</tr>
<tr>
<td>$\tau'$</td>
<td>apparent latency</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>epsilon correction factor for degrees of freedom</td>
</tr>
<tr>
<td>$\phi_{onset}$</td>
<td>onset phase</td>
</tr>
<tr>
<td>$\phi_{delay}$</td>
<td>phase delay</td>
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ASSRs reflect sinusoidal activity from central auditory neurons in response to repetitive stimulation, which can be recorded using scalp electrodes. These responses may be used as indicators of hearing and may be useful in estimating thresholds, providing several advantages over conventional techniques. Further research is needed in the following areas: ASSR generators, place specificity, reduced recording time, and validation of multiple-ASSRs in estimating hearing thresholds. The chapters of this current thesis present individual studies that investigate these areas.

Chapter 1 introduces ASSRs with respect to their underlying physiology and clinical utility. Additionally, a discussion of methodologies used within the present thesis is given. Chapter 2 presents the first research paper of this thesis. It provides information regarding the level of the auditory system where ASSRs are generated. Chapter 3 presents the second paper that investigates the possible advantage of ASSRs using highly acoustically-specific stimuli to obtain more place specific responses. Chapter 4 features the third paper that extends the literature on threshold testing in normal-hearing adults. It also evaluates the advantage of using multiple-stimuli to reduce recording time. Material in Chapter 4 is previously published in: Herdman, A. T., & Stapells, D. R. (2001) Thresholds determined using the monotic and dichotic multiple auditory steady-state response technique in normal-hearing subjects. Scandinavian Audiology, 30: 41-49. For the aforementioned publication, Herdman and Stapells together designed the objectives and methods and wrote the manuscript. Herdman also recorded and analysed all the data. Chapter 5 presents the final paper, which examines the clinical utility of ASSRs in estimating thresholds of individuals with hearing losses. Furthermore, it investigates the place-specificity of ASSRs using hearing-impaired subjects. Chapter 6 discusses the dissertation's overall results and places them into context with future uses of ASSRs for testing hearing thresholds and for investigating the neurophysiological function of the human auditory nervous system.
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To my family and friends, thank you for putting up with my shortage time in your lives. I will forever be grateful for your constant encouragement and unconditional love.

To my wife, no amount of thank yous can ever be enough for your unselfish support and inspiring words. I am truly blessed to have someone like you during the late nights, early mornings, grumpy days, and happy days. You are my inspiration for being.
Dedication

To my loving wife, Dana E. Herdman.
Chapter 1: Introduction to Auditory Steady-State Responses
Auditory steady-state responses\(^1\) (ASSRs) are becoming prominent in the field of objective audiometry. This is due to potential advantages that the ASSR method has over conventional techniques. Chapter 1 begins by examining ASSRs with respect to their underlying physiology and response analysis. The latter part of Chapter 1 will look at the clinical application of ASSRs and identify areas in need of further investigation.

**Physiology of Steady-State Responses**

Steady-state responses in the visual system are well described by Regan (1966, pp. 380-390). A repetitive (flicker) presentation of light produces sinusoidal electrical potentials that can be recorded on the scalp. These sinusoidal potentials have the same frequency as the rate of flicker of the light. Similar sinusoids can be recorded from scalp electrodes when the auditory system is repetitively activated by acoustic stimuli, such as clicks (Galambos, Makeig, & Talmachoff, 1981; Geisler, 1960). As in the visual system, the recorded waveforms match the frequency of the repetition rate of the acoustic stimuli. Furthermore, amplitudes of the steady-state responses are dependent on the rate of stimulation (Galambos et al., 1981; Stapells et al., 1984). Supplemental work has shown that these ASSRs can be recorded up to rates of 450 Hz (Cohen, Rickards, & Clark, 1991), yet the largest response occurs at 40 stimuli per second in an awake adult. When stimulus rate is increased or decreased from 40 Hz, amplitudes of ASSRs

\(^1\)ASSRs are also commonly referred to as amplitude-modulated following responses or steady-state evoked potentials (SSEP). A common nomenclature is needed for ease of discussion and clarity when considering evoked potentials in other sensory modalities. For instance, the acronym SSEP – customarily used for somatosensory evoked potentials – has been used for steady-state evoked potentials. This will lead to confusing dialogues between scientists and clinicians, a consensus is, therefore, needed. The term auditory steady-state responses, with the acronym ASSR, has been chosen for this thesis.
This amplitude-rate function has clinical implications and will be discussed later.

This section will start with a description of a model that presents the underlying physiology of ASSRs. Discussions regarding cochlear and cortical processing of sinusoidally amplitude-modulate (AM) stimuli, as well as neural generators of ASSRs, will follow.

**ASSR Model**

John and Picton (2000) present a reasonable model of the auditory system to explain the underlying physiology of ASSRs. The following description is based on their model and will consider an ASSR to a 1000-Hz AM tone modulated at 80 Hz. Similar processing would occur for ASSRs to AM tones modulated near 10 and 40 Hz. In order to provide clarity and brevity, stimulus processing of the outer and middle ear will not be addressed.

To begin, sound pressure of a 1000-Hz AM tone (Figure 1.1) transferred to the inner ear via the outer and middle ear, sets up a travelling wave within the cochlea. The travelling wave causes maximal displacement of the basilar membrane region that has a characteristic frequency of 1000 Hz. Amplitude of the displacement envelope at the 1000-Hz region will follow the modulation envelope of the AM tone, assuming a non-compressive transfer function within the cochlea. Naturally, there is some compression of intensity transfer across the basilar membrane which would cause some attenuation of high-level inputs and amplification of low-level inputs (see Pickles, 1988, pp. 123). Note that there is a delay in the basilar membrane response, which can be attributed to travel time down the cochlea and filter build-up time (John & Picton, 2000). Motion of the basilar membrane causes deflections of the hair cell stereocilia towards or away from the kinocilium (rudimentary stereocilia) causing depolarizing and hyperpolarizing current
Figure 1.1. Modelling the physiological processes. This figure illustrates the processing of acoustic stimuli through the various steps in the model. The hair cell filter intervenes between the acoustic stimulus and the hair cell potential. Rectification then occurs to give the synaptic potential. The refractoriness of the nerve fibres determines the fibre discharge pattern. Note, “fibre discharge” represent the summation of extracellular field potentials of a population of nerve fibres. The scalp potentials are then determined by both the jitter and the field pattern of the unit discharges. (Reproduced from John & Picton, 2000)
across the hair cell membrane on a cycle-by-cycle basis (Pickles, 1988, pp.123). The degree of
deflection depends on the amplitude of the basilar membrane displacement. Thus, hair cell
potentials will also follow the modulation envelope (Figure 1.1). Compressive rectification
(favouring the depolarization phase) exists in inner hair cells for increasing stimulus intensities
(Dallos, 1996, pp. 24-34), but it is not shown in Figure 1.1 and will not be considered further for
this discussion. Depolarization of inner hair cells cause synaptic release of neurotransmitters
that bind to postsynaptic butons of the auditory nerve fibre. This in turn opens ion channels
producing generator potentials (i.e., “Synaptic Potentials” in Figure 1.1) that trigger action
potentials in the fibre’s active zone. Because depolarization only releases neurotransmitter, the
transduction of the input signal from inner hair cells to auditory nerve fibres is rectified (Figure
1.1). The time for release, dissociation, and binding of the neurotransmitter brings about further
delay of the input, seen as a latency shift in the response envelope. Due to the all-or-none
characteristic of an action potential, the amount of depolarization in a single nerve fibre cannot
code for the modulation envelope seen so far in a single inner hair cell. However, a population of
nerve fibres can represent the 80-Hz modulation in their rate of firing by increasing the number
of synchronized action potentials to be in phase with the stimulus input. Because action
potentials contribute to the extracellular field potential, more neurons firing at once (due to a
large displacement of the basilar membrane) will give a large extracellular potential. The fibre
discharge (Figure 1.1) shows the summation of extracellular fields produced by active individual
nerve fibres. It is apparent from looking at this discharge pattern (Figure 1.1), that the resulting
extracellular field potentials has a response envelope at the frequency of modulation (i.e., 80 Hz).
Higher order neurons (within the brainstem, thalamus, and cortex) will discharge in phase with
auditory nerve fibres. Thus, extracellular fields from these neurons will produce steady-state
responses at the stimulus modulation frequency, assuming serial processing in the auditory system. Scalp recorded field potentials of activity within the brainstem or cortex elicited by AM tones would, consequently, be phase locked to the modulation frequency of the stimulus. Although, this model depicts some of the processes involved in generating ASSRs, many aspects are only partially covered. For example, the acoustic input to the system will have a direct consequence on the output. More detailed discussions of such issues will follow.

**Acoustics**

ASSRs can be evoked by repetitive presentation of many types of acoustic stimuli, such as clicks or tones. For simplicity, the more commonly used stimulus, AM tones (Figure 1.2A), will be considered for the remainder of this discussion. For eliciting ASSRs, carrier frequencies typically range from 250 to 6000 Hz, whereas modulation frequencies range from 10 to 200 Hz, depending on the situation. An AM tone consists of a carrier frequency that is 100% amplitude modulated at a given modulation frequency (Figure 1.2A). Frequency analysis of an AM tone reveals a very specific acoustic spectrum. The amplitude spectra of an AM tone consists of three line spectra: one at the carrier frequency and two at frequencies equal to the carrier frequency plus/minus the modulation frequency. Comparing the frequency spectra for AM tones (Figure 1.2A) to brief tones (Figure 1.2B) used to evoke auditory brainstem responses (ABRs) or middle latency responses (MLRs), shows a greater acoustic specificity\(^2\) for AM tones. Because ASSRs are evoked by AM tones, a person might infer that ASSRs reflect more frequency-specific activation of the cochlea. However, this may not be the case because of processing in the cochlea.

\(^2\) width of the acoustic spectrum centred around the carrier frequency of the stimulus
Figure 1.2. (A) Fast Fourier Transform (FFT) of the time domain waveform (left) of a 500-Hz AM tone modulated at 80 Hz. (B) FFT of the time domain waveform of a 500-Hz brief tone presented at a stimulus rate of 40 per second.
Chapter 2 presents results of an experiment that investigates the spread of cochlear activation by AM tones as reflected in ASSRs.

**Cochlear Processing**

*Place specificity* is classified as the spread of cochlear activation by a stimulus. Place specificity for an AM tone depends on the stimulus intensity and the mechanical properties of the cochlea. For our consideration, a moderately intense (e.g., 60 dB SPL) AM tone may deflect a 1-octave-wide region of the basilar membrane. In turn, this excites a large portion of auditory nerve fibres with different characteristic frequencies. Dispersion of spectral energy along the basilar membrane may be measured using several different techniques.

One such technique is to take advantage of the excitation pattern of a pathological cochlea. For example, if an auditory evoked potential (AEP) method significantly underestimates elevated behavioural pure-tone thresholds, then it can be assumed that frequency regions other than those at or near the stimulus frequency are involved in producing an evoked response (Picton et al., 1979). Consider a person that has a steeply sloping (> 30 dB/octave) hearing loss between 2 and 4 kHz with a 4 kHz pure-tone threshold of 60 dB HL (Figure 1.3). If an ASSR to a 4-kHz AM tone significantly underestimates the elevated pure-tone threshold, then frequency regions with better thresholds (i.e., 2 kHz regions) are most likely responding to the stimulus. This would indicate poor place specificity on the part of the ASSR to a 4-kHz AM tone. The amount of underestimation can be compared across subjects with differing slopes of hearing losses to estimate the degree of place specificity. Assessing subjects with sensorineural hearing loss has seldom been used for the specific purpose of determining place specificity, possibly because of difficulty in knowing exactly which regions of the cochlea are being activated.
Figure 1.3. Hypothetical example of thresholds for ASSRs to multiple AM tones presented simultaneously (open triangles) and behavioural responses to pure-tones (closed circles). Note that at 4000 Hz, ASSRs would underestimate behavioural thresholds by 30 dB.
Regions with residual hearing or lower thresholds may be primarily contributing to the response. Nevertheless, Purdy and Abbas (in press) have recently evaluated the place specificity of tone-ABRs by using subjects with relatively steeply sloping hearing losses. Results revealed good correlation between the 4000-Hz tone-ABR and behavioural thresholds \( (r = .95) \) in subjects with sensorineural hearing loss. Chapter 5 evaluates the place specificity of ASSR using individuals with steep-sloping \( (\geq 30 \text{ dB/octave}) \) hearing losses.

Another effective means of determining place specificity is taking advantage of changes in AEP responses by altering the number of auditory nerve fibres responding to the stimulus. Masking noise can be used to restrict the number of responding auditory nerve fibres to tonal stimuli, thereby reducing response amplitudes (Delgutte, 1996). Methods that estimate place-specificity use masking stimuli, such as pure-tones, notched noise, or high-pass noise (HPN). Sweeping the pure-tone masking frequency, notched-noise centre frequency, or HPN cut-off frequency can reveal the amount of contribution of the non-masked cochlear regions. Amplitudes of responses from non-masked regions can be graphed across frequency to produce a masking profile. From such a profile, measures of bandwidth and centre frequency can be calculated to identify the place specificity of an AEP method (Oates & Stapells, 1997b).

The high-pass noise derived-band response (HPN/DR) method is used in a study presented in Chapter 3 and will, therefore, be further discussed in detail. The HPN/DR method pioneered by Teas, Eldridge, and Davis (1962), is a subtraction technique involving conditions of HPN masking and is used to determine which cochlear regions contribute to an AEP. This method has been used to determine the place specificity of compound action potentials, ABRs and MLRs (Don, Eggermont, & Brackman, 1979; Eggermont, Spoor, & Odenthal, 1976; (Elberling, 1974; Elberling, 1979; Oates & Stapells, 1997b). The HPN/DR technique requires
recordings of AEPs to stimuli with ipsilateral HPN at various high-pass cut-off frequencies (either in 1-octave or ½-octave steps). Derived-band responses (DRs) are then determined by subtracting a response in ipsilateral HPN masking at a lower cutoff frequency from a response in ipsilateral HPN masking that had a cut-off frequency 1-octave (or ½-octave) higher (Figure 1.4). For example, subtraction of an AEP recorded in HPN with a cutoff frequency of 4 kHz from an AEP response in HPN with a cutoff frequency of 8 kHz will result in a DR reflecting cochlear activation between 4 and 8 kHz. A fundamental assumption of the DR method is that unmasked low-frequency regions are not affected by the HPN. With notched noise masking, the low-pass noise can cause an upward spread of masking that extends into the notch. The frequency specificity of HPN/DR method has been validated by using narrow-band masking within the derived-band frequency response region (Parker & Thornton, 1978; Stapells & So, 1999) and by recording auditory nerve fibre responses in animals (Evans & Elberling, 1982). There is some controversy as to where the centre frequency of a derived band actually occurs. DR centre frequencies (frequency regions of greatest response) are considered to be closer to the lower HPN cutoff frequency, at least for ABRs (Stapells & So, 1999), although this depends on the slope characteristics of the HPN filter and whether 1-octave or ½-octave DRs are calculated. The true DR centre frequency may be different when using different parameters between studies.

Nevertheless, many researchers designate the DR centre frequency as the lower HPN cutoff frequency (Don & Eggermont, 1978; Don, Eggermont, & Brackmann, 1979; Nousak & Stapells, 1992; Oates & Stapells, 1997a). A further technical issue is the use of ½-octave-wide versus 1-octave-wide derived bands. Derived band subtraction increases the residual EEG noise by the square root of 2, therefore, DRs using ½-octave-wide derived bands result in low signal-to-noise
Figure 1.4. Diagram of the HPN/DR technique. A cochlear response (in black) to a 2-kHz tone is masked by HPN (left side in grey) at varying cutoff frequencies. The non-masked cochlear response is in solid black and an outline reveals the masked response. Subtraction of a response in a condition with a lower HPN cutoff frequency from a response in a condition with a higher HPN cutoff frequency will yield a derived-band response (shown to the right). The lower HPN cutoff frequency is designated as the centre frequency for the derived band.
levels because of moderate variability in responses. This results in variable DR amplitudes between subjects. Full-octave-wide derived bands, on the other hand, contain larger response areas and more stable response amplitudes. Thus, they are more often used for the analysis of place specificity. Results of an investigation using the HPN/DR procedure to determine the place specificity for ASSRs are presented in Chapter 2.

ASSRs may be evoked by more acoustically specific stimuli (i.e., AM tones) than the brief-tones used for ABR or MLR (see Figure 1.2A). Accordingly, it has been speculated that ASSRs to AM tones reflect narrower regions of cochlear activation (i.e., better place specificity) than ABRs or MLRs to brief tones (Lins et al., 1996). Whether or not this is true has yet to be determined. A review of the literature on place specificity for ABR, MLR, and ASSR is warranted.

_Cochlear place specificity of the ABR._ Abdala and Folsom (1995) used the notched noise method to evaluate the place specificity for ABRs to brief tones. By varying the centre frequency of the notch around the stimulus frequency, they found a high degree of place specificity for 1,- 4-, and 8-kHz brief tones. Wave V amplitudes for both adults and infants were largest for notches centred at the stimulus frequencies (1, 4, and 8 kHz) and substantial reduction occurred at surrounding notch frequencies. Wave V amplitudes in the notched-noise masking were substantially smaller (40-60% at maximum) than that for the unmasked condition, due to the restriction of contributing fibres and possibly upward spread of masking into the notch. The degree of tuning, measured as Q5% (i.e., bandwidth at 5% down from maximum amplitude normalized to notched-noise centre frequency), reveals narrow bandwidths across all frequencies and age groups. In more comprehensive studies, Oates and Stapells (1997a&b) reported
comparable place specificity for brief-tones in HPN and for DRs. Functions of amplitude versus HPN centre frequency for 80 dB SPL 500- and 2000-Hz tones reveal low amplitudes for wave V at the tone’s nominal frequency and significantly larger amplitudes at least 1-octave above (Figure 1.5A). The steep slopes of these “S-shaped” functions indicate that most higher frequency contributions to the ABR are within 1-octave of the stimulus frequency. Derived bands were calculated for these HPN data and indicate favourable place specificities because most of the contributing frequency regions are within 1-octave of the stimulus frequency (Figure 1.5B; Oates & Stapells, 1997a).

In the two studies by Oates and Stapells (1997a&b), stimulus gating functions (exact-Blackman versus linear) were investigated for their place specificity. Given that exact-Blackman gating shows a more frequency-specific acoustic spectrum, one would expect a more discrete cochlear activation than linear-gated tones. However, both HPN and DR data indicate no difference in amplitudes as a function of HPN/DR frequency between linear- or exact-Blackman-gated tones (Oates & Stapells, 1997a&b). This demonstrates that acoustic specificity does not always directly translate to place specificity of a response. Nevertheless, masking profiles for notched noise, HPN, and DR methods reveal that tone-ABRs are adequately specific (i.e. within a 1-octave-wide region) for cochlear activation around the stimulus frequency.

Cochlear place specificity of the MLR. In their extensive two-part study, Oates and Stapells (1997a&b) investigated the place specificity of the ABR and MLR to 80 dB SPL, 500-Hz and 2000-Hz probe tones (linear or Blackman gated) using HPN masking and DRs. They found no significant difference between linear and exact-Blackman gated tones for ABR or MLR (Figure 1.5A). HPN masking profiles for amplitudes of MLR waves Na-Pa to 500- and 2000-Hz
Figure 1.5. (A) Mean and standard deviation (SD) response amplitude profiles for ABR wave V-V' and MLR wave Na-Pa to 500- and 2000-Hz exact-Blackman- versus linear-gated tones recorded in the HP noise masking conditions. (B) Mean and standard deviation (SD) amplitude profiles for one-octave-wide derived responses (ABR wave V-V'; MLR wave Na-Pa) to 80 dB ppe SPL 500- and 2000-Hz exact-Blackman- versus linear-gated tones. (Reproduced from Oates & Stapells, 1997a&b).
tones exhibit steep-sloping “S-shaped” functions (Figure 1.5A). Responses had significantly decreased amplitudes when the HPN was at a half-octave above the stimulus frequency compared to higher HPN cut-off frequencies. This indicates that a significant amount of the response occurs no greater than a half-octave above the stimulus. Upward spread of excitation, therefore, can be concluded to be within this region for 80 dB SPL, 500- and 2000-Hz brief tones.

DRs were calculated for the HPN data in Oates and Stapells (1997b; Figure 1.5B). A good degree of place specificity is revealed with narrow (approximately 1-octave-wide) DR amplitude profiles. Maximum DR amplitudes were at the stimulus frequency for both tones, with the exception of the 2000-Hz exact-Blackman-gated tone being at 1410-Hz. However, the calculated centre frequency of the DR amplitude profiles for the 500- and 2000-Hz tones are within a ¼-octave of the stimulus frequency (Oates, 1996). Cochlear contributions are within ½- to 1-octave around the centre frequency, indicated by the low DR amplitudes outside this zone.

*Cochlear place specificity of the ASSR.* To date, there are limited data regarding the place specificity for ASSRs. Stapells, Picton, Perez-Abalo, Read, and Smith (1985) reported that addition of ipsilateral HPN (1300-Hz cut-off) reduced the amplitudes of the 40-Hz ASSR to 500-Hz brief tones of 60 or 80 dB SPL. Because there was a loss of responsiveness from the cochlea when the HPN masker was added, it suggests that regions with characteristic frequencies greater than 1300 Hz contribute to the overall 40-Hz response to 500-Hz brief tones. There are no extensive studies investigating the excitation pattern along the entire cochlea for the 40-Hz ASSR. Also, there is limited research published with respect to the spread of excitation for ASSRs evoked by AM tones with modulation frequencies between 77-110 Hz (i.e., 80-Hz
ASSRs). Results from a two-tone masking study by John, Lins, Boucher, and Picton (1998) suggest that a 60 dB SPL, 1000-Hz AM tone modulated at 80 Hz mostly activates the basilar membrane within a ½-octave on either side of the nominal stimulus frequency. There was significant decrease in 80-Hz ASSR amplitude when the masker was at or within a ½-octave of the stimulus frequency. These results indicate good place specificity, although they only inform us about presentation of a single 1000-Hz AM tone at 60 dB SPL as opposed to other stimulus frequencies and the use of multiple stimuli. There is need, then, to further investigate the place specificity for ASSRs evoked by AM tones (see Chapter 3 and 5).

**ASSR Phase/Latency**

Amplitude is not the only information obtained and analysed from ASSRs. Phase of an ASSR is also an important measure. Phase, however, is difficult to interpret because of implicit assumptions that must be made to transform phase into latency (John & Picton, 2000; Regan, 1966). This may be why phase is left out of the results in many papers. Even though there is difficulty interpreting phase, assumptions can be made which allow for phase to be transformed into latency.

The measured ASSR phase is termed “onset phase” (\( \phi_{\text{onset}} \)) and can be converted to “phase delay” (\( \phi_{\text{delay}} \)) by the following (John & Picton, 2000):

\[
\phi_{\text{delay}} = 360^\circ - \phi_{\text{onset}}
\]  

(Equation 1)

This conversion is typically performed because phase delay is more interpretable. It gets larger as the peak of the ASSR gets further away from the peak of the modulation envelope. Figure 1.6 shows that phase delay is the phase of the AM tone’s modulation envelope at which the ASSR peaks.
Circular Ambiguities

Steady-State Ambiguities

Delay may include an unknown number of preceding cycles

Responses at different stimulus rates help determine this number

Figure 1.6. Ambiguities in the measurement of phase. The upper half of the figure shows the ambiguities that occur because phase is a circular rather than linear measurement, if the phase increases as some other parameter is varied, it may exceed 360° and revert to 0°, causing a sudden fall in the regularly increasing measurements. This can be handled by ‘unwrapping’ the measurements by adding 360° (upgoing arrow in the upper right section of the figure). The bottom half of the figure illustrates the ambiguities that occur because the response is recorded in steady state. The cosine onset phase of the response recorded in the second line was measured as 150°. Phase delay is measured as the phase difference from the stimulus waveform (onset at 0° cosine) to the same part of the response waveform. This is equivalent to 360° minus the measured phase or 210°. Translated to latency, this is 210/(360 x 100) or 5.8 ms. Unfortunately, there is no way of knowing whether the 0° point of the ongoing stimulus is evoking the point on the response waveform where the phase is 240° or a point occurring one or two cycles later (at latencies 15.8 or 25.8 ms for 570° and 930° phase delays). If we record the response at another stimulus rate (and if we can assume that the response has the same latency for the two rates), then we can determine which of the possibilities is most likely. At 85 Hz the phase delay was 130°. This gives a latencies of 4.2, 16.0 and 27.8 ms. The measurements of 15.8 and 16.0 ms are the most similar between the two stimulus rates. An “apparent latency” can also be calculated from the slope of the phase with stimulus frequency divided by 360. For these measurements, this latency is 80/(15 x 360) or 14.8 ms. (Reproduced from John & Picton, 2000)
Phase delay may be converted into latency ($L$) by the following equation (John & Picton, 2000):

$$L = \frac{\phi_{\text{delay}}}{(360^\circ \times f_m)}$$

(Equation 2)

This conversion does not account for two ambiguities in the phase measurement which makes this calculation inaccurate for determining the true latency of an ASSR. First, phase is circular in nature whereas latency is linear. This means that a change of $10^\circ$ in measured phase from $359^\circ$ to $9^\circ$ should actually be a phase of $369^\circ$ not $9^\circ$. To resolve such an ambiguity, John and Picton (2000) suggest an “unwrapping” of the phase measurement by adding one cycle where the function of phase delay by modulation frequency (Figure 1.6, upper right panel) shows a jump across the $0^\circ$ measured phase. This assumes that a full cycle of the stimulus occurs prior to the peak of the ASSR. The second ambiguity is not knowing how many stimulus cycles occur prior to the measured response, regardless of unwrapping. To overcome such ambiguities, Regan (1966) proposed the method of calculating an “apparent latency” by using the slope of the phase delay by modulation frequency function, given by:

$$\tau' = \frac{1}{360^\circ}(\delta\phi_{\text{delay}}/\delta f_m)$$

(Equation 3)

where, $\tau'$ is apparent latency, $\delta\phi_{\text{delay}}$ is equal to the difference in phase delay at two different modulation frequencies, and $\delta f_m$ is the difference between the two modulation frequencies. Calculation for apparent latency must be done between modulation frequencies where phase changes linearly. If it is not linear, then phase may be changing due to different phase generators (i.e., different neural populations) which will not provide an accurate measure of latency.

Another approach to determining latency was recently proposed by John and Picton (2000). Instead of using the slope of the function, they suggested to add cycles to the phase delay and compare these values across modulation frequencies for each carrier frequency. Whatever the
number of cycles added to produce similar latencies at each modulation frequency was then assumed to be the number of cycles occurring prior to the measured ASSR. John and Picton (2000) thus proposed the following equation to accurately estimate latency by accounting for the two major ambiguities in ASSR phase measurements.

\[
L = \frac{\phi_{\text{delay}} + n \times 360^\circ + m \times 360^\circ}{360^\circ \times f_m}
\]  

(Equation 4)

where \(L\) is the latency, \(\phi_{\text{delay}}\) is the phase delay, \(n\) is an integer number of cycles needed to unwrap the phase, \(m\) is an integer number of stimulus cycles that occur prior to the measured ASSR, and \(f_m\) is the modulation frequency. Latencies calculated by John and Picton's (2000) method were found to be close to results calculated using the "apparent latency" method proposed by Regan (1966).

Latency delays are considered to have several main contributing factors (Eggermont, 1979; John & Picton, 2000). They are: the acoustic delay between the transducer and the oval window, transport time of the travelling wave down the cochlea, filter build-up time in cochlea, synaptic delay in transmission of electrical signals across synapses, conduction time for action potentials to travel along axons, and delays introduced by changes in neurophysiological responses to continuous AM stimuli. For a more in-depth explanation of these factors, see John and Picton (2000).

There are limited results for latencies of ASSR to AM tones modulated at low rates (i.e., < 25 Hz). Stapells, Makeig, and Galambos (1987) reported an apparent latency of 74.7 ms for a 500-Hz tone-burst presented between 19 to 29 per second (Table 1.1). Latencies for the 40-Hz
# Table 1.1

Reports of ASSR Latencies (ms) Estimated from Phase Delays for Ranges of Modulation Frequency (fm)

<table>
<thead>
<tr>
<th>Study and fm range</th>
<th>500 Hz</th>
<th>1000 Hz</th>
<th>2000 Hz</th>
<th>4000 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohen et al., 1991</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-60 Hz</td>
<td>33 ± 1.6</td>
<td>24.8 ± 4</td>
<td>28.9 ± 3.1</td>
<td>28.6 ± 2.1</td>
</tr>
<tr>
<td>90-185 Hz</td>
<td>12.7 ± 7.2</td>
<td>13 ± 3.9</td>
<td>9.4 ± 1.2</td>
<td>8.9 ± 0.8</td>
</tr>
<tr>
<td><strong>John &amp; Picton, 2000a§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80-100 Hz</td>
<td>21.5 ± 1.6</td>
<td>18.9 ± 0.8</td>
<td>16.7 ± 0.5</td>
<td>16.1 ± 0.7</td>
</tr>
<tr>
<td>150-190 Hz</td>
<td>12.2 ± 1.7</td>
<td>10.3 ± 1.1</td>
<td>7.8 ± 0.7</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td><strong>Kuwada et al., 1986</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>25-55 Hz</td>
<td></td>
<td>31.9 ± 2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-350 Hz</td>
<td></td>
<td>7.5 ± 0.8</td>
<td></td>
<td></td>
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<tr>
<td><strong>Linden et al., 1985</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>30-46 Hz</td>
<td>36 ± 12</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Picton et al., 1987a</strong>*</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>27-43 Hz</td>
<td></td>
<td></td>
<td></td>
<td>37.2</td>
</tr>
<tr>
<td><strong>Stapells et al., 1984</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-60 Hz</td>
<td>34 ± 10.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stapells et al., 1987</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19-29 Hz</td>
<td></td>
<td>74.4 ± 15.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29-54 Hz</td>
<td></td>
<td>41.1 ± 5.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Latencies calculated using the "apparent latency" method by Regan (1966)
§ Latencies calculated using the method proposed by John & Picton (2000)

*Note.* Mean ± one standard deviation.
ASSR have been estimated to range from 24.8 to 41.1 ms, depending on carrier frequency (Cohen et al., 1991; Kuwada, Batra, & Maher, 1986; Linden, Campbell, Hamel, & Picton, 1985; Picton, Skinner, Champagne, Kellett, & Maiste, 1987a; Stapells et al., 1984; Stapells et al., 1987). John and Picton (2000) and Cohen et al. (1991) reported similar latencies for ASSR to AM tones modulated between 150-190 Hz. Note, that several of studies presented in Table 1.1 used different stimulus levels or did not report dB SPL levels for dB SL. Interpretation between studies, therefore, should be made with caution. Additionally, John and Picton (2000) used their method of calculating ASSR latency as opposed to the “apparent latency” method used by the other studies.

The difference in ASSR latency between carrier frequencies of 500 and 4000 Hz is approximately 4.7 ms (averaged across studies in Table 1.1). This suggests that there is a 4.7 ms cochlear transport delay from the 4000-Hz cochlear region to the 500-Hz region, provided all other factors that contribute to latency delay are equal across carrier frequencies. This ASSR latency delay is slightly longer than latency differences of 4.4 ms and 3.6 ms reported by Stapells et al. (1985) and Van Zanten and Brocaar (1974), respectively. Van Zanten and Brocaar determined these values for click-ABR wave V in notched noise centred at 500 and 4000 Hz, whereas Stapells and colleagues used the better technique of the HPN/DR to estimate the latency differences. Differences, if any, between ASSR and ABR delays could be a result of the notched noise technique, such that the notched noise may allow the click to activate broader regions of the cochlea than those activated by AM tones. For example, AM tones of 500 and 4000 Hz should activate cochlear regions specific to their carrier frequencies, thus the disparity between regions of activation should be 3 octaves (i.e., 500 to 4000 Hz). Compared to clicks in 1-octave-wide notched noise, the regions of activation may range from 2 octaves (707 to 2830 Hz) to 4
octaves (354 to 5656 Hz), thus providing a shorter distance between stimulated regions. This explanation depends on the pattern of cochlear activation of AM tones and clicks in notched noise. Moreover, differences in latency delays are small between ASSR and ABR measures and may not be significant.

Because most generators of transient AEPs are reasonably well known, comparing ASSR latencies with those of transient evoked potentials may help to predict possible origins of ASSRs (Rickards & Clark, 1984). For example, apparent latencies for the 90-125 Hz modulation rates range from 7.5 to 12.7 ms and are in close approximation to wave V latencies of the ABR. This suggests a similar level of ASSR generation, in the brainstem, as the ABR wave V. Generators for modulation frequencies of 80-100 Hz may be a little higher in the auditory system than the ABR wave V because latencies range from 16.1 to 18.9 ms. Latencies for the 30-60 Hz modulation rates range from 24.8 to 41.1 ms, which are similar to Pa/Nb latencies of the transient middle latency response. For lower modulation rates, Stapells et al. (1987) reported an apparent latency of 74.4 ms. This is similar to an ASSR apparent latency of 80 ms reported by Rickards and Clark (1984), which they compared to the latency for transient N1 cortical potential (approximately 83 ms). These comparisons are only an approximation because neural networks and pathways may be different between transient and steady-state responses. For one conceivable example, a greater delay could exist if there are a greater number of synapses within the networks at lower brainstem centres that generate ASSRs than that for ABRs. Higher than actual levels would, consequently be inappropriately assumed to be generating ASSRs (John & Picton, 2000). Nevertheless, these latencies can be used for comparison after the generators of ASSRs have been established by other methods, such as dipole source modelling (Chapter 2). Latencies from
the previously mentioned studies will be considered in Chapter 2, which reports on latency estimates for modelled ASSR generators.

_Dipole Field Generation_

Before describing the current literature on ASSR generators, a more in-depth review of the neurophysiological processes underlying AEPs will be presented together with modelling techniques used to locate source activity.

_Neurophysiology of auditory evoked potentials_. AEPs, such as ASSRs, reflect changes in electrical charge distribution across cell membranes. Galambos (1989), suggested that glial cells may play a role in evoked potential generation; nevertheless this hypothesis is highly controversial. The time constant for ionic (typically potassium) conduction into glial cells precludes them from substantially participating in the generation of short-latency AEPs (Buchwald, 1983). Neuronal transmembrane potentials are considered the main origins of evoked potentials (Picton, 1990).

To start, let us consider how neurons may contribute to extracellular potentials recorded at the scalp. Excitatory post-synaptic potentials result from movement of positive ions into pyramidal dendrites due to opening of ligand-gated channels (Kandel & Schwartz, 1991). This causes the surrounding extracellular space to become deficient in positive charge (Figure 1.7A). Axonal resistance is lower than transmembrane resistance, hence current flow is primarily restricted along the dendrite, consequently depolarizing neighbouring membrane sections. Passive membrane channels (primarily potassium channels) allow current to source out from the neuron into the extracellular space, completing the circuit as it travels back to the site of the
Figure 1.7. Illustration of current sinks in the apical dendrite with a current source from soma (A) and current sources from the apical dendrite with a current sink in the soma (B). The arrows are current flow (i) and the magnitude of current is arbitrarily designated as the thickness of the lines. For simplicity, basal and distal apical dendrites are not illustrated.
initial current sink in the dendrites. This local field distribution can be modelled as a dipole, with a negative pole at the current sink and a positive pole at the current source. Inhibitory post-synaptic potentials result from an active current source in the dendrites due to opening of potassium or chloride channels. A dipole with opposite polarity as that described for an excitatory post-synaptic potential will result from an inhibitory post-synaptic potential (Figure 1.7B).

Thalamocortical afferent fibres primarily synapse on the dendrites in cortical layer 4 and 6 (Martin, 1991). Excitatory input from such afferents create a current sink in the somatic layer and a source in the dendritic layer (Figure 1.8). The orientation of this dipole will produce a positive scalp potential directly above the active cortical neurons (Martin, 1991). For cortical activation by commissural afferents, the polarity of the dipole inverts because these fibres synapse in layer 2, 3 (Figure 1.8).

Action potential initiation in cortical neurons typically occurs in the soma or axon hillock, except under conditions of large electrical orthodromic stimulation (Herdman, 1998; Stuart, Spruston, Sakmann, & Hausser, 1997; Turner, Meyers, & Barker, 1989; Turner, Meyers, Richardson, & Barker, 1991). Action potential generation at the level of the soma produces a current sink in layer 5 and current sources in layers 2-4. This distribution of the current sink and source represents a dipole of the same orientation as excitatory synaptic activation from thalamocortical afferents. Action potentials in cortical neurons, however, are suggested to negligibly contribute to evoked cortical field potentials measured on the scalp (Humphrey, 1968). Most scalp-recorded cortical activity, therefore, reflects post-synaptic potentials and not action potentials. However, the short-latency evoked potentials, such as the ABR wave I and II, are due
Figure 1.8. Scalp recordings depend on the depth of synaptic activity in the cortex.

Left: A potential recorded from a scalp electrode following activation of thalamic inputs. The terminal of thalamocortical neurons make excitatory connections on cortical neurons predominantly in layer 4. Thus, the site of inward current flow (sink) is in layer 4 and the sit of inward current flow (source) is in the superficial cortical layers. Since the recording electrode on the scalp is closer to the site of outward current flow, it records a positive potential.

Right: A potential recorded from excitatory inputs from callosal neurons in the contralateral cortex. The axons of callosal neurons terminate in the superficial cortical layers. A negative potential (upward deflection) is recorded because the electrode is closer to the site of inward current flow than that of the outward flow. (Reproduced from Martin, 1991; Fig. 50-10)

Magnitudes of field potentials are inversely proportional to the distance from a dipole (Picton, Lins, & Scherg, 1995; Vaughan & Arezzo, 1988). Field potentials are, therefore, greatest locally and less at distant locations, such as on the scalp. Deep neural activities are reflected on the scalp by small potentials with a broad distribution of isopotential lines. Another key factor that affects the magnitude of scalp recorded potentials is the conductance of the cortical tissue, meninges, bone, and scalp through which the current must flow. Furthermore, the configuration of the neural dipoles plays a role in distribution and magnitude of an evoked potential. Activation of neurons organised in laminar arrangements (e.g., cortical layers) will produce an “open field” that can travel beyond the extent of the active tissue (Picton et al., 1995; Vaughan & Arezzo, 1988). Neurons oriented in a cluster, with dendrites projecting radially from the centre, produce a “closed field” as the dipoles from individual neurons will cancel current flow from going beyond the active tissue. A combination of both open and closed fields typically represent most cell arrangements in the central nervous system (Vaughan & Arezzo, 1988).

Synchrony of discharge probably plays the most important role in AEP generation (Vaughan & Arezzo, 1988). An increase in synchronously firing neurons with the same spatial orientation (i.e., laminar) will produce a larger dipole. Greater fields are consequently recorded at distant locations. This is a primary reason why most AEPs require fast onset stimuli. Keeping in mind these principal factors that affect the scalp recorded AEPs, most of the generators will be from synchronously active neurons in “open field” configurations.
Dipole source modelling. Location of dipoles may be inferred from the distribution of field potentials over the scalp (Picton et al., 1995; Vaughan & Arezzo, 1988). Such interpretations are limited due to the fact that any given scalp topography can be generated by more than one arrangement or number of underlying sources. For instance, widespread cortical activity and discrete deeply based activity can result in similar scalp distributions. Also, the location of maximal amplitude of the field distribution does not necessarily indicate that the source is in the immediate vicinity. Two dipole sources similarly oriented in the temporal lobes can produce fields that summate producing maximum amplitude at the vertex (Vaughan & Ritter, 1970).

To estimate dipole sources, current source density maps may be calculated from scalp distribution of field potentials (Picton et al., 1995). These maps will reveal current sinking and sourcing from scalp locations. However, this technique is an extension of interpreting field topography (discussed in the previous paragraph) and the same issues apply to their interpretation.

Sources may be better localized within the head by dipole source modelling. Picton and colleagues (1995) present a detailed discussion regarding the principles and methods regarding dipole source modelling. Two major approaches to modelling dipoles are “instantaneous” (Wood, 1982) and “spatio-temporal” (Scherg, 1984). The instantaneous method aims to determine single or multiple dipole sources for a distribution of scalp potentials at one point in time (Wood, 1982). This procedure calculates a unique and independent solution for the dipole location at each time point. Thus, dipole location moves in space over time. The number of sources that can be determined using instantaneous dipole source modelling is severely limited by the six required parameters (three locations, two orientations, and dipole strength) and by
considering only one point in time (see Picton, Lins et al. 1995). The number of electrodes divided by 6 (corresponding to the number of parameters), determines the maximum number of sources that can be modelled. Accordingly, a 32-channel recording can only identify a maximum of five dipole sources (see Picton et al., 1995). Also, instantaneous dipole source modelling is limited because it does not account for temporal overlap of generators; each time point has a unique solution. Scherg and von Cramon overcame these limitations, to some degree, by restricting dipole activity to stationary sources (Scherg, 1984; Scherg & von Cramon, 1985). This method, referred to as spatio-temporal dipole source modelling, constrains dipole activity to a stationary source(s) that can vary in magnitude over time. Although dipole source activity can be modelled as monophasic waveforms, Scherg and von Cramon have demonstrated that biphasic waveforms yield better source localization (Scherg & von Cramon, 1985). The maximum number of sources that can be modelled is limited by the number of electrode locations and the degrees of freedom from the waveform (Picton et al., 1995). Nevertheless, this allows for a greater maximum number of sources that can be modelled compared to instantaneous dipole source modelling. Principal component analysis of the scalp waveforms can provide additional information by predicting the lower limit of the number of dipole sources that account for the recorded scalp waveforms (Picton et al., 1995).

Principal component analysis only considers the temporal aspects of the source activity. Thus, multiple generators that have the same temporal waveform, but are spatially separated, are considered as a single source. Spatio-temporal dipole source modelling can use the information from principal component analysis to determine the minimum number of spatially distributed sources needed to explain the surface recorded waveforms. Spatio-temporal dipole source modelling is based on the following assumptions; (1) sources are enclosed in a small volume of
active neural tissue compared to the large volume of the skull, (2) scalp potentials reflect the
linear summation of fields from the neural generators, (3) dipole sources are stationary with
respect to their location and orientation, and (4) the magnitude of a dipole over time reflects the
compound discharge of the neural generators (Scherg & Von Cramon, 1985). These assumptions
need to be considered when modelling dipole source activity for AEPs.

Inherent to both dipole source modelling techniques are the “forward’ and “inverse”
solutions (Picton et al., 1995; Scherg & Von Cramon, 1985). The forward solution predicts the
distribution of potentials on the scalp from known or proposed locations, orientations and
temporal waveforms of the underlying neural generators. Because all the parameters are known
an accurate derivation of the scalp potentials can be made for a given head model. Conversely,
the inverse solution attempts to predict the dipole parameters (location, orientation, and
waveform) of the neural generators from a distribution of scalp recorded potentials (Scherg &
Von Cramon, 1985). The inverse solution is not as simple as the forward solution because an
infinite number of combinations of dipole parameters can produce equivalent distributions of
field potentials on the scalp. Balish and Muratore (1990) presented an intelligible analogy that
contrasts the forward and inverse solutions:

Consider the operation of translating coins into monetary value. If I note that I have
four quarters in my pocket, one can say that I have $1.00 [i.e., the forward solution].
But if I say that I have $1.00 worth of coins in my pocket, one can only guess whether
the coins are four quarters, 10 dimes, etc. For this operation, the inverse [solution] is
not unique.

Thus, knowing the exact scalp distribution, conductivities of the brain, skull and scalp, and shape
of the skull will not allow for an exact identification of the location and orientation of the dipole
source(s). For predicting dipole sources within the brain, the inverse solution is commonly used. In order to reduce the number of possible sources, restrictions must be made to the number of single or multiple dipoles and/or to the possible locations within a volume of neural tissue that are theoretically plausible, as shown by other methods such as intercellular recordings (Nunez, 1990). Constraining such parameters reduces the extent of iterative modelling that is necessary to fit the model-predicted scalp waveforms to the real scalp-recorded waveforms. A least-squares fitting procedure can be used to minimize the variance between the predicted and recorded distributions (for equation, see Scherg, 1984). Moreover, these restrictions introduced by the human modeller introduces inherent assumptions into the source model that may lead to ambiguous results.

Dipole source modelling typically uses a 3-sphere head model consisting of inner, middle and outer spheres that depict the neural tissue, skull, and scalp, respectively (Nunez, 1990). Each modelled sphere represents a transition between media that have different conductivities. The 3-sphere head model allows for good approximation of the scalp potentials; however, there are some limitations (Nunez, 1990). First, the human skull has a non-spherical geometry that will produce slightly different scalp potentials than those modelled on a sphere. Second, openings in the skull, such as foramen, provide a lower resistance conduit for current flow compared to the high resistivity across the skull. Third, skull thickness varies over the extent of the head. Fourth, resistivity estimates for the model may be inaccurate. These errors in the 3-sphere head model may produce inaccurate predictions of scalp potential differences, which must be considered when interpreting dipole source models.

In summary, dipoles are iteratively modelled within a 3-sphere head model to produce field potential distributions projected onto the scalp that minimizes the variance between these
modelled scalp potentials and the actual scalp-recorded potentials. The dipoles can then be translated onto magnetic resonance imaging tomograms for identifying anatomical locations.

Generators of ASSR

Overlap Theory versus Intrinsic Rate Theory. Galambos et al. (1981) hypothesized that ASSRs to auditory stimuli presented at a rate of 40-Hz result from sequential overlap of the transient MLRs – classified as the “Overlap Theory” (Figure 1.9). Another hypothesis arose to explain the nature of the 40-Hz response – termed the “Intrinsic Rate Theory”. It proposes that neural units have an intrinsic rhythm of firing that best resonates in phase with a stimulus presented at 40 Hz (Azzena et al., 1995; Basar, Rosen, Basar-Eroglu, & Greitschus, 1987; Santarelli et al., 1995). Nonetheless, the former theory has gained greater acceptance from supporting evidence showing a close correspondence of superimposed transient MLRs and 40-Hz ASSR (Galambos et al., 1981; Hari, Hamalainen, & Joutsiniemi, 1989a; Plourde, Stapells, & Picton, 1991; Stapells, Galambos, Costello, & Makeig, 1988). Such direct inference of equivalent MLR and ASSR generators may be amiss because neural processing may be altered by the repetitive nature of ASSR stimuli compared to transient stimuli.

To date, the most convincing research for 40-Hz ASSR generators comes from dipole source analysis of magnetoencephalography (MEG). Investigators have predicted dipole sources to lie within a region of the superior temporal gyrus (Gutschalk et al., 1999; Hari et al., 1989a; Mäkelä & Hari, 1987; Pantev et al., 1993; Pantev, Roberts, Elbert, Rob, & Wienbruch, 1996). Even though these researchers agree upon the general locale of the magnetic equivalent of ASSRs, termed auditory stead-state fields (ASSFs), evidence has been presented that both refutes and supports the premise that ASSFs result from superimposition of transient middle-latency
Figure 1.9. (A) Block diagram of equipment for extracting auditory ERPs. Electrodes pasted to the subject’s scalp (left) conduct brainwaves to amplifier and computer. A stimulator simultaneously energizes the earphone and initiates the computer averaging process. After the subject receives several hundred stimuli the computer memory contains only those brain potentials time locked to the stimuli, the others having algebraically summed toward zero. (B) Upper, time-locked brain potentials evoked during the first 100 msec after 500-Hz stimuli (arrow; 10 per sec) consist of the brainstem wave V (latency about 6 msec) and the MLR, a sequence of negative (N) and positive (P) waves subscripted a, b, c, and d (subject S.M.). Lower, diagram to show how the computer could sum the several MLR waves shown above into a single wave if the stimuli were presented at a rate of 40 per sec. (C) Recordings from a subject (R.G.) Receiving 500-Hz tone bursts at different rates (including the 40 per sec rate of B) to illustrate actual synthesis of the single wave at 40 Hz from the multiple waves at lower stimulus frequencies. dB, decibel; dB SL, decibels above threshold; \( \Sigma \) indicates the number of responses averaged. (Reproduced from Galambos et al., 1981; Fig. 1)
fields (MLFs). Pantev et al. (1993) suggested that the close proximity of the sources from MLFs and ASSFs provides evidence for equivalent generators. This supports the theory of overlapping transient MLFs. Nevertheless, studies investigating the tonotopic organization of ASSFs revealed that the sources within the superior temporal gyrus shifted medially (an increase in depth from the scalp) with a logarithmic increase in stimulus frequency (Pantev et al., 1996; Romani & Williamson, 1982). This medially directed tonotopy is opposite to what was found for wave Pa of the transient MLF (Pantev et al., 1995). Logically, they asserted that generators for the transient MLFs are unlikely to be candidates for the 40-Hz ASSFs. Further investigation by Gutschalk and co-workers provided contrary evidence by demonstrating a high degree of correspondence for ASSF and MLF dipole-sources (Gutschalk et al., 1999). They suggested that analysing MLFs and ASSFs using two dipoles instead of the single dipole source, used by Pantev and colleagues, might provide for more homologous generators. While Santerelli et al. (1995) were in agreement with the overlap theory, they also showed evidence for additional 40-Hz source activity. They proposed that field potentials from resonating neurons added to potentials from the overlapping of transient MLRs. Their concept of mutually non-exclusive theories has yet to catch on. Because 40-Hz activity is also prevalent in other sensory modalities that would not produce constructive overlapping of transients, it seems reasonable that 40-Hz ASSRs are produced by both resonating neural generators and overlapping transient MLR generators (Bouyer, Montaron, & Rougeul, 1981; Bressler & Freeman, 1980; Franzen & Offenloch, 1969; Namerow, Sclabassi, & Enss, 1974; Regan, 1966). More evidence to support the concept that ASSR may represent neurons resonating at their best modulation frequency comes from animal studies (Frisina, Smith, & Chamberlin, 1990a; Langer, 1992; Langer & Schreiner, 1989; Palombi, Backoff, & Caspray, 2001). Langer (1992) described periodotopic maps (neural organization of best modulation
frequency) that were orthogonally oriented to tonotopic maps (neural organization of best carrier frequency) in the central nucleus of the cat midbrain. This shows that the auditory neurons are tuned to different modulation frequencies and may not respond at the specific modulation rate of the stimulus, unless it is at or near the neuron’s best modulation frequency.

The “overlap” and “intrinsic rate” theories also pertain to ASSRs evoked by stimuli modulated between 70 to 110 Hz. Considering ASSR latency as described above, one can surmise that the 70- to 110-Hz ASSR may be a result of overlapping ABR wave Vs. However, they may also reflect responses from neurons resonating at their best modulation rate of 70 to 110 Hz. There are no data, to date, to support either such a claim and further research is needed.

**Location of ASSR generators.** Evidence from intracranial recordings in animals (Franowicz & Barth, 1995) has been supportive of 40-Hz ASSR cortical generation (as discussed previously), with the possible additions of subcortical origins (Hori, Yasuhara, Naito, & Yasuhara, 1993; Karmos, Mäkelä, Ulbert, & Winkler, 1993). Franowicz and Barth (1995) showed that ASSR isopotential maps from subdural recordings in rats were centred over primary auditory cortices and were spatially different from MLRs. Conversely, Karmos and colleagues (1993), demonstrated a lack of polarity inversion through the cat auditory cortex for 40-Hz ASSRs, which suggests no dipole sources in the cortex. They surmised that the 40-Hz ASSR must be generated by subcortical neurons. Hori et al. (1995) identified the possible location of a subcortical generator by comparing the scalp 40-Hz ASSR to intercerebral recordings ranging in depth from the trapezoid body to the medial geniculate nucleus. They disclosed the largest amplitude enhancement at a stimulus rate of 50 Hz, consistent with the scalp recorded amplitude/rate functions, for neurons within the inferior colliculus but not within the trapezoid
body, lateral lemniscus, or medial geniculate nucleus. ASSRs in the inferior colliculus also
corresponded in latency to those recorded at the scalp. These findings suggest that the inferior
colliculus is an important contributor to the scalp-recorded 40-Hz ASSR. The inferior colliculus
may, therefore, represent the driving force behind the 40-Hz ASSRs recorded at the scalp.

A study by Harada, Aoyagi, Suzuki, Kiren, and Koike (1994), investigating the
detectability of ASSRs in patients with brainstem and cerebral lesions, supports the notion of
subcortical 40-Hz ASSR generators. Lesions involving regions within the midbrain and
thalamus caused significant abnormalities or absence of the 40-Hz ASSRs. In a supplementary
report, equivalent results were disclosed for lesions to the inferior colliculus in cats (Kiren,
Aoyagi, Furuse, & Koike, 1994). Correlation between lesions and 40-Hz ASSRs may reinforce
subcortical origins, except that the disruption of nervous tissue at lower levels may cause
alteration in higher centres. These findings are, therefore, only suggestive of brainstem or
thalamic generators for the 40-Hz response.

There are limited data regarding generators for the 80-Hz ASSR. Inferences from
intercellular recordings within the cochlear nucleus and inferior colliculus stimulated by AM
tones have predominantly suggested subcortical origins (Batra, Kuwada, & Stanford, 1989;
Creutzfeldt, Hellweg, & Schreiner, 1980; Frisina et al., 1990a; Rees & Møller, 1983). Neurons
within the cochlear nucleus respond best to modulation rates above 80 Hz (Frisina et al., 1990a;
Møller, 1976), whereas those in the inferior colliculus respond best to rates between 20 to 40 Hz
(Batra et al., 1989). This implies that possible generation of the 40- and 80-Hz ASSRs arise from
the inferior colliculus and cochlear nucleus, respectively. A study by Kiren and associates (1994)
ruled out the cortex as a possible generator of the 80-Hz ASSR, by aspirating bilateral auditory
cortices in cats and showing no change in 80-Hz ASSR phase. Within this same study, they
demonstrated significant phase changes in ASSRs for both ipsilateral and contralateral lesions to
the inferior colliculus. The inferior colliculus may, thus, play an important role in the generation
of 40-Hz and 80-Hz ASSRs.

In summary, multiple generators involving the auditory cortex and brainstem may be
responsible for 40-Hz ASSRs. Although there is limited evidence for the origins of 80-Hz
ASSRs, the most likely generators seem to be within the brainstem.

**Physiology underlying ASSR Threshold**

The lowest intensity just sufficient to resolve an ASSR (after reasonable a reasonable
amount of averaging) is considered to be the physiological threshold for that stimulus.
Physiological thresholds for ASSRs are higher, on average, than those obtained behaviourally to
the same stimulus (Aoyagi et al., 1994b; Lins et al., 1996; Perez-Abalo et al., 2001; Picton et al.,
1998). Behaviourally, subjects do not require as much synchrony of neural discharges to detect a
response (Kraus et al., 2000; Starr, Picton, Sininger, Hood, & Berlin, 1996), whereas,
physiologically, a large amount of neural synchrony is required to produce a recordable field
potential at the surface of the scalp, as discussed above. For low-intensity stimuli, field potentials
generated within the head may be significantly reduced by the time they reach the surface of the
scalp due to resistivity of neural tissue, meninges, skull and scalp. Thus, ASSR amplitudes may
be too small to be identified from the background EEG noise, even with a reasonable amount of
averaging. This is not to say that the subject does not perceive the stimulus, but that examiners
are unable to identify a response indicating the subject may be able to hear the sound. For
threshold detection using ASSRs, neural synchrony is therefore needed to produce a large local
field potential that can be recorded on the scalp to indicate that the brain has responded to the stimulus at that intensity.

A further requirement for identifying ASSR thresholds is the need for a sufficient number of neurons to be stimulated. Again, this is because local field potentials diminish in amplitude before reaching the surface of the scalp. Obtaining a sufficient signal-to-noise ratio is mandatory to determine if a response is present or absent. Thus, to resolve a signal for threshold detection, a large amount of neurons may need to be synchronously active. The number of neurons active to provide a sufficient amplitude for threshold detection is not yet known.

Presenting single stimuli may activate large regions of neurons; however, when presenting multiple-stimuli these regions could overlap and decrease the ASSR amplitude to a specific frequency. As a result, threshold may be elevated when presenting multiple stimuli compared to just one stimulus at a time. Interactions between stimulus frequency and modulation frequency were previously examined for the multiple-stimulus method (John et al., 1998; Lins & Picton, 1995). Results from these studies showed that stimuli interact if carrier frequencies are separated by less than 1-octave or if modulation frequencies are less than 3 Hz apart. The amount of interaction may depend on stimulus intensity because the greater the intensity, the greater the spread of cochlear activation and this is transmitted up the auditory pathway where ASSRs are being generated. Such interactions may be due to overlapping cochlear regions, at least when considering carrier frequencies. It seems likely that the interactions between modulation frequencies are due to overlapping neural population within the central auditory system, because periodicity coding (i.e., coding for modulation frequencies) takes places within the brainstem (Langer, 1992).
Another interaction that may occur for obtaining ASSRs thresholds for both ears simultaneously is a “binaural interaction”. It may result from neurons that respond to a specific carrier frequency having a response area that overlaps for inputs from each ear. For example, if a population of neurons responds to 1000-Hz AM tone from the right ear as well as from the left ear, then it would be hard to distinguish which ear is responsible for the ASSR. What is advantageous about using ASSRs is that different modulation frequencies can be used to differentiate responses between ears and thus provide a means of assessing thresholds simultaneously in both ears. At least for supra-threshold stimuli, a binaural interaction does not seem to occur provided that the carrier frequencies in each ear are an octave different and that modulation frequencies are separated by 3 Hz (John et al., 1998; Lins & Picton, 1995). There may be some interaction at near threshold intensities that could not be resolved at higher stimulus intensities due to the high input from either ear. A possible explanation for a binaural interaction at near threshold intensities is that input from one ear could cause inhibition of incoming signals from the other ear. This inhibitory process may be over-ridden at high intensities, where it is not at lower intensities (i.e., near threshold). Because such interactions may exist at low intensities, thresholds for the dichotic multiple-ASSR technique may be higher than those for the single-ASSR method.

Auditory sensitivity is not equal across stimulus frequency when tested behaviourally. Thresholds for mid frequencies (1000 - 3000 Hz) are better than for low- and high-frequencies (American National Standards Institute, 1996). From this, one may surmise that ASSR thresholds should show a similar pattern. Research comparing thresholds across carrier frequencies has tended to show elevated low-frequency thresholds (i.e., 250 and 500 Hz) compared to those for frequencies between 1000 and 4000 Hz, at least for normal hearing subjects (Aoyagi et al.,
1994b; Lins et al., 1996; Perez-Abalo et al., 2001; Picton et al., 1998). Results showing this elevation, even after adjusting for differences in auditory sensitivity, may be due to less-than-optimal stimulus and recording parameters for the 500-Hz stimulus or to actual differences in ASSR sensitivity between frequencies.

Chapter 4 presents results from an investigation of possible stimulus interactions and carrier frequency sensitivity by comparing thresholds between carrier frequencies when presenting them to one ear separately or to one or both ears simultaneously, at least for subjects with normal-hearing. A review of the literature regarding ASSR threshold results is given in the following section.

Clinical Utility of ASSRs

Identifying individuals with hearing impairments, and the extent of their losses, is essential for early and effective intervention. For most individuals, hearing can be tested by means of behavioural audiometry, which estimates hearing thresholds by asking an individual to respond to speech or pure tones presented at various intensities. Even so, some adults may not respond reliably due to cognitive disabilities, or they may falsify responses to receive greater restitution from compensation claims. Infants, under the age of 6 months, are another population that cannot provide a reliable behavioural response. Infants, with a hearing impairment, especially need to be identified during early months of life, because research has shown considerable improvements in speech and language development in infants who are properly identified and managed (such as hearing aid and therapy) at an early age (Markides, 1986; Moeller, 2000; Ramakalawan & Davis, 1992; Yoshinaga-Itano, 1999; Yoshinaga-Itano, Sedey, Coulter, & Mehl, 1998). Although there are some concerns with universal newborn hearing
screening (Thompson et al., 2001), it is often necessary to use objective methods to evaluate hearing thresholds in young infants after they have failed a hearing screen because behavioural methods for testing hearing thresholds are limited to infants older than 5-6 months of age with normal vision and motor development (Dobie, 1993). Objective tests do not require any conscious response by the patient. Currently, clinical objective audiometry includes immittance measurements, otoacoustic emissions and AEPs. Immittance audiometry tests the function of the middle ear and screens for conductive impairments. Otoacoustic emissions evaluate the functioning of outer hair cells within the cochlea and are present in over 99% of persons who have normal hearing and middle ear function (Lonsbury-Martin, Whitehead, & Martin, 1991). Otoacoustic emissions, however, cannot evaluate the magnitude of a hearing loss. AEPs, on the other hand, correlate well with the level of hearing impairments and are useful for evaluating the degree of sensorineural hearing loss (Picton, 1990).

ABRs and cortical auditory evoked potentials (CAEPs) are currently used for evaluating hearing impairments in infants and hard-to-test adults (Hyde, 1994; Stapells, 2000b; Stapells, 2002). Each method has been investigated for its usefulness when testing these populations. For instance, CAEPs are unreliably recorded in infants in natural or sedated sleep (Osterhammel, Davis, Wier, & Hirsh, 1973), whereas ABRs can be consistently recorded (Stapells, 2000b). The ABR is, therefore, the most widely accepted method for testing infants (Stapells, 2000b). CAEPs may be used as an objective method for estimating hearing in adults with compensation claims (Stapells, 2002). For the most part, these methods are useful tools to clinicians. Nevertheless, there are some drawbacks. For example, the recording time needed to obtain frequency-specific thresholds using ABRs can be too long (approximately 45 to 90 minutes for 4 frequencies for both ears) for a one-session visit because infants tend not to sleep (a necessity) for the required
amount of time. Sedation is sometimes used to overcome this obstacle, which may add risk and additional costs. Another drawback is that response identification for the ABR and CAEP typically requires highly experienced judges (clinicians or technicians), thereby adding to the overall cost.

A continuing goal of evoked-potential audiometry is to develop a technique that will quickly and accurately estimate frequency-specific hearing thresholds in individuals who cannot reliably respond behaviourally. ASSRs have the potential to be used as an objective method for estimating hearing thresholds after individuals have failed a hearing screen (Lins et al., 1996; Rance, Dowell, Rickards, Beer, & Clark, 1998; Rickards et al., 1994) and may not have as many drawbacks as the ABR.

Early ASSR studies used modulation frequencies between 35 and 55 Hz (i.e., 40-Hz response) to assess hearing thresholds (Galambos et al., 1981; Griffiths & Chambers, 1991; Kuwada et al., 1986; Milford & Birchall, 1989; Picton et al., 1987a; Plourde et al., 1991; Rodriguez, Picton, Linden, Hamel, & Laframboise, 1986; Stapells et al., 1984; Stapells et al., 1987; Szyfter, Dauman, & De Sauvage, 1984). Several of these studies established that 40-Hz ASSR can be recorded, on average, to within 6-27 dB of behavioural thresholds. Most importantly, 40-Hz responses had similar thresholds and configurations as compared to behavioural pure-tone audiograms (250 to 8000 Hz) for low-, mid-, and high-frequency hearing losses (Griffiths & Chambers, 1991; Kuwada et al., 1986). Consequently, using the 40-Hz ASSR may be advantageous for testing uncooperative adult patients. However, there are several limitations to using 40-Hz ASSRs for testing hearing thresholds. First, response amplitudes are significantly reduced during sleep or anaesthesia (Linden et al., 1985; Jerger et al. 1986; Plourde & Picton, 1990; Cohen et al., 1991; Dobie & Wilson, 1998). Second, simultaneously presenting
Chapter 1: Introduction to ASSRs

multiple carrier frequencies modulated at different rates near 40 Hz can significantly reduce ASSR amplitudes compared to separately presenting the stimuli (John et al., 1998). Third, 40-Hz ASSRs are difficult to obtain and unreliable in estimating thresholds in infants and young children (Aoyagi et al., 1993; Maurizi et al., 1990; Stapells et al., 1988; Suzuki & Kobayashi, 1984).

In contrast to 40-Hz ASSRs, AM tones modulated between 70-110 Hz evoke stable ASSRs in infants and adults, whether sleeping or awake (Aoyagi et al., 1993; Cohen et al., 1991; Levi, Folsom, & Dobie, 1993; Lins, Picton, Picton, Champagne, & Durieux-Smith, 1995; Rickards & Clark, 1984). ASSRs at these higher rates (i.e., 80-Hz ASSRs) have recently been shown to be a useful technique in estimating hearing thresholds in individuals with normal or impaired hearing (Aoyagi et al., 1994a; Aoyagi et al., 1999; Lins et al., 1995; Lins & Picton, 1995; Lins et al., 1996; Picton et al., 1998; Rance et al., 1998; Rickards et al., 1994). Results show that ASSRs to 80-Hz AM tones can estimate behavioural thresholds to within 18 dB (range 3 to 18 dB) for subjects with normal or impaired hearing. Correlations between behavioural and 80-Hz ASSR thresholds are moderate to high, ranging from .54 to .99 for carrier frequencies from 500 to 4000 Hz. These results suggest that 80-Hz ASSRs would be useful indicators of hearing thresholds in difficult-to-test subjects. Nevertheless, conclusions drawn in each study regarding the utility of ASSRs in estimating hearing thresholds are either limited by high levels of ambient noise, small sample sizes, and/or use of the single-stimulus ASSR method. The studies presented in Chapters 4 and 5 were designed to minimize such limitations and estimate hearing thresholds in subjects with normal and impaired hearing, respectively.
Researchers have proposed and investigated some potential advantages of using 80-Hz ASSRs to identify hearing thresholds compared to conventional AEP methods, such as the ABR. They are:

i) More robust statistical methods can be used, online, to objectively identify the presence or absence of ASSRs (Dobie & Wilson, 1996; Valdes et al., 1997); compared to the visual observation of tone-ABR replicability methods used by audiologists, which can lead to errors in threshold determination (Stapells, 2000b).

ii) Multiple, frequency-specific, thresholds may be simultaneously obtained by using ASSRs because they can be evoked by concurrently presenting multiple AM tones to both ears (John et al., 1998; Lins & Picton, 1995). This can reduce recording time compared to conventional single-stimulus methods, such as the ABR. Recording time becomes an important issue when testing infants. Infants typically do not sleep for the time required to assess all frequencies using the single-stimulus ABR method. This, however, should be sufficient time for the multiple-Assr method to obtain an audiogram for each ear.

iii) ASSRs may provide a more frequency-specific assessment of hearing than the ABR, because the AM tones used to elicit ASSRs have a narrower spectrum than the brief tones used for the ABRs (Hartmann, 1997, pp. 400-401). The narrower spectra may translate into a more discrete activation of the cochlea (termed place-specificity).

This thesis investigates the potential advantage of using a more frequency-specific stimulus (Chapters 3 and 5) and of simultaneously presenting multiple stimuli to reduce recording times when estimating hearing thresholds in subjects with normal and impaired hearing.
(Chapter 4 and 5). Furthermore, the sensitivity of using ASSRs for the estimation of hearing thresholds is investigated in Chapter 4 and 5.

*General Remarks for Methods used to Record and Analyse ASSRs*

ASSRs are typically recorded in humans using scalp electrodes. Placement and number of electrodes depend on the information one wishes to obtain.

For localising generators, the number of sources able to be modelled and the spatial resolution depend on the number of electrodes used for recording. Thus, it is beneficial to maximize the number of recording electrodes, except that there may be an upper limit due to spatial constraints and inaccuracy in electrode placement that restricts the spatial resolution for dipole source analysis. Between 32 and 64 electrodes distributed in the conventional “Ten-Twenty” system may be optimal for source analysis (Picton et al., 1995). The electrode set-up for identifying generators, used in Chapter 2 of this thesis, is an adapted “Ten-Twenty” system.

For threshold evaluation, the simpler the set-up the faster it is to obtain information. Thus, it is important to minimize the number of electrodes required. Placement of these few electrodes becomes important because one wishes to get the greatest signal-to-noise ratio. Thus, the most commonly used electrode setup for differential recording of ASSRs to evaluate threshold (Lins et al., 1996; Perez-Abalo et al., 2001; Picton et al., 1998), which is the one used in this thesis, is as follows: three electrodes are placed on the scalp, a ground placed on the high forehead, a non-inverting electrode on the vertex of the head, and an inverting electrode on the nape of the neck or on the mastoid. This minimizes the number of electrodes needed to be applied, while maximizing their placement to obtain the greatest signal-to-noise ratio for response identification.
Visually identifying ASSRs in the time domain becomes increasingly difficult as stimulus modulation-frequency increases. This is because the reduced ASSR amplitudes for higher modulation frequencies result in responses that may not be visually discernable in time domain waveforms, even after a reasonable amount of averaging. For a stimulus presented at a rate of 40 Hz, ASSR amplitude is relatively large compared to the overall background electroencephalographic (EEG) noise. For higher rates of stimulation, ASSR amplitudes are small and become obscured in the time domain by relatively large amplitude background EEG noise. A way to distinguish an ASSR is to analyse the frequency spectra of the recorded EEG. Fast Fourier Transform (FFT) of the time-domain waveform provides real and imaginary values over several frequency components. These can be used to determine amplitude and phase spectra of the EEG. Figure 1.10 shows the average time domain waveform and amplitude spectra for an ASSR to a 60-dB SPL AM tone (4000 Hz) modulated at 96 Hz. A 96-Hz ASSR is not visible in the time domain waveform, yet a large amount of energy at the modulation frequency is clearly seen to be greater in amplitude compared to the background EEG noise at surrounding frequencies.

As the stimulus intensity approaches hearing threshold, response identification becomes increasingly difficult and reduced ASSR amplitudes may not be visually discernable in either the time or frequency domain. Thus, statistical methods may be needed to help identify if a response is present or absent to within a specified degree of confidence. Researchers have investigated the performance of several statistical indicators used to evaluate response presence for ASSRs (Champlin, 1992; Dobie, 1993; Dobie & Wilson, 1994a; Dobie & Wilson, 1994b; Dobie & Wilson, 1996; Picton, Dimitrijevic, John, & Van Roon, 2001; Stapells et al., 1987; Valdes et al., 1997). These statistical tests include Phase Coherence, Magnitude Squared Coherence, Circular
Figure 1.10. Fast Fourier Transform (FFT) of an ASSR time domain (top panel) into the frequency domain (bottom panel). Large-amplitude slow cortical activity, not associated with the stimulus, obscures a small amplitude ASSR to an 2000-Hz AM tone modulated at 96 Hz, which is clearly visibly in the frequency domain.
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The $T^2$ test, F-test, and Hotellings $T^2$ test. Valdes et al. (1997) evaluated each of these statistics for determining ASSR thresholds to AM tones modulated around 80 Hz and showed that all tests provided accurate and reliable indications of threshold. The statistical method chosen for objective response detection throughout this thesis is the F-test described by Zurek (1992). Because time-domain averaging is employed, the F-test is sensitive to both amplitude and phase of an ASSR. The F-test determines the probability of a response being present or absent by measuring the variance of the ASSR at the frequency of stimulus presentation and comparing this to the variance of the surrounding EEG noise frequencies. If the probability reaches criterion (e.g., $p<.05$), then a response is deemed present. If it doesn’t reach criterion and the noise floor is below an acceptable level (e.g., 10 nV), then one can conclude a no-response.

Chapter 4 differs from Chapters 3 and 5 in statistical methods for response detection because a newer version of the “MASTER” program for recording ASSRs became available after results were collected for the study presented in Chapter 4. The difference in the way that an ASSR is evaluated between these two methods is that the frequency bins used to estimate the background EEG noise are slightly different when presenting multiple stimuli. The new version estimates the EEG noise floor from 120 frequency bins (0.061 Hz per bin) surrounding each modulation frequency, whereas the old version estimates the noise floor from 120 bins surrounding the frequency that is the average of the modulation frequencies presented. For example, if stimuli are simultaneously presented at 77, 85, 93, and 101 Hz then the newer version calculates the variance in EEG noise amplitude between four separate ranges of modulation frequencies: 73.4-80.6 Hz, 81.4-88.6 Hz, 89.4-96.6 Hz, and 97.4-104.6 Hz, respectively. This variance in noise amplitude is then compared to the variance in amplitude at the stimulus’ modulation frequency to obtain a statistical probability of a response being present or not. The
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The older version first calculates the average between the stimulus modulation frequencies (i.e., 89Hz for this example) and then calculates the variance in amplitudes for frequencies between 85.4 and 92.6 Hz. The F-statistic uses only this single noise estimate when determining probabilities for each response detection. Because the newer version uses the noise estimate for frequency bins directly surrounding each of the stimulus' modulation frequency, it provides a better evaluation for response detection.

Another difference in recording parameters used in this thesis is that the studies presented in Chapters 3 and 5 used a high-pass EEG filter setting of 30 Hz compared to that of 5 Hz used in Chapter 4. This was done to attenuate the large amplitude alpha activity (i.e., 8-13 Hz; associated with relaxed wakefulness) that was exceeding artefact rejection limits and making it difficult to obtain electrically quiet recordings. To make sure that raising the high-pass EEG filter to 30 Hz would not affect responses in the 70-110 Hz range, a pilot study of 5 subjects was carried out, which showed that there was no difference in ASSR amplitudes when the high-pass filter was set at 30 Hz versus 5 Hz. The 30-Hz filter setting was thus used for the subsequent studies that are presented in Chapters 3 and 5.

Detailed descriptions of the methods used in a study are provided in their respective chapter.
Chapter 2: Intracerebral Sources of Human Auditory Steady-State Responses
Abstract

The objective of this study was to localize the intracerebral generators for auditory steady-state responses. The stimulus was a continuous 1000-Hz tone presented to the right or left ear at 70 dB SPL which was sinusoidally amplitude-modulated to a depth of 100% at 12, 39, or 88 Hz. Responses recorded from 47 electrodes on the scalp were transformed into the frequency domain. Brain electrical source analysis treated the real and imaginary components of the response in the frequency domain as independent samples. The latency of the source activity was estimated from the phase of the source waveform. The main source model contained a midline brainstem generator with two components (one vertical and one lateral) and cortical sources in the left and right supratemporal plane, each containing tangential and radial components. At 88 Hz, the largest activity occurred in the brainstem and subsequent cortical activity was minor. At 39 Hz, the initial brainstem component remained and significant activity also occurred in the cortical sources, with the tangential activity being larger than the radial. The 12-Hz responses were small, but suggested combined activation of both brainstem and cortical sources. Estimated latencies decreased for all source waveforms as modulation frequency increased and were shorter for the brainstem compared to the cortical sources. These results suggest that the whole auditory nervous system is activated by modulated tones, with the cortex being more sensitive to slower modulation frequencies.
Chapter 2: Sources of ASSRs

**Introduction**

Steady-state responses evoked by regularly repeating auditory stimuli and recorded from the scalp can be used to demonstrate that the human brain is responding to sound. Determining the intracerebral sources of these responses is important for both scientists and clinicians. Knowing the sources of normal responses will increase our understanding of the human auditory system and may help us to localize the level of a hearing impairment when the responses are abnormal or absent.

There has not been much work on the sources for the electrically recorded steady-state responses. Johnson, Weinberg, Ribary, Cheyne, and Ancill (1988) performed a 21-channel mapping study and demonstrated clear polarity-inversions of the response to 40-Hz brief tones over the midtemporal regions in some of their subjects. Mauer and Döring (1999) reported in an abstract that both brainstem and cortical (temporal lobe) sources are active during ASSRs (using modulation frequencies between 24 and 120 Hz). However, the size of the cortical activity decreased with increasing modulation frequency, and the brainstem was the dominant source at modulation rates greater than 50 Hz.

Several magnetoencephalographic (MEG) studies have localized generators for ASSRs to 40-Hz stimuli to be within the supratemporal gyrus of the auditory cortex (Gutschalk et al., 1999; Hari et al., 1989a; Mäkelä & Hari, 1987; Pantev et al., 1993; Pantev et al., 1996). These sources are similarly located to those for the transient middle-latency responses (Pantev et al., 1993; Yvert, Crouzeix, Bertrand, Seither-Preisler, & Pantev, 2001). MEG studies have difficulty recognizing sources that are tangential or that are deeply located in the brain. Gutschalk et al. (1999) identified two overlapping sources for the ASSR in the supratemporal plane. The more
lateral of these might have represented a source that was partially radial in its orientation.

Electric recordings might help to disentangle these components.

Animal and human investigations have led to some controversy regarding the neural substrates of the middle-latency responses. However, results from many human studies suggest that the early negative component (Na) of the middle-latency response has subcortical contributions, whereas the later positive component (Pa) is primarily generated within the auditory cortex (Fischer, Bognar, Turjman, & Lapras, 1995; Hashimoto et al., 1995; Jacobson, Privitera, Neil, Grayson, & Yeh, 1990; Knight, Hillyard, Woods, & Neville, 1980; Kraus, Ozdaman, Hier, & Stein, 1982; Kuriki, Nogai, & Hirata, 1995; Pelizzone et al., 1987). Results of intracranial recordings from animals corroborate these results in humans (Arezzo, Pickoff, & Vaughan, 1975; Knight & Brailowsky, 1990; Littman, Kraus, McGee, & Nicol, 1992; Smith & Kraus, 1988). The 40-Hz response might, therefore, represent overlapping fields from both the cortex and the thalamus. Deep-seated sources are difficult to see using MEG, but might be recognizable in electric recordings.

Galambos, Makeig, and Talmachoff (1981) suggested that the 40-Hz ASSR represents the superimposition of individual middle-latency responses. Because the main waves of the middle-latency responses have peak latencies separated by approximately 25 ms between adjacent waves of the same polarity, the overlapping of responses will enhance the response when the stimulus rate is 40 Hz (i.e., 25 ms inter-stimulus interval). Another hypothesis, contrary to this “overlap theory”, proposes that neural units have an intrinsic rhythm of firing that best resonates in phase with a stimulus presented at 40 Hz (Azzena et al., 1995; Basar et al., 1987; Santarelli et al., 1995). Nonetheless, the former theory has gained greater acceptance from supporting evidence showing a close correspondence of superimposed transient MLRs and 40-Hz ASSR (Hari,
Joutsiniemi, Hamalainen, & Vikman, 1989b; Plourde et al., 1991; Stapells et al., 1988). Such a
direct inference of equivalent MLR and ASSR generators may be amiss because neural
processing may be altered by the repetitive nature of ASSR stimuli compared to transient stimuli.

There are limited data regarding neural generators for ASSRs to AM tones modulated at
rates between 70-110 Hz. Animal recordings have shown units and fields in the brainstem that
respond at these rates (Batra et al., 1989; Creutzfeldt et al., 1980; Frisina, Smith, & Chamberlin,
1990b; Rees & Möller, 1983). However, Hari et al. (1989) reported dipole activity within the
auditory cortex for MEG responses to clicks presented at 70 Hz. Recently, Mauer and Döring
(1999), using dipole source analysis, suggested that both brainstem and cortical sources are
responsible for the ASSRs to stimuli modulated at low rates (20-40 Hz), whereas the brainstem is
the primary generator when stimuli are modulated at higher rates (70-100 Hz). Ross et al. (2000)
studied the MEG steady-state responses concentrating on modulation frequencies near 40 Hz.
However, they also reported a secondary maximum at stimulus rates near 80 Hz with an apparent
latency of 26 ms for these responses. The sources for these ASSRs were found in the superior
temporal plane. Schoonhoven, Boden, Verbunt, and de Munck, (2001) also found similar sources
for both 40 Hz and 80 Hz responses. These results indicate the cortex is activated by rapid
modulations of 80 Hz. Because MEG does not easily pick up deep sources, these studies do not
rule out concomitant activity in the brainstem.

The intent of this study was to identify the neuroanatomical substrates for ASSRs to AM
tones modulated at frequencies of 12, 39 and 88 Hz. ASSRs were analysed in the frequency
domain and brain electrical source analysis was used to model the location and orientation of the
their neural generators.
Methods

Subjects

Ten right-handed subjects (5 females) with an average age of 30 (range 17 to 50) years participated in this study. Data were missing for some conditions for three subjects. Subjects were screened for normal hearing at 1000 Hz at 20 dB HL. All subjects provided informed consent.

Recordings

EEG data were collected from 46 tin electrodes mounted in an electrode cap and placed on the scalp. The cap electrodes were Fp1, Fp2, AF3, AFz, AF4, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P3, P7, Pz, P4, P8, PO3, PO4, Oz, O1, O2, Cb1, Cb2 and Iz. Three additional electrodes were placed on the left and right mastoids and on the back of the neck at a distance of 10% of the nasion-inion distance below the Iz electrode. Five electrodes were placed on the face to monitor eye movements. These electrodes were placed at the nasion, just inferior to the eye (IO1, IO2) and at the outer canthus of the eye (LO1, LO2). Inter-electrode impedances were maintained below 10 kOhms at 10 Hz. All electrodes were referenced to Cz electrode for the online recording. EEG potentials were collected at a sampling rate of 2000 Hz, amplified 2500 times (0.034 mV/bit resolution), and bandpass filtered (slope 12 dB/octave) between 1 and 200 Hz. Artefacts, such as eye movements or muscle activity, with potentials greater than ±200 µV in any channel, were automatically rejected prior to averaging. For each stimulus condition, average steady-state responses were obtained by averaging 200 EEG epochs of 1023 ms each. The average responses were then recalculated relative to an average reference and the Cz waveform added to give a 47-channel recording for source analysis.
Stimuli

The stimuli were produced by digitally modulating a sine wave by another sine wave to obtain a 1000-Hz waveform with 100% amplitude modulation. The digital waveform was then converted into analog form with a 12-bit resolution digital-to-analog converter running at a 10-kHz rate. The stimulus was amplified to a calibration level then attenuated to 70 dB SPL (approximately 60 dB nHL, see Chapter 4) and presented to the subject through Eartone 3A insert earphones to the right and left ear, separately.

The stimulus was constructed and presented using a program that continuously recycled a buffer containing 10,240 values. The frequencies of both carrier and modulation signals were adjusted to give an integer number of cycles in the buffer. This ensured that no acoustic artifacts occurred as the buffer was recycled, and that the FFT analysis could measure responses at exactly the modulation frequency. Three frequencies of modulation were used: 11.72, 39.06 and 87.89 Hz (equivalent to 12, 40 and 90 cycles per sweep).

The FFT also required that the number of points in the response waveform was a power of two and that the response was exactly triggered by the onset of the stimulus buffer. These criteria are reviewed more extensively in John and Picton (2000).

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3 The procedure of synchronizing the stimulus computer and the Neuroscan amplifiers used the Neuroscan clock. The program presenting the stimuli used the clock operating the analog-to-digital conversion of the Neuroscan recording system to time its own digital-to-analog conversion. Pin 3 of the S/H DEBLOCK connector at the back of the Synamps amplifier provided a clock signal at 10 kHz when the Analog-to-digital conversion rate of the amplifier was set at 2 kHz. The Neuroscan was set to record sweeps using an external trigger. The stimulus-computer provided this trigger each time the buffer was recycled. The sweep of the Neuroscan recording was set to be 2046 points to allow the next sweep (beginning 1024 ms or 2048 addresses after the first) to be triggered and averaged. For the FFT analysis, the recorded sweep was increased to 2048 addresses by including two zeros at the end.
Experimental Protocol

EEG recordings were obtained in a two-hour session. During this time, subjects relaxed quietly in a comfortable chair. Their state of alertness was maintained by reading (novels or magazines of the subject's choosing). The presentation of the AM tones was randomized for the different modulation frequencies (12, 39, and 88 Hz) and between ears. For each frequency of modulation and ear of stimulation, we obtained responses from two separate recording trials (each containing 200 epochs and lasting about four minutes).

Scalp Waveforms

In order to assess the actual time-domain waveforms of the response, we collapsed the 1.024-second sweep down to the equivalent of two cycles of the stimulus. Because this was not an integer factor of the available 2,048 points, we initially spline-fit the full sweep with a set of data containing an integer number of points per two-cycle period. For example, the responses recorded with the 90 cycles per sweep were splined from 2,048 to 2,070 points and then averaged every 46 points. We also splined the 12-Hz responses to obtain a single cycle of the response.

FFT Analysis

Each averaged sweep was analysed at each of the 47 electrodes using an FFT. The real and imaginary values at the frequency of stimulation were then plotted using vector diagrams (with the real values on the x-axis and the imaginary values on the y-axis) and stored for evaluation in the source analysis programs.
Maps

The vector data from the FFT can be portrayed over the scalp using a graphical
convention similar to that used by meteorologists when portraying the strength and direction of
the wind. However, contour-mapping two-dimensional data over the scalp is not simple. One
cannot just map the amplitude because the amplitude will be large for responses with inverted
polarity. Additionally, phase maps are not easy to understand. We therefore, used the techniques
described by Lehman and Michel (1989, 1990) to project the activity onto a dominant phase axis
and then we mapped the projected activity onto the scalp. The dominant phase axis was
calculated from the slope of the regression line of the imaginary values versus the real values at
each electrode. The individual data were then projected onto this axis to give values that could
then be mapped.

Brain Electric Source Analysis (BESA)

Our “overall” source model is based on our grand-mean results and previous research
(Mauer & Döring, 1999; Rees & Möller, 1983; Scherg, Vajsar, & Picton, 1989; Scherg & von
Cramon, 1986) that supports our hypothesis that ASSR sources may be constrained to the cortex
and brainstem. The goodness of fit of our source model may be assessed by looking at the
residual variances between the source-model’s projected scalp-waveforms and the actual scalp-
recorded waveforms. For this study, we consider a residual variance less than 10% to be a
reasonable goodness of fit for our model and would suggest that our hypotheses are valid.
Source analysis was carried out using BESA version 3.0 (Scherg, 1998). This source analysis used two points in the frequency domain (real and imaginary) per electrode to evaluate dipole sources. Appendix A describes dipole source modelling in greater detail.

A brainstem source was initially fit using the 88-Hz grand-mean data because we hypothesised that a brainstem source could best represent the 88-Hz data. We were able to fit separate sources for the responses to left- and right-ear stimulation with each source being at the same level, a little to the side of stimulation and oriented towards the contralateral side. However, these sources were rather close together and we could not, therefore, use them simultaneously if the data for left and right ears were analysed together. This is because the close proximity of these sources causes them to be linearly dependent and produce instability in the iterative calculations of modelling the scalp-recorded waveforms (Picton et al., 1995). We therefore decided to use a single midline source (S1) and to allow it to fit its orientation only in the mid-sagittal plane. Once this was fit, we added a second dipole (S2) at the location of the first and fixed its orientation laterally to the right. This would pick up the main differences between the left- and right-ear responses.

In order to fit the 39-Hz grand-mean data, we added two symmetrical sources (S3 and S4) to the two brainstem sources (S1 and S2) and fit their location and orientation using the 39-Hz grand-mean data. Additionally, radial dipoles (S5 and S6) were added at the location of dipoles S3 and S4, because previous studies have shown activity in the auditory cortex has radial as well

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4 Because BESA requires a time waveform, each value was inserted into an .avr file at eleven “times” so that it could be read (although the analysis was only carried out at one of these values). In order to analyse the real and imaginary data simultaneously the files containing these data were read in sequentially (“read data” then “read extra”). Ultimately we could read in and simultaneously analyse the data for all stimulus rates and both ears of stimulation.
as tangential components (Scherg et al., 1989; Scherg & von Cramon, 1986). Then dipoles S3 and S4 were refit. This resulted in an “overall” model that was based on the grand-mean responses at both 88 and 39 Hz. This model was then used to model both the grand-mean data and each subject’s data for all three rates of stimulation

Using the data obtained from the individual subjects, two 3-way repeated-measures analyses of variance (ANOVA) compared the amplitudes and the estimated latencies (see below) at each of the six sources across the different conditions (ear by modulation frequency). For ease of interpreting the ANOVAs, the sources were reclassified to a vertically oriented brainstem source (i.e., S1), a laterally oriented brainstem source (i.e., S2), a tangentially oriented ipsilateral cortical source (i.e., S3 for left ear stimulation and S4 for right ear stimulation), a tangentially oriented contralateral cortical sources (i.e., S4 for the left ear stimulation and S3 for the right ear stimulation), a radially oriented ipsilateral cortical source (i.e., S5 for left ear stimulation and S6 for right ear stimulation), a radially oriented contralateral cortical sources (i.e., S6 for the left ear stimulation and S5 for the right ear stimulation). Results of the ANOVAs were considered significant if p<.01. Greenhouse-Geisser epsilon correction factors for degrees of freedom were used when appropriate. Newman Keuls post hoc comparisons were performed only for significant main effects and interactions. Results of the post hoc tests were considered significant if p<.05.

Amplitudes and Latencies of Source Activity

Each source “waveform” consisted of a component in the real and imaginary dimension of the frequency domain. Amplitudes of the source waveforms were calculated as the vector sum of the real and imaginary components of source waveforms. Units for amplitude of the source...
waveforms are in terms of effective microvolts (µVeff), which is related to the source's dipole moment by a constant factor that is based on the head model (Scherg, 1998).

From the real and imaginary components, we could additionally derive a phase, calculated as the cosine onset phase ($\phi_{\text{onset}}$). This value was adjusted to give a phase delay ($\phi_{\text{delay}}$) using the equation $360 - \phi_{\text{onset}} - 90$, with the final term compensating for the fact that the stimulus modulation used a sine rather than a cosine function (John & Picton, 2000). The latency of the source activity was estimated from the phase delay. Unfortunately, the phase of a steady-state response cannot be directly converted into latency because it is impossible to know how many cycles intervened between the stimulus and the recorded cycle of the response. We calculated the latency in seconds as $\phi_{\text{delay}}/(360f) + N/f$; where $\phi_{\text{delay}}$ is the phase delay in degrees, N is the number of preceding modulation cycles, and f is the modulation frequency in Hz. For the 12-Hz and 39-Hz data, we arbitrarily set N to 0 and 1 for brainstem and cortical sources, respectively. For the 88-Hz data, N was set to 1 and 2 for brainstem and cortical sources, respectively. This provided a more realistic model and adjusted for travel-time delays between the cochlea and brainstem and between the brainstem and cortex.

*Test Data for Source Model Verification*

The overall model fit to the data in this experiment was also evaluated using another set of data, which recorded multi-channel ASSRs. These ASSRs were evoked by tones of 1000 Hz presented at 75 dB SPL to the right ear. The AM depth was 100% and the modulation frequencies were 40 and 80 Hz. Responses were recorded from 10 normal-hearing subjects using 27 electrodes placed in an adapted “10-20” system.
Chapter 2: Sources of ASSRs

Results

Scalp Recorded Responses

Figures 2.1, 2.2 and 2.3 show, as an example, how the scalp-recorded responses were analysed using the grand-mean response to left-ear stimulation at 39 Hz. Figure 2.1 shows the average time-domain response to 2-cycles of stimulation. As can be seen the response inverts in polarity between the neck and the frontocentral regions of the scalp. The inversion occurs over a curved line running through the mid-temporal and mid-parietal regions. Figure 2.2 shows the amplitude spectrum of the response derived from the full 1.024 second sweep rather than the 2-cycle sweep. The response shows a peak at the frequency of 39.06 Hz, which corresponds to the modulation frequency. Low-frequency noise in the recordings, deriving from the EEG rhythms and eye movements, is largest in the electrodes around the eyes. The noise levels at the higher frequencies, deriving from muscle artifacts, is greater in the electrodes over the neck and mastoids. The response peak in the amplitude spectrum does not show the phase of the response. This can be seen in Figure 2.3, which depicts the polar plots of the responses. The phase is the cosine onset phase, measured in a counter-clockwise direction from the right-sided horizontal axis. The cosine onset phase of the response is approximately 250° at the vertex electrode and 60° at the neck electrode. These phases can be estimated from the time-domain waveforms in Figure 2.1. For example, at the vertex, the time-domain waveform approximates a sine wave beginning with a phase of about -20°. This would be equivalent to a cosine wave beginning at -110° (or +250° if one cycle was to be added). The phases also agree with the inversion in polarity (a phase shift of 180°) seen in Figure 2.1 between the vertex and neck. The response to the right-ear stimulation is very similar to that recorded to left-ear stimulation. The overall
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Figure 2.1. Top view of time-domain waveforms for grand-mean 39-Hz ASSRs recorded from 47 scalp electrodes. The scalp is represented in two-dimensions by an oval oriented anteriorly towards the top of the figure. Waveforms represent responses to 2-cycles of a 1000-Hz AM tone modulated at 39 Hz, presented at 70 dB SPL to the left ear. Positive is polarity is above the horizontal axis. Cz = vertex.
39 Hz  
Left Ear  
1000 Hz  
70 dB SPL

Figure 2.2. Top view of amplitude spectra for grand-mean 39-Hz responses recorded from 47 scalp electrodes. The scalp is represented in two-dimensions by an oval oriented anteriorly towards the top of the figure. Responses are to a 1000-Hz AM tone modulated at 39 Hz, presented at 70 dB SPL to the left ear. Note the large amplitude response at 39 Hz, which correspond to the stimulus modulation frequency. Cz = vertex.
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39 Hz  
Left Ear  
1000 Hz  
70 dB SPL

Figure 2.3. Top view of polar plots representing the amplitude and phase of the grand-mean ASSRs to a 1000-Hz AM tone modulated at 39 Hz, presented at 70 dB SPL to the left ear. The magnitude of a vector in a polar plot represents the amplitude of the response and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. The scalp is represented in two-dimensions by an oval oriented anteriorly towards the top of the figure. Cz = vertex.
amplitudes and phases of the responses are similar between electrodes over the fronto-central regions but inverted in phase compared to the similar responses between electrodes over the mastoid and neck region. Responses at electrodes over the ipsilateral mastoid region show slightly larger amplitudes than over the contralateral region.

The responses to 88-Hz stimuli are smaller in amplitude than those recorded at 39 Hz, and are more variable from subject to subject. Figure 2.4 shows the grand-mean time-domain waveform for the 88-Hz response to left-ear stimulation. As well as being smaller than the response at 39 Hz, the responses show a greater asymmetry in the mastoid regions, being larger at electrodes ipsilateral to the stimulated ear. This is more clearly shown in the contour maps plotted in Figure 2.5.

The time-domain waveforms for the 12-Hz stimuli, shown in Figure 2.6, are clearly not sinusoidal at the frequency of stimulation. A single cycle of the grand-mean response to left-ear stimulation is shown in Figure 2.6. The vertex response shows a prominent vertex positive wave peaking at 21 ms after the onset of the sweep (0° on the sinusoidal modulation waveform at the half-amplitude point). The frequency spectrum of the response at the vertex contains as much activity at the second and third harmonics as at the modulation frequency (Figure 2.7). Interestingly, the amplitude-spectrum varies across the scalp and the lateral temporal electrode has its dominant activity at the modulation frequency. Figure 2.7 also compares the spectra for the responses at two scalp location for three different modulation frequencies. Note the relatively larger amplitude for the 39-Hz ASSR compared to the 12- and 88-Hz responses.
Figure 2.4. Top view of time-domain waveforms for grand-mean 88-Hz ASSRs recorded from 47 scalp electrodes. The scalp is represented in two-dimensions by an oval oriented anteriorly towards the top of the figure. Waveforms represent responses to 2-cycles of a 1000-Hz AM tone modulated at 88 Hz, presented at 70 dB SPL to the left ear. Positive is polarity is above the horizontal axis. 
Cz = vertex.
Figure 2.5. Scalp distributions and current source density maps for 39- and 88-Hz vector data projected onto the dominant phase axis. Positive voltages are represented by dashed lines and negative voltages by solid lines. Contour-interval scales are provided to the right for each modulation frequency.
12 Hz
Left Ear
1000 Hz
70 dB SPL

1 cycle (85.3 ms)

Figure 2.6. Top view of time-domain waveforms for grand-mean 12-Hz ASSRs recorded from 47 scalp electrodes. The scalp is represented in two-dimensions by an oval oriented anteriorly towards the top of the figure. Waveforms represent responses to 1-cycle of a 1000-Hz AM tone modulated at 12 Hz, presented at 70 dB SPL to the left ear. Positive is polarity is above the horizontal axis. Cz = vertex.
Figure 2.7. Amplitude spectra at electrodes Cz and T8 for responses to 100-Hz AM tones modulated at 12, 39, and 88 Hz. Arrows designate large-amplitude responses and their harmonics.
Source Analyses

Figure 2.8, 2.9, and 2.10 represent the model used to analyse the scalp-recorded data in the frequency domain. For each frequency of stimulation, the analysis is shown for left-ear stimulation. The analysis for the mean data is shown by the thick lines ending with a closed circle, and the analysis for the individual subjects by the thin lines. For the 39- (Figure 2.8) and 88-Hz (Figure 2.9) responses, individual subject data show similar phases compared to the mean responses. For the 12-Hz responses (Figure 2.10), phases are quite variable between subjects. Table 2.1 shows the residual variance for fitting the scalp-recorded grand-mean and individual responses using the overall model.

When dipoles are fit to the individual subjects' data, the locations are quite variable because certain subjects show unusual waveforms at some electrode locations, particularly the neck, mastoid and facial electrodes. Examining the scalp-recorded waveforms shows that this is related to increased noise or unusually large responses at specific electrodes that the analysis is attempting to fit. Nevertheless, the mean locations of the three sources used in this analysis are similar to those obtained by fitting the grand-mean data (Table 2.2).

Table 2.3 presents the amplitudes and estimated latencies of the source waveform from the grand-mean data. For 12-Hz modulation, there is little difference in amplitudes between source waveforms. Conversely, at a modulation frequency of 39 Hz, the vertically oriented brainstem source (source 1) and the two tangential cortical sources (sources 3 and 4) are larger in amplitude compared to the other sources. For the 88-Hz modulation, the vertically oriented brainstem is relatively larger than all other sources. These results can also be seen in Figures 2.8, 2.9, and 2.10. Table 2.3 shows that latencies increase with decreasing modulation frequency, with brainstem latencies being shorter than cortical sources.
Figure 2.8. Polar plots for source (1-6) activity to a 39-Hz AM tone (1000 Hz) presented at 70 dB SPL to the left ear. The magnitude of a vector in a polar plot represents the amplitude of the source activity and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. Mean vector results are designated by thick lines ending with a filled circle, while vectors for each subject are designate by thin lines. The inner diagram of the head shows the location and orientation of the dipole sources. Scale for both axes is μVeff.
Figure 2.9. Polar plots for source (1-6) activity to a 88-Hz AM tone (1000 Hz) presented at 70 dB SPL to the left ear. The magnitude of a vector in a polar plot represents the amplitude of the source activity and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. Mean vector results are designated by thick lines ending with a filled circle, while vectors for each subject are designated by thin lines. The inner diagram of the head shows the location and orientation of the dipole sources. Scale for both axes is μVeff.
Figure 2.10. Polar plots for source (1-6) activity to a 12-Hz AM tone (1000 Hz) presented at 70 dB SPL to the left ear. The magnitude of a vector in a polar plot represents the amplitude of the source activity and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. Mean vector results are designated by thick lines ending with a filled circle, while vectors for each subject are designate by thin lines. The inner diagram of the head shows the location and orientation of the dipole sources. Scale for both axes is µVeff.
Table 2.1

Residual variances (in percent) for source models fitting either grand-mean data or individual data

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Grand mean</th>
<th>Individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz(^a)</td>
<td>12.2</td>
<td>22.8 ± 16.4</td>
</tr>
<tr>
<td>39 Hz(^b)</td>
<td>3.3</td>
<td>12.2 ± 7.4</td>
</tr>
<tr>
<td>88 Hz(^a)</td>
<td>9.6</td>
<td>30.6 ± 14.0</td>
</tr>
<tr>
<td>Right ear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz(^a)</td>
<td>11.3</td>
<td>21.0 ± 8.0</td>
</tr>
<tr>
<td>39 Hz(^b)</td>
<td>3.0</td>
<td>11.8 ± 9.2</td>
</tr>
<tr>
<td>88 Hz(^a)</td>
<td>6.8</td>
<td>32.8 ± 18.1</td>
</tr>
</tbody>
</table>

*Note.* Mean ± one standard deviation are given for individual data.

\(^a\) N = 8. \(^b\) N = 10.
Table 2.2

Locations of sources

<table>
<thead>
<tr>
<th>Source and coordinate</th>
<th>Overall Model</th>
<th>From Individual Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brainstem</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>y</td>
<td>1</td>
<td>-1±15</td>
</tr>
<tr>
<td>z</td>
<td>-4</td>
<td>-8±11</td>
</tr>
<tr>
<td><strong>Cortical (right side)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x</td>
<td>54</td>
<td>43±20</td>
</tr>
<tr>
<td>y</td>
<td>6</td>
<td>-1±16</td>
</tr>
<tr>
<td>z</td>
<td>15</td>
<td>3±10</td>
</tr>
</tbody>
</table>

*Note.* Location-coordinates are in millimeters relative to the centre of the sphere used to analyse sources. The x dimension is from left (-) to right (+), the y-dimension from back (-) to front (+), and the z dimension from below (-) to above (+). The left cortical source (not shown) is located symmetrically to the right cortical source (i.e., has a negative x coordinate).
Table 2.3

Amplitudes and estimated latencies for source waveforms fit using the grand-mean data

<table>
<thead>
<tr>
<th>Ear and fm</th>
<th>Brainstem</th>
<th>Ipsilateral Cortex</th>
<th>Contralateral Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertical</td>
<td>Lateral</td>
<td>Tangential</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>1.16</td>
<td>2.03</td>
<td>1.30</td>
</tr>
<tr>
<td>39 Hz</td>
<td>3.39</td>
<td>0.95</td>
<td>1.75</td>
</tr>
<tr>
<td>88 Hz</td>
<td>1.40</td>
<td>0.64</td>
<td>0.45</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>0.88</td>
<td>0.78</td>
<td>0.93</td>
</tr>
<tr>
<td>39 Hz</td>
<td>3.98</td>
<td>0.29</td>
<td>2.33</td>
</tr>
<tr>
<td>88 Hz</td>
<td>1.75</td>
<td>0.49</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Estimated latency (ms)

| Left       |            |                    |                      |                    |
| 12 Hz      | 21         | 58                 | 154                  | 165                | 166        | 168    |
| 39 Hz      | 29         | 26                 | 48                   | 52                 | 50         | 34     |
| 88 Hz      | 18         | 17                 | 26                   | 27                 | 26         | 35     |
| Right      |            |                    |                      |                    |
| 12 Hz      | 63         | 90                 | 186                  | 176                | 181        | 171    |
| 39 Hz      | 27         | 18                 | 49                   | 32                 | 48         | 53     |
| 88 Hz      | 18         | 24                 | 26                   | 33                 | 25         | 25     |

*Note.* fm = modulation frequency
Table 2.4 shows the mean amplitudes (averaged across subjects) for the different sources at different modulation frequencies (12, 39, and 88 Hz) and for left- and right-ear stimulation. Averaged across modulation frequency, tangentially oriented cortical sources are significantly larger than radially oriented cortical sources ($F = 19.8; \ df = 5, 30; p < .0001$). Tangentially oriented cortical sources are significantly larger at 39 Hz than at 88 or 12 Hz and vertically oriented brainstem sources are larger for 39 Hz than the other modulation frequencies ($F = 4.98; \ df = 10, 60; p < .0001$). The main effect for ear stimulation is nearly significant ($F = 9.45; \ df = 1, 6; p = .022$). However, averaged across modulation frequency and sources, the mean amplitudes for left- and right-ear stimulation are not considerably different from one another (means = 1.69 and 1.45 $\mu$Veff, respectively). There was no evidence that the contralateral cortical responses were larger than the ipsilateral.

Table 2.5 presents the mean estimated latencies of the source waveforms from the individual data. As modulation frequency is decreased from 88 Hz to 12 Hz, latencies become significantly prolonged ($F = 478.4; \ df = 2, 12; p < .0001$). Latencies for the brainstem sources are significantly shorter than the cortical sources ($F = 57.3, \ df = 5, 30; p < .0001$). Analyses of interactions between modulation frequencies and sources reveal no significant differences between ipsilateral and contralateral cortices for any of the modulation frequencies. Furthermore, there are no differences between latencies for tangential and radial components. However, tangentially oriented cortical (both ipsilateral and contralateral) activity is significantly prolonged for 12 Hz compared to that for 39 or 88 Hz ($F = 19.8; \ df = 10, 60; p < .0001$).
Table 2.4

Amplitudes (µVeff) for source waveforms from individual data included in the ANOVA

<table>
<thead>
<tr>
<th>Ear and fm</th>
<th>Brainstem</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vertical</td>
<td>Lateral</td>
<td>Tangential</td>
<td>Radial</td>
<td>Tangential</td>
<td>Radial</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>3.56 ± 2.38</td>
<td>2.03 ± 0.84</td>
<td>1.30 ± 0.93</td>
<td>0.96 ± 0.83</td>
<td>2.36 ± 1.69</td>
<td>1.37 ± 0.73</td>
</tr>
<tr>
<td>39 Hz</td>
<td>4.95 ± 1.71</td>
<td>1.27 ± 1.26</td>
<td>2.32 ± 1.28</td>
<td>0.99 ± 0.54</td>
<td>3.36 ± 1.42</td>
<td>1.40 ± 0.92</td>
</tr>
<tr>
<td>88 Hz</td>
<td>1.77 ± 0.62</td>
<td>0.82 ± 0.38</td>
<td>0.58 ± 0.40</td>
<td>0.31 ± 0.22</td>
<td>0.63 ± 0.37</td>
<td>0.42 ± 0.24</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>1.98 ± 1.66</td>
<td>0.95 ± 0.82</td>
<td>1.41 ± 0.94</td>
<td>0.46 ± 0.22</td>
<td>1.50 ± 1.03</td>
<td>0.89 ± 0.66</td>
</tr>
<tr>
<td>39 Hz</td>
<td>5.22 ± 2.75</td>
<td>0.96 ± 0.41</td>
<td>3.02 ± 1.27</td>
<td>1.21 ± 0.79</td>
<td>2.49 ± 0.90</td>
<td>0.94 ± 0.47</td>
</tr>
<tr>
<td>88 Hz</td>
<td>2.14 ± 0.91</td>
<td>0.71 ± 0.36</td>
<td>0.74 ± 0.24</td>
<td>0.38 ± 0.20</td>
<td>0.57 ± 0.26</td>
<td>0.50 ± 0.41</td>
</tr>
</tbody>
</table>

Note. Mean ± one standard deviation are given for individual data. N = 7.
Table 2.5

Estimated latencies (ms) for source waveforms from individual data included in the ANOVA

<table>
<thead>
<tr>
<th>Ear and fm</th>
<th>Brainstem</th>
<th></th>
<th>Ipsilateral Cortex</th>
<th></th>
<th>Contralateral Cortex</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>Lateral</td>
<td>Tangential</td>
<td>Radial</td>
<td>Tangential</td>
<td>Radial</td>
</tr>
<tr>
<td>Left</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>67 ± 28</td>
<td>57 ± 11</td>
<td>155 ± 24</td>
<td>138 ± 30</td>
<td>146 ± 25</td>
<td>146 ± 32</td>
</tr>
<tr>
<td>39 Hz</td>
<td>22 ± 10</td>
<td>23 ± 7</td>
<td>47 ± 3</td>
<td>51 ± 3</td>
<td>49 ± 3</td>
<td>39 ± 8</td>
</tr>
<tr>
<td>88 Hz</td>
<td>19 ± 2</td>
<td>17 ± 1</td>
<td>29 ± 5</td>
<td>28 ± 4</td>
<td>31 ± 5</td>
<td>32 ± 4</td>
</tr>
<tr>
<td>Right</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 Hz</td>
<td>63 ± 26</td>
<td>68 ± 25</td>
<td>150 ± 32</td>
<td>158 ± 27</td>
<td>160 ± 29</td>
<td>149 ± 28</td>
</tr>
<tr>
<td>39 Hz</td>
<td>25 ± 9</td>
<td>19 ± 6</td>
<td>47 ± 4</td>
<td>47 ± 8</td>
<td>48 ± 3</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>88 Hz</td>
<td>19 ± 1</td>
<td>21 ± 4</td>
<td>31 ± 4</td>
<td>25 ± 0</td>
<td>28 ± 4</td>
<td>33 ± 3</td>
</tr>
</tbody>
</table>

*Note.* Mean ± one standard deviation are given for individual data. N = 7.
Test Data for Source Model Verification

Figure 2.11 and 2.12 show the source activity obtained using the "overall model" to model the responses from the extra data set. Although source amplitudes for these test data are approximately half of those for the original data, they show relatively large brainstem activity for both modulation frequencies of 40 and 80 Hz. For the 40-Hz response (Figure 2.11), tangentially oriented cortical activity (S3 and S4) was much smaller than what was seen in the original 40-Hz data (Figure 2.8). The major brainstem component (S1) has a latency of 15 and 17 ms for the 40- and 80-Hz data, respectively. Tangential cortical sources have latencies of 48 and 31 ms (averaged between hemispheres) for the 40- and 80-Hz responses, respectively. Our source model yields residual variances of 6.0% and 20.3% for fitting the test data for the 40- and 80-Hz responses, respectively.
Figure 2.11. Polar plots from the extra data set for source (1-6) activity to a 40-Hz AM tone (1000 Hz) presented at 75 dB SPL to the right ear (i.e., test data). The magnitude of a vector in a polar plot represents the amplitude of the source activity and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. Mean vector results are designated by thick lines ending with a filled circle, while vectors for each subject are designate by thin lines. The inner diagram of the head shows the location and orientation of the dipole sources. Scale for both axes is $\mu$V eff.
Figure 2.12. Polar plots from the extra data set for source (1-6) activity to an 80-Hz AM tone (1000 Hz) presented at 75 dB SPL to the right ear. The magnitude of a vector in a polar plot represents the amplitude of the source activity and the angle between the vector and horizontal axis (right side), when measured counter-clockwise, represents the onset phase. Mean vector results are designated by thick lines ending with a filled circle, while vectors for each subject are designate by thin lines. The inner diagram of the head shows the location and orientation of the dipole sources. Scale for both axes is μVeff.
Discussion

Sources

The model that we used to fit the scalp-recorded data contains brainstem sources and bilateral cortical sources localized near the supratemporal plane. This model suggests that both the brainstem and the cortex are active during the processing of sinusoidally AM tones. For our responses, the brainstem is consistently active at all rates of stimulation, whereas the cortical sources are relatively more active at slower rates (i.e., 39 Hz). This general idea is consistent with recordings from animals showing that the cortex does not respond at rapid rates as well as the brainstem auditory nuclei (Batra et al., 1989; Creutzfeldt et al., 1980; Fastl, Hesse, Schorer, Urbas, & Muller-Preuss, 1986; Frisina et al., 1990b; Kiren et al., 1994; Rees & Möller, 1983).

Our scalp-recorded data for the 39-Hz response are similar to those reported by Johnson et al. (1988). On the basis of the polarity inversion over the mid-temporal regions, they suggest that the response is partially generated in the auditory cortices on the upper surface of the temporal lobe. They also suggest that thalamic activity and thalamo-cortical circuits might be involved in the response. Our analyses suggest that both the cortex and brainstem are simultaneously active and that the scalp-recorded fields result from overlapping fields from multiple generators. This is similar to the interpretation by Mauer and Döring (1999). The brainstem responses are activated at shorter latencies, but the latency difference between the activation at brainstem and cortex at 39 Hz is roughly equivalent to one cycle of the stimulus and thus, the responses would add together in the overlap.

Spydell, Pattee, and Goldie (1985) reported that the auditory 40-Hz ASSR is reduced in patients with brainstem or thalamic lesions, but not in patients with unilateral lesions of the temporal lobe. The 40-Hz ASSR is usually absent in comatose patients and in patients with brain
death, in keeping with a crucial role for the upper brainstem in generating this response (Firsching et al., 1987). The absence of effects of unilateral temporal lobe lesions may be related to the remaining temporal lobe generating a response that can be recorded from the vertex.

Our data suggest that the 88-Hz ASSRs are mainly generated in the auditory pathways of the brainstem. There are limited data regarding generators for the 80-Hz ASSR. Inferences from intercellular recordings within the cochlear nucleus and inferior colliculus to sinusoidally AM tones (modulated near 80 Hz) predominantly suggest subcortical origins (Batra et al., 1989; Creutzfeldt et al., 1980; Frisina et al., 1990b; Rees & Møller, 1983). Neurons within the cochlear nucleus respond best to modulation rates above 80 Hz (Frisina et al., 1990b; Møller, 1976); those in the inferior colliculus respond best to rates between 20 to 40 Hz (Batra et al., 1989). This implies that possible generation of the 40- and 80-Hz ASSR arise from the inferior colliculus and cochlear nucleus, respectively. Kiren and associates (1994), ruled out the cortex as a possible generator of the 80-Hz ASSR by bilaterally aspirating the auditory cortices in cats. They revealed no change in 80-Hz ASSR phase, thus providing evidence for non-cortical generators. Within this same study, they demonstrated significant phase changes in ASSRs for both ipsilateral and contralateral lesions to the inferior colliculus. The inferior colliculus may play an important role in the generation of 80-Hz ASSRs. Species differences may make it difficult to translate these findings to humans, however our results do confirm that, in humans, the brainstem is the primary source of the scalp-recorded responses to AM tones modulated at fast rates (i.e., 88 Hz).

The responses to the 12-Hz stimulus did not show much energy at the frequency of modulation. Picton, Skinner, Champagne, Kellett, and Maiste (1987) found that the responses at these modulation frequencies are often difficult to distinguish from the background EEG noise. The spectrum of the response shows significant activity at higher harmonics. This is the pattern
that one gets from a repeating transient response. This response peaking at 21 ms, recorded in the time domain (Figure 2.6), is likely triggered by the beginning of the rise in the tonal amplitude in each cycle of the modulation. We used a sinusoidal modulation envelope, thus the onset of the rise in amplitude would occur one-quarter cycle (i.e., 21 ms) before the onset of the recording sweep. This would give the vertex positive wave a peak latency of 42 ms (21 ms plus one-quarter cycle). The wave is, therefore, likely homologous to the Pa wave of the transient response. This occurs with a peak latency of about 30-35 ms for a transient response (Picton, Hillyard, Krausz, & Galambos, 1974). One would estimate the latency to be delayed by the longer rise time of the modulated stimulus (Brinkmann & Scherg, 1979).

Using our "overall model" to model sources for the test data resulted in similar findings to those of the experimental data, except that the residual variance was quite large (20%) for the 80-Hz test data. This could be caused by differences in EEG noise levels for the test data. However, modelling the 40-Hz test data resulted in a good fit (i.e., 6%) of the scalp-recorded waveforms.

**Latency Estimations**

As discussed in Chapter 1, estimating the latency of steady-state responses can be problematic (John & Picton, 2000). One does not know how many cycles have intervened between the stimulus and the response that one is recording. Furthermore, one does not know whether the modulation waveform evokes a similar response waveform or one inverted in polarity and, therefore, 180° different in phase. Our calculations arbitrarily assumed intervening cycles and similar response and stimulus waveforms (i.e., that the peak of the modulation envelope evoked a positive wave at the vertex). Calculating apparent latencies can obviate some of these problems (Regan, 1989). In order to make such calculations, one needs to record
responses at different modulation frequencies within each frequency region and this was not done in the present study.

Although we cannot conclusively determine the latency for our source waveforms our estimated latencies for brainstem and cortical dipoles do agree with the apparent latencies previously reported for scalp-recorded ASSRs (Cohen et al., 1991; Kuwada et al., 1986; Linden et al., 1985; Picton et al., 1987a; Rickards & Clark, 1984; Stapells et al., 1984; Stapells et al., 1987).

A limited number of investigations of ASSR to AM tones modulated at low rates (i.e., <25 Hz) have reported apparent latencies of 75 ms (Stapells et al., 1987) and 80-153 ms (Rickards & Clark, 1984). From our 12-Hz data, averaged across cortical sources, estimated latencies of approximately 150 ms are similar to those previously reported by Rickards and Clark (1984); however, there is considerable variability in onset phase between subjects (see Figure 2.10). Therefore, they cannot be interpreted with much confidence.

For the 1000-Hz AM tone modulated at 39 Hz, our estimated latencies for cortical sources are 48 ms (averaged across cortical sources and ear stimulation). These are approximately 11-23 ms longer than apparent latencies for the scalp-recorded ASSRs to 1000-Hz AM tones reported to be 37 ms (Picton et al., 1987), 31 ms (Kuwada et al., 1986) and 25 ms (Stapells et al., 1984; Cohen et al., 1991). Differences between results may be due to different stimulus and recording parameters, such as alertness of participants or intensity of the ASSR stimuli. As pointed out by Rickards and Clark (1984), ASSR latencies for 40-Hz modulation rates are similar to those of the transient middle-latency responses (Picton et al., 1974). Furthermore, magnetically recorded 40-Hz ASSRs have been shown to have comparable latencies to those for their transient middle-latency counterparts (Hari et al., 1989a; Ross,
Borgmann, Draganova, Roberts, & Pantev, 2000). Our estimated latencies and locations for cortical sources are in agreement to those reported for these magnetically recorded ASSRs. Such similarities may further indicate that ASSRs have a cortical generator comparable to that for transient middle-latency responses (Scherg & von Cramon, 1986).

Although we introduced a one-cycle difference between the brainstem and cortical sources, latency differences between cortical and brainstem sources could have been longer or shorter than 25 ms because brainstem and cortical neurons do not necessarily fire concomitantly. Thus, for the 39-Hz modulation rate, the approximate latency difference of 25 ms between brainstem and cortical sources (see Table 2.5) suggests some type of 40-Hz oscillatory behaviour between cortical and subcortical generators (Ribary et al., 1991).

The latencies for the brainstem sources are more delayed at 12 Hz as compared to 39 and 88 Hz. This may be a result of the longer modulation envelopes of the 12-Hz AM tones as compared to the 39- and 88-Hz AM tones.

For ASSRs evoked by AM tones modulated at 88 Hz, the small-amplitude cortical sources had shorter latencies than for the 39-Hz modulation rate. Nevertheless, they are still near the latencies for the transient middle-latency response. From the present study, the large amplitude vertically oriented brainstem source for the 88-Hz modulation rate has an estimated latency of 19 ms that is comparable to previously reported apparent latencies of the 19 ms (John & Picton, 2000; Lins et al., 1995) and 13 ms (Cohen et al., 1991). Slightly shorter latencies from Cohen et al. (1991) may be a result of different calculation methods used as compared to John and Picton (2000) or Lins et al., (1995).
Because our estimated latencies for the source waveforms correspond well with previously published apparent latencies (see Table 1.1), our results seem to be valid approximations of the true latencies.

Some Caveats

Source modelling for these responses is limited by the amount of data available for each response: two values (real and imaginary) at each electrode location. This approach increases the signal-to-noise ratio of the recordings, because only data that is exactly time locked to the stimulus would be evaluated in the frequency bin of the FFT that equals the modulation frequency. However, it does limit the amount of data that is submitted to the source analysis. The analysis is, therefore, performed using many constraints: e.g., fixing the brainstem sources to the midline and making the cortical sources symmetric. The modelling is thus more confirmatory than analytic. We show that the data could be reasonably interpreted (i.e., low residual variance, at least for grand-mean data) using the combination of brainstem and cortical dipoles. We must note, however, that these dipoles are derived as much from our hypotheses as from our data.

The scalp-recorded waveforms of the 39-Hz responses are about five times larger than the 88-Hz responses. Although the noise levels near 88 Hz are less than those near 39 Hz, this difference is not sufficient to counteract the differences in response amplitude, thus the signal-to-noise ratio was lower for the 88-Hz responses. Because responses recorded with slower rates are larger in wakefulness than in sleep (Dobie & Wilson, 1998; Linden et al., 1985), we decided to have our subjects awake for all recordings. However, one generally records the 80-100 Hz ASSRs from sleeping subjects because this reduces the background noise at these frequencies (mainly from muscle activity) without affecting the response (Cohen et al., 1991). In retrospect,
it might have been better to have recorded the 88-Hz response in sleeping subjects and the 39-Hz responses in waking subjects.

Repeating sound patterns can evoke reflexes in the scalp muscles and these can affect the recordings in unpredictable ways. These reflexes are usually evoked by high-intensity sounds and are usually bilateral. However, they may be asymmetric and variable in location from one subject to another (Picton et al., 1974; Gibson, 1979). These may, therefore, have contributed to our scalp-recorded responses. Recent work has shown that the postauricular muscle reflex may be quite asymmetrical if the eyes look in one direction (Patuzzi & Thomson, 2000). Looking toward the stimulated ear might have increased the size of the postauricular muscle response on the mastoid near the stimulated ear. This may, in some subjects, have accentuated the asymmetry for the 88 Hz response, because this muscle reflex has a negative wave peaking at about 12 ms after the stimulus. This negativity could add with the inverse of the vertex recorded positive wave.

Clinical Significance

Because ASSRs are becoming an alternate means of objectively evaluating hearing thresholds in hard-to-test patients, it is essential for clinicians to know the level of the auditory system being evaluated (Picton, 1990). Based on the results from the present study, as well as others, obtaining ASSRs to AM tones modulated between 70-110 Hz at normal threshold levels would suggest normal auditory function (i.e., hearing sensitivity) up to the level of the brainstem. Dysfunction further along the auditory pathway may not be resolved unless slower rates (e.g., 40-Hz) are used. Slowing the rate of modulation may only be useful, though, in adult patients
because 40-Hz responses are not reliably recorded in infants (Aoyagi et al., 1993; Maurizi et al., 1990; Stapells et al., 1988; Suzuki & Kobayashi, 1984).

There are limited data to date to suggest the effects of auditory dysfunctions such as auditory neuropathy or central auditory lesions on ASSRs (Rance, Beer, Cone-Wesson, et al., 1999). Because it is believed that ASSRs require synchronous activity (see John & Picton, 2000), the desynchronization due to auditory neuropathy (Starr et al., 1996) may disrupt the phase of ASSRs (possibly increasing apparent latencies). Upper brainstem lesions have been reported to produced abnormal 40-Hz ASSRs (Rei & Fu, 1988; Spydell et al., 1985); however, unilateral cortical lesions did not alter the phase of the 40-Hz response (Spydell, et al., 1985). This could be a result of the contralateral (non-lesioned) cortex generating a stable 40-Hz ASSR.

Our results suggest that central abnormalities might be identified by using ASSRs modulated at several different rates. Rates around 80-Hz may provide a means of identifying brainstem abnormalities, whereas rates near 40-Hz may help to locate cortical lesions. However, the effects of lesions within the auditory system require further investigation and such statements are only speculative at this time.

Acknowledgements

This research was supported by a grant from the Canadian Institutes of Health Research. I thank James Knowles and the Baycrest Foundation for additional support. I also thank Terry Picton, David Stapells, Otavio Lins, Patricia Van Roon, and Michael Scherg for their contributions to this research.
Chapter 3: Place Specificity of Multiple Auditory Steady-State Responses
ASSRs (auditory steady-state responses) were elicited by simultaneously presenting multiple AM (amplitude-modulated) tones with carrier frequencies of 500, 1000, 2000, and 4000 Hz and modulation frequencies of 77, 85, 93 and 102 Hz, respectively. Responses were also evoked by separately presenting single 500- or 2000-Hz AM tones. The objectives of this study were (i) to determine the cochlear place-specificity of single and multiple ASSRs using high-pass noise masking and derived-band responses, and (ii) to determine if there were any differences between single- and multiple-stimulus conditions. For all carrier frequencies, derived-band ASSRs for 1-octave-wide derived bands ranging in centre frequency from 0.25 to 8 kHz had maximum amplitudes within a ½-octave of the carrier frequency. For simultaneously presented AM tones of 500, 1000, 2000, and 4000 Hz, bandwidths for the function of derived-band ASSR amplitude by derived-band centre frequency were 476, 737, 1177, and 3039 Hz, respectively. There were no significant differences when compared to bandwidths of 486 and 1371 for ASSRs to single AM tones of 500 or 2000 Hz. Results indicate that ASSRs to moderately-intense stimuli (60 dB SPL) reflect activation of reasonably narrow cochlear regions, regardless of presenting AM tones simultaneously or separately.
Introduction

A continuing goal of evoked potential audiometry is to develop a technique that will quickly and accurately estimate hearing thresholds in individuals who cannot reliably respond behaviourally. Auditory steady-state responses (ASSRs) may theoretically be recorded more quickly and recognized more objectively than the more widely accepted auditory brainstem response (ABR) (Lins, Picton, Boucher et al., 1996; Rance, Dowell, Rickards et al., 1998; Rickards, Tan, Cohen et al., 1994; Chapter 4). In addition, ASSRs may provide a more frequency-specific assessment of hearing than the ABR because the amplitude-modulated (AM) tones used to elicit ASSRs have a narrower acoustic spectrum than the brief tones used to elicit ABRs (Hartmann, 1997).

To establish a frequency-specific threshold in humans, two criteria must be met. The first criterion -- acoustic specificity -- requires the acoustic energy of the stimulus to have minimal spectral splatter and to be centred at the frequency of interest (Stapells, Picton, & Durieux-Smith, 1994; Stapells et al., 1985). Limiting the spectral splatter lessens the activation of responses by frequencies other than the frequency of interest. A classic problem involving reduced acoustic specificity is when a brief high-frequency toneburst is heard by an individual with a severe high-frequency hearing loss and near-normal hearing at lower frequencies. The hearing (and thus the ABR) may be mediated by the lower-frequency energy in a brief high-frequency toneburst (Picton, Ouellette, Hamel, & Smith, 1979). Acoustic specificity is measured by analysing the spectrum of the stimulus. The AM stimuli used to evoke the ASSRs are acoustically very frequency specific. Sinusoidally amplitude-modulated tones have an acoustic spectrum with three peaks of energy, one centred at the carrier frequency and two side bands at the carrier frequency plus/minus the modulation frequency (Hartmann, 1997).
Chapter 3: Place Specificity of ASSRs

The second criterion -- cochlear place specificity -- requires that the cochlear activation occurs at the location on the basilar membrane where continuous pure tones of that frequency have their maximal activation (Starr & Don, 1988). A large spread of activation to other regions of the basilar membrane will make it difficult to determine which cochlear place is producing the response. A classic problem involving reduced place specificity occurs when a low-frequency tone is still heard by an individual with no functioning hair cells beyond the first turn of the cochlea. The response is initiated through regions of the cochlea that respond best to higher frequency tones. Place specificity may be measured by analysing the extent of the cochlea that is activated by the stimulus using high-pass noise (HPN) masking to isolate responding regions of the cochlea (Teas et al., 1962). Presenting HPN masking at different cutoff frequencies together with stimuli may be used to limit the cochlea’s response. Subtractions can then determine “derived responses” that reflect the activation of the cochlear regions between the two cutoff frequencies of the HPN (Don, Eggermont, & Brackmann, 1979; Eggermont, Spoor, & Odenthal, 1976; Nousak & Stapells, 1992; Oates & Stapells, 1997b; Ponton, Don, & Eggermont, 1992; Stapells et al., 1994).

Place specificity of ASSRs to AM tones is still under investigation. Early ASSR studies, using AM tones modulated between 40-50 Hz, revealed good place specificity by estimating behavioural thresholds in hearing-impaired individuals and by using high-pass noise masking techniques (Griffiths & Chambers, 1991; Kuwada et al., 1986). Although these results seemed promising for using ASSRs in a clinical setting, the 40-Hz response was found to be inconsistent and unreliable in infants (Aoyagi et al., 1993; Maurizi et al., 1990; Stapells et al., 1988; Suzuki & Kobayashi, 1984). Modulating AM tones between 70-110 Hz can evoke stable ASSRs in infants and adults, whether sleeping or awake (Aoyagi et al., 1993; Cohen et al., 1991; Levi et al., 1993;
Lins et al., 1995; Rickards et al., 1994). Results from studies comparing behavioural and ASSR thresholds in individuals with different configurations and magnitudes of hearing impairments have shown correlations of .69 to .99 between these measure (Aoyagi et al., 1994b; Lins et al., 1996; Picton et al., 1998; Rance et al., 1998). However, the extent of the place specificity has not been quantified. Thus, it is important that the place specificity of the 70-110 Hz ASSR be assessed by means of masking.

Results from a two-tone masking study by John and colleagues (John et al., 1998) suggest that a 1000-Hz AM tone (60 dB SPL) modulated at 80 Hz activates the basilar membrane within a ½-octave on either side of the stimulus carrier frequency. These data warrant further investigation using other carrier frequencies and noise-masking techniques.

This paper reports results of an investigation of place specificity for the single- and multiple-ASSR methods using derived responses. We obtained amplitudes for ASSRs to single AM tones and to multiple (four) AM tones presented at 60 dB SPL in high-pass filtered noise masking with cutoff frequencies at ½-octave steps (ranging from 0.25 to 16.0 kHz). Amplitudes for 1-octave-wide derived bands for each stimulus frequency were calculated, providing amplitude profiles as a function of derived-band centre frequency. Bandwidths and centre frequencies (CFs) were determined for each derived-band amplitude profile. By examining these measures, we were able to demonstrate the place-specificity for ASSRs and to investigate whether differences exist between ASSRs to single- and multiple-stimulus methods or between different carrier frequencies.
Methods

Subjects

Nine adults (4 females) volunteered for this study. Their ages ranged from 18 to 30 years (mean age 21 years). Normal middle-ear compliance and reflexes were confirmed for all participants at each test session using tympanometry and ipsilateral acoustic-reflex measures. All participants had pure-tone behavioural thresholds of 15 dB HL (ANSI, 1996) or better for octave frequencies between 500 and 4000 Hz.

Stimuli

The stimuli were sinusoidal AM tones that were generated and presented by the MASTER system (John & Picton, 2000b). Parameters for these stimuli are based on those previously reported (Chapter 4; Lins et al., 1996). AM tones were presented to a test ear (chosen randomly between right and left ears for each subject) through ER-3A insert earphones. AM tones had carrier frequencies \( f_c \) of 500, 1000, 2000, and 4000 Hz that were 100% amplitude-modulated at frequencies of 77.148, 84.961, 92.773, and 100.586 Hz, respectively. These modulation frequencies \( f_m \) were used to obtain an integer number of cycles for the \( f_m \) in an EEG recording section of 1.024 seconds.

AM tones were presented to the subject under two conditions: (1) Single: AM tones of 500 or 2000 Hz were presented separately to the test ear; and (2) Multiple: simultaneous presentation of four AM tones (500, 1000, 2000, and 4000 Hz) to the test ear.

The intensity of the AM tones was 60 dB SPL (49-53 dB nHL; Herdman & Stapells, 2001), calibrated for each tone separately. The intensity of the combined stimulus was 66 dB SPL.
High-Pass Noise Masking

All stimuli were combined with ipsilateral HPN. Broadband white noise was generated (Tucker Davis Technologies WG1) and then high-pass filtered (96 dB/octave slope; Wavetek model 852 filter) using cutoff frequencies at ½-octave steps: 0.25, 0.354, 0.5, 0.707, 1.0, 1.41, 2.0, 2.83, 4.0, 5.66, 8.0, 11.31 and 16.0 kHz. The HPN cutoff frequency of 16.0 kHz was used to provide response measures in a "non-masked" condition. This was done to account for possible effects of broadband noise leaking through the filter (Oates & Stapells, 1997a) and to keep the filter in the stimulus/masker setup for all conditions. All ½-octave HPN cutoff frequencies between 0.25 and 16.0 kHz were used in the multiple-stimulus condition. Different HPN cutoff frequencies were used for the single presentations of 500- and 2000-Hz tones. HPN cutoff frequencies were between 0.25 and 4.0 kHz, for the single 500-Hz AM tone presentation, and between 0.5 and 8.0 kHz for the single 2000-Hz AM tone presentation. These cutoff frequencies were chosen to obtain results for at least one octave below and two octaves above the stimulus carrier frequency.

The intensity of the broadband noise was adjusted for each subject to a level just sufficient to mask ASSRs for all carrier frequencies in both conditions. Behavioural masking levels were established first by asking subjects identify AM tones presented for one second while broadband noise was continually delivered ipsilaterally. The intensity of the broadband noise was increased by 2 dB SPL for correct response trials, then decreased by 1 dB SPL for no response trials. The behavioural masking level for each condition was at the noise intensity for which the participant indicated no more than one correct response out of five, with at least three out of five correct responses 1 dB lower. The mean (±1 standard deviation) behavioural masking level for the 60 dB SPL stimuli was 80 ± 2 dB SPL. The highest level of behavioural masking just needed
to mask any stimulus (including the multiple-stimulus condition) was used as a starting intensity for determining the broadband noise level required to mask ASSRs. In order to determine the physiological (ASSR) masking levels for each subject, the broadband noise was increased using 2-dB steps for “response present” recordings and decreased using 1-dB steps for “no-response” recordings. ASSR masking levels were determined as the lowest broadband noise intensity that just sufficiently masked all ASSRs for all conditions. The mean ASSR masking level was $82 \pm 2$ dB SPL.

**Derived-band Auditory Steady-state Responses**

Derived-band ASSRs were obtained by subtracting ASSRs with HPN masking from ASSRs with HPN masking that had a cutoff frequency 1-octave higher (Don et al., 1979; Eggermont, 1976). Subtractions were performed on the time-domain waveforms (rather than frequency spectra) and the results transformed into the frequency domain. This was simpler than performing subtraction in the frequency domain, which would require vector arithmetic to consider both the amplitude and phase of a response. The schematic in Figure 3.1 shows the frequency spectra of the subtraction of ASSR time domain averages. ASSRs to multiple AM tones in 1.0-kHz HPN masking were subtracted from ASSRs to multiple AM tones in 2.0-kHz HPN masking in order to obtain derived-band ASSRs in a derived band centred at 1.0 kHz (i.e., representing contributions from cochlear regions with characteristic frequencies between 1.0 and 2.0 kHz). The figure shows only the amplitude spectra of the responses because these are the most informative, and shows only those portions of the spectra near the response frequencies. The design of the study was fortuitous in that the modulation rate (at which the brain responds) increased as the carrier frequency increased. This is not a necessary requirement but it does allow
the brain response to be lined up in the figure above the acoustic spectra for the AM tones. Note that the frequency axis is different between EEG and acoustic spectra. Obtaining the acoustic response area for the derived-band procedure was done by subtracting the unmasked part of the 1-kHz HPN response from the masked part of the 2-kHz HPN response. The response area is conceptually similar to that obtained with notched noise, with one important exception: the derived-response method shows substantially less of the “upward spread of masking” seen with notched noise (Picton et al., 1979). Note, the derived-band subtraction technique will increase the background residual noise of the ASSR by the square root of 2 compared to the HPN averages. Sufficient averaging was performed to adjust for this factor.

Half-octave-wide derived bands were not utilized because these narrower derived bands result in very low signal-to-noise levels and thus highly variable response amplitudes across subjects. This has previously been shown by Oates and Stapells (1997b). Derived responses were therefore calculated for one-octave-wide bands with centre frequencies separated by \( \frac{1}{2} \)-octave intervals. The derived-band centre frequency was designated as the lower HPN cutoff frequency in the subtraction procedure. There is some controversy concerning the designation of the centre frequency of the derived band (discussed in detail by Oates and Stapells, 1997b). Several earlier studies chose the lower HPN cutoff frequency as the centre frequency based on subtractions of HPN acoustic spectra (Don & Eggermont, 1978; Don et al., 1979; Eggermont & Don, 1980; Nousak & Stapells, 1992; Oates & Stapells, 1997b). Results from a recent within-band masking study in our lab (Stapells and So, 1999) indicate that the centre frequency of the derived band is close to the lower HPN cutoff frequency. This result is due to the finite slope of the filter, and would only be applicable to 1-octave-wide derived bands and similar filter slopes.
Figure 3.1. HPN/DR technique. The upper traces depict the EEG amplitude spectrum for multiple-ASSRs to AM tones of 500, 1000, 2000, and 4000 Hz. Statistically significant (p<.01) ASSRs are designated by arrowheads. These responses correspond to the acoustic line spectra of the AM tones which are presented directly below each EEG spectrum. This may be illustrated in such a manner because the modulation frequency (at which neurons respond) increases with carrier frequency. In addition to the AM tone spectra, HPN masking is depicted as the grey box that has a cutoff frequency at 2 kHz for the upper left graph and 1 kHz for the lower left graph. Subtraction of these two responses yields a derived-band with a center frequency of 1 kHz (lower right acoustic spectra) and the corresponding EEG spectrum for the multiple derived-band ASSR depicted above.
Derived-band ASSR amplitudes were determined for each derived-band centre frequency in each condition to obtain amplitude profiles. Amplitude profiles were used to calculate the bandwidth and the centre frequencies (CFs) for the derived-band ASSRs. Bandwidth at 50% (or -6 dB: BW_{6db}) of the maximal derived-band ASSR was determined for each subject’s amplitude profile and then averaged across subjects. To compare the width of the BW_{6db} across carrier frequency, two types of transformations were used. The first transformation was conversion into an octave scale, given by the following equation:

\[ \text{BW(octaves)} = \log_2 \left( \frac{\text{HF} - \text{LF}}{2} \right) \]

(Equation 1)

where HF is high-frequency edge (in Hz) and LF is the low-frequency edge (in Hz) of the amplitude profile at 50% maximal peak derived-band ASSR amplitude. For example, a bandwidth of 1-octave centred at 1000 Hz would have a low frequency edge equal to 707 Hz and a high-frequency edge of 1414 Hz, giving a linear bandwidth of 707 Hz. The second transformation of the BW_{6db} was conversion into a Q_{6db} measurement, given by:

\[ Q_{6db} = \frac{\text{BW}_{6db}}{\text{carrier frequency}} \]

(Equation 2)

(Hartmann, 1997)

Derived-band centre frequencies were calculated as the geometric mean of the low- and high-frequency edges at 50% maximal amplitude on the amplitude profiles, given by:

\[ \text{Center Frequency} = \sqrt{\text{LF} \times \text{HF}} \]

(Equation 3)

Centre frequencies (CFs) were compared between stimuli of different carrier frequencies as a percent of stimulus carrier frequency or as octaves from the carrier frequency, given by:

\[ \%\text{CF} = 100\% \times \left( \frac{\text{CF}}{\text{Carrier Frequency}} \right) \]

(Equation 4)

\[ \text{CF(octaves)} = \log_2 \left( \frac{\text{CF}}{\text{Carrier Frequency}} \right) \]

(Equation 5)
Procedure

For each subject, this study consisted of three recording sessions, each requiring 2-3 hours, for a total of 6-9 hours. An exception was one participant who completed the study in one overnight session of 7 hours. During behavioural measures, participants relaxed in a comfortable reclining chair in a double-walled sound-attenuated booth. During ASSR measures, participants slept or relaxed in the same recliner and booth. Background acoustic noise levels of the booth, which were below the recommended maximum ambient noise levels for audiometric threshold testing using insert earphones (ANSI S3.11, 1999), were 12, 10, 10 and 12 dB SPL for 1-octave-wide bands centred at 0.5, 1, 2, and 4 kHz, respectively.

Evoked Potentials

ASSR data were collected from recording electrodes at the vertex (Cz) and on the back of the neck, in the mid-sagittal plane just below the hairline. A forehead placement was used for the ground electrode. Inter-electrode impedances were less than 3 kOhms at 10 Hz. The EEG was filtered using a bandpass of 30 to 250 Hz (12 dB/octave), amplified 80,000 times, and AD-converted at a rate of 500 Hz. An EEG recording sweep contained 16 sections of 1.024 seconds each. Sections contaminated by muscle or movement artifacts (i.e., having voltages exceeding ±40 μV) were rejected from averaging. EEG recordings ranged from 6 to 48 sweeps per condition by HPN cutoff frequency, taking approximately 2 to 14 minutes per recording.

For online analysis, Fast Fourier Transform (FFT) converted ASSR average time-domain waveforms into the frequency domain. The FFT resolution was 0.061 Hz, spanning from 0 to 250 Hz. Amplitudes were measured from baseline-to-peak. Relative ASSR amplitudes were calculated as percentages of an individual’s “non-masked” ASSR amplitude (i.e., 16-kHz HPN
masker). These were then averaged across subjects to obtain mean relative amplitudes. Additionally, grand-mean waveforms were obtained by averaging the time-domain waveforms across all subjects and then transforming this grand average into the frequency domain. This procedure takes into account the phases of the individual responses and was used to determine if averaging individuals’ amplitudes was valid. ASSRs were determined as “response present” or “no response” by comparing the amplitude at \( f_m \) and the average amplitude of the background noise in 60 adjacent spectral frequencies on either side of \( f_c \) (Dobie & Wilson, 1996; Lins et al., 1995; Zurek, 1992). A response was considered present when the F-ratio of the signal to noise was significant at p-values < .01. A “no response” required averaging of the EEG until a level of average background noise amplitude was less than 8.5 nanovolts (nV) \( \text{and} p > .20 \). Non-significant response amplitudes were given a value equal to the average background noise amplitude in adjacent frequencies (i.e., residual noise).

**Statistical Analysis**

For statistical analyses, the HPN cutoff frequencies and derived-band centre frequencies were normalized to the stimulus carrier frequency. For example, a HPN cutoff frequency or a derived-band centre frequency of 1 kHz was classified as “plus 1 octave” for the 500-Hz AM tone and “minus 1 octave” for the 2000-Hz AM tone. This allowed for comparisons of results across all carrier frequencies.

Three-way repeated-measures analyses of variance (ANOVA) were used to analyze ASSR or derived-band ASSR relative amplitudes across two conditions (single and multiple), two carrier frequencies (500 and 2000 Hz), and six normalized HPN cutoff frequencies (-1.0, -0.5, 0.0, 0.5, 1.0, and 1.5 octaves) or five normalized derived-band centre frequencies (-1.0, -0.5,
Chapter 3: Place Specificity of ASSRs

0.0, 0.5, and 1.0 octaves). Two-way repeated-measures ANOVAs were used to analyze ASSR or derived-band ASSR relative amplitudes for the multiple-stimulus condition across four carrier frequencies (500, 1000, 2000, and 4000 Hz) and six normalized HPN cutoff frequencies (-1.0, -0.5, 0.0, 0.5, 1.0, and 1.5 octaves) or five normalized derived-band centre frequencies (-1.0, -0.5, 0.0, 0.5, and 1.0 octaves). One-way repeated-measures ANOVAs were used to analyze $Q_{6dB}$ or %CF across four carrier frequencies (500, 1000, 2000, and 4000 Hz) in the multiple-stimulus condition. Two-way repeated-measures ANOVAs were used to analyze $Q_{6dB}$ or %CF across two conditions (single and multiple) and two carrier frequencies (500 and 2000 Hz). Huynh-Feldt epsilon correction factors for degrees of freedom were used when appropriate. Results of these ANOVAs were considered significant if $p < .01$. Newman-Keuls post hoc comparisons were performed only for significant main effects and interactions. Results of the post hoc tests were considered significant if $p < .05$.

Results

Multiple-Stimulus Condition

Figure 3.2 shows the grand-mean amplitude spectra for ASSRs to multiple AM tones in HPN masking and for derived-band ASSRs. When the HPN cutoff frequency changed from 8.0 to 4.0 kHz, ASSRs to 500-, 1000-, 2000-, and 4000-Hz AM tones decreased by 10 (19%), 5 (10%), 8 (22%), and 23 nV (82%), respectively. These attenuations were reflected in the derived band centred at 4.0 kHz, and that there were significant ($p < .01$) derived-band ASSRs with amplitudes of 10, 8, 8, and 23 nV for the 500-, 1000-, 2000-, and 4000-Hz AM tones, respectively. Lowering the HPN cutoff frequency from 4.0 to 2.0 kHz, resulted in a 21 nV (72%) attenuation of the grand-mean ASSRs to the 2000-Hz AM tone modulated at 93 Hz, whereas the
### Table 3.3.1: Cutoff Frequency vs. Derived-band ASSR Center Frequency

<table>
<thead>
<tr>
<th>Cutoff Frequency (kHz)</th>
<th>ASSR with high-pass noise</th>
<th>Derived-band ASSR</th>
<th>Center Frequency (kHz)</th>
</tr>
</thead>
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<tr>
<td>8.0</td>
<td><img src="image" alt="ASSR spectrum" /></td>
<td><img src="image" alt="Derived-band spectrum" /></td>
<td><img src="image" alt="Center frequency" /></td>
</tr>
<tr>
<td>4.0</td>
<td><img src="image" alt="ASSR spectrum" /></td>
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<td><img src="image" alt="Center frequency" /></td>
</tr>
<tr>
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<td><img src="image" alt="ASSR spectrum" /></td>
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<td><img src="image" alt="Center frequency" /></td>
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<tr>
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</tr>
<tr>
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<td><img src="image" alt="ASSR spectrum" /></td>
<td><img src="image" alt="Derived-band spectrum" /></td>
<td><img src="image" alt="Center frequency" /></td>
</tr>
</tbody>
</table>

**Figure 3.2.** Grand mean EEG spectra for the multiple-stimulus condition. On the left are EEG spectra for multiple ASSRs in the presence HPN with cutoff frequencies ranging from 0.5 to 8.0 kHz (designated on the far left). Statistically significant (p<.01) ASSRs are designated by arrowheads. On the right are shown derived-band ASSRs for 1-octave derived bands obtained by sequential subtraction of the ASSR in the presence of HPN.
largest change in grand-mean ASSR amplitude for the other AM tones was 1 nV. The differences in these grand-mean ASSR amplitudes between the two HPN conditions was revealed in the derived band centred at 2.0-kHz, such that the only significant derived-band ASSR was to the 2000-Hz AM tone (21 nV). Lowering of the HPN cutoff frequency from 2.0 to 1.0 kHz resulted in grand-mean ASSR amplitude reductions of 10 (23%), 35 (74%), 6 nV (75%) and 0 nV (0%) for the 500-, 1000-, 2000- and 4000-Hz AM tones. The corresponding derived band centred at 1.0 kHz had significant responses only to 500- and 1000-Hz AM tones (10 and 37 nV, respectively). Similar grand-mean amplitude attenuation and derived-response patterns were seen for other HPN cutoff frequencies, except that there were significant responses in derived bands centred at 4.0 to 8.0 kHz (not shown) for all AM tones.

HPN masking. Figure 3.3 depicts the average of individual ASSR relative amplitudes, plotted as a function of HPN cutoff frequency (in ½-octave steps) obtained in the multiple-stimulus condition. Mean (± standard deviation) non-masked ASSR amplitudes for multiple AM tones of 500, 1000, 2000, and 4000 Hz were 65 ± 33, 68 ± 24, 60 ± 16, and 45 ± 17 nV, respectively. Looking across AM tones, the means of individual ASSR amplitudes for HPN cutoff frequencies greater than the carrier frequency were reduced by 0 to 48% from non-masked ASSRs. For HPN cutoff frequencies at and below the carrier frequency, means of individual amplitudes were attenuated by at least 80% from non-masked ASSR amplitudes and typically fell to the EEG residual noise floor (plotted at 0.15 kHz) within the first ½-octave of the stimulus frequency.

To identify any differential masking effects across carrier frequencies, HPN cutoff frequencies were normalized to the stimulus carrier frequency. Overall, there were no significant differences between carrier frequencies, as shown by ANOVA results in Table 3.1 (left half).
Figure 3.3. Mean and standard deviation (SD; lower panel) of relative amplitudes (% of "non-masked") for ASSRs to 60 dB SPL AM tones of 500, 1000, 2000, and 4000 Hz recorded in HPN masking for the multiple-stimulus condition. Mean estimates of the noise floor (% of "non-masked") with respect to stimulus carrier frequency are designated at the HPN cutoff frequency of 0.150 kHz.
Table 3.1

Comparison of ASSRs to multiple (four) stimuli at different carrier frequencies. Results of 2-way repeated measures ANOVAs for ASSRs in HPN and derived-band ASSR

<table>
<thead>
<tr>
<th>Effect</th>
<th>ASSR in HPN</th>
<th>Derived-band ASSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>F</td>
</tr>
<tr>
<td>Carrier Frequency a</td>
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<td>HPN b or CF c</td>
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<td>40</td>
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<td>15</td>
<td>120</td>
</tr>
<tr>
<td>HPN or CF</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Carrier Frequency: 500, 1000, 2000, and 4000 Hz. b High pass noise cutoff frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, 1.0, and 1.5 octaves from stimulus frequency. c Derived-band center frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, and 1.0 octaves from stimulus frequency. d Huynh-Feldt epsilon correction factor for degrees freedom. e Probability reflects corrected degrees of freedom.

* significant (p < .01)
However, ASSR relative amplitudes in response to 2000-Hz AM tones were significantly lower than responses to 1000- and 4000-Hz AM tones, for cutoff frequencies greater than a ½-octave above the carrier frequency \((\text{post hoc analyses of the significant carrier frequency by HPN interaction shown in Table 3.1)}\). When collapsed across carrier frequency, ASSR relative amplitudes for HPN cutoff frequencies above the carrier frequency were significantly larger than amplitudes for HPN cutoff frequencies at and below the carrier frequency (significant HPN effect, Table 3.1).

\textit{Derived-band ASSR.} Figure 3.4 illustrates the place specificity as determined by the derived-band response technique for the multiple-stimulus ASSR. The maxima of the mean of individual ASSR relative amplitudes for the derived-band ASSR profiles ranged from 55 to 70% of “non-masked” ASSR amplitudes. These maxima occurred in derived-bands at or a ½-octave below the carrier frequency. Mean amplitudes for derived-bands 1-octave below the carrier frequency are not different from the noise. The response amplitudes for derived-bands 1-octave above the carrier frequency are greater than the noise floor for the 500- and 4000-Hz stimuli. Mean amplitude profiles for the 1000- and 2000-Hz stimuli do not show this asymmetry in amplitude profiles.

No significant differences in derived-band ASSR amplitude profiles occurred between carrier frequencies (500 to 4000 Hz) when derived-band centre frequencies were normalized to octaves above and below the carrier frequency (carrier frequency effect and interaction, Table 3.1). A significant main effect of derived-band centre frequency (Table 3.1) was caused by the expected peak-like shape of the amplitude profile. \textit{Post hoc} tests revealed that amplitudes for derived-band centre frequencies at and ½-octave below the carrier frequency were significantly larger than those at other derived-band frequencies.
Figure 3.4. Mean and standard deviation (SD; lower panel) of relative amplitudes (% of “non-masked”) for 1-octave-wide derived-band ASSRs to 60 dB SPL AM tones of 500, 1000, 2000, and 4000 Hz for the multiple-stimulus condition. Mean estimates of the noise floor (% of “non-masked”) with respect to stimulus carrier frequency are designated at the derived-band centre frequency of 0.150 kHz.
Place specificity for the multiple-stimulus condition was evaluated by calculating the \(BW_{6\text{dB}}\), \(\text{CF}\), \(Q_{6\text{dB}}\), and \(%\text{CFs}\) for derived-band ASSR amplitude profiles (Table 3.2). Amplitude profiles for all carrier frequencies had \(BW_{6\text{dB}}\) approximately 1-octave wide and \(\text{CFs}\) within a \(\frac{1}{4}\)-octave of the stimulus frequency. One-way ANOVAs revealed no significant differences between carrier frequencies for \(Q_{6\text{dB}}\) or for \(%\text{CF}\) (\(p=.28\) and \(p=.13\), respectively).

**Single- versus Multiple-Stimulus Condition**

Figure 3.5 shows the grand mean amplitude spectra for ASSRs to single 500-Hz AM tones (modulated at 77 Hz) in HPN masking and for the corresponding derived-band ASSRs. The derived band centred at 2.0 kHz had a 13 nV ASSR to the 500-Hz AM tones, which is more than twice the difference (6nV) in ASSR amplitudes between the two corresponding HPN cutoff frequencies of 2.0 and 4.0 kHz. The derived band centred at 1.0 kHz showed there was a small, yet significant, 9 nV ASSR to the 500-Hz AM tone. This is not consistent with the very small difference (1 nV) between ASSR amplitudes in HPN with cutoff frequencies of 2.0 and 1.0 kHz (27 nV and 26 nV, respectively). The derived band centred at 0.5 kHz had a large 24 nV ASSR to the 500-Hz AM tone, which corresponded to the amplitude reduction when the HPN cutoff frequency was lowered from 1.0 to 0.5 kHz. No change in ASSR amplitude to the 500-Hz AM tone occurred when the HPN cutoff frequency decreased from 0.5 to 0.25 kHz. The corresponding derived band centred at 0.25 kHz showed no significant ASSR to the 500-Hz AM tone.

Figure 3.6 shows the grand mean amplitude spectra for ASSRs to single 2000-Hz AM tones, modulated at 93 Hz, in HPN masking and for the corresponding derived-band ASSRs. The ASSR amplitude to the 2000-Hz AM tone was reduced by 11 nV (50%) when the HPN cutoff
Table 3.2

Measurements for derived-band multiple-stimulus ASSRs (means and standard deviations)

<table>
<thead>
<tr>
<th>Measure</th>
<th>AM tone carrier frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>500 Hz</td>
</tr>
<tr>
<td><strong>BW_{6db} (Hz)</strong></td>
<td></td>
</tr>
<tr>
<td>(Octaves)^a</td>
<td>1.21 ± 0.30</td>
</tr>
<tr>
<td><strong>CF (Hz)</strong></td>
<td>555 ± 253</td>
</tr>
<tr>
<td>(Octaves)^b</td>
<td>0.05 ± 0.53</td>
</tr>
<tr>
<td><strong>Q_{6db}</strong></td>
<td>1.23 ± 0.32</td>
</tr>
<tr>
<td><strong>% CF (%)</strong></td>
<td>111 ± 51</td>
</tr>
</tbody>
</table>

^a Octave scale for BW_{6db}. ^b Octaves from carrier frequency
<table>
<thead>
<tr>
<th>Cutoff Frequency (kHz)</th>
<th>ASSR with high-pass noise</th>
<th>Derived-band ASSR</th>
<th>Center Frequency (kHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td></td>
<td></td>
<td>2.0</td>
</tr>
<tr>
<td>2.0</td>
<td></td>
<td></td>
<td>1.0</td>
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<tr>
<td>1.0</td>
<td></td>
<td></td>
<td>0.50</td>
</tr>
<tr>
<td>0.50</td>
<td></td>
<td></td>
<td>0.25</td>
</tr>
<tr>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Figure 3.5.* Grand mean EEG spectra for the single 500-Hz AM tone condition. On the left are EEG spectra for an ASSR evoked by a 2000-Hz AM tone in the presence HPN with cutoff frequencies ranging from 0.25 to 4.0 kHz (designated on the far left). Statistically significant (p<.01) ASSR are designated by arrowheads. On the right are shown derived-band ASSRs for 1-octave derived bands obtained by sequential subtraction of the ASSR in the presence of HPN.
Figure 3.6. Grand mean EEG spectra for the single 2000-Hz AM tone condition. On the left are EEG spectra for an ASSR evoked by a 2000-Hz AM tone in the presence HPN with cutoff frequencies ranging from 0.5 to 8.0 kHz (designated on the far left). Statistically significant (p<.01) ASSR are designated by arrowheads. On the right are shown derived-band ASSRs for 1-octave derived bands obtained by sequential subtraction of the ASSR in the presence of HPN.
frequency decreased from 8.0 to 4.0 kHz. This amplitude reduction was revealed by the small but significant derived-band ASSR (12 nV) in the derived band centred at 4.0 kHz. Lowering of the HPN cutoff frequency 4.0 to 2.0 kHz resulted in an additional 10 nV (90%) reduction in ASSR amplitude. This reduction was reflected by a significant derived-band ASSR of 11 nV for the derived band centred at 2.0 kHz. Further lowering of the HPN cutoff frequency resulted in no more than a 2 nV change in amplitude and the corresponding derived bands revealed non-significant ASSRs.

**HPN masking.** Figure 3.7 shows a comparison of the mean of individual ASSR relative amplitudes between single- and multiple-stimulus conditions, plotted as a function of HPN cutoff frequency (in ½-octave steps). Mean (± standard deviation) non-masked ASSR amplitudes for single AM tones of 500 and 2000 Hz were 72 ± 56 and 58 ± 20 nV, respectively. This figure shows that the HPN amplitude profiles were similar between single- and multiple-stimulus conditions. However, there are somewhat larger mean amplitudes at some HPN cutoff frequencies for the single-stimulus compared to the multiple-stimulus condition.

Results from a 3-way ANOVA on the HPN data, however, indicated no significant differences for relative ASSR amplitude between single- and multiple-stimulus conditions, as well as no significant interactions involving condition (Table 3.3). There was no significant effect of carrier frequency; however, there was an interaction of carrier frequency by HPN cutoff frequency (Table 3.3). Post hoc analyses revealed that ASSR amplitudes for HPN cutoff frequencies greater than a ½-octave from the carrier frequency were significantly larger for 500-Hz than for 2000-Hz AM tones. As expected, there was a significant effect of HPN cutoff frequency when averaged across conditions and carrier frequencies (Table 3.3). Post hoc analyses
Figure 3.7. Mean and standard deviation (SD; lower panel) of relative amplitudes (% of “non-masked”) for ASSRs to 60 dB SPL AM tones of 500 and 2000 Hz recorded in HPN masking for single- and multiple-stimulus conditions. Mean estimates of the noise floor (% of “non-masked”) with respect to stimulus carrier frequency and condition are designated at the HPN cutoff frequency of 0.150 kHz.
Table 3.3

Comparison of ASSRs for single- and multiple-stimulus conditions. Results of 3-way repeated measures ANOVAs for ASSR in HPN and derived-band ASSR

<table>
<thead>
<tr>
<th>Effect</th>
<th>ASSR in HPN</th>
<th>Derived-band ASSR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>df</td>
<td>F</td>
</tr>
<tr>
<td>Condition</td>
<td>1, 8</td>
<td>1.05</td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>1, 8</td>
<td>2.83</td>
</tr>
<tr>
<td>HPN or CF</td>
<td>5, 40</td>
<td>243.5</td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>1, 8</td>
<td>0.02</td>
</tr>
<tr>
<td>Condition x HPN or CF</td>
<td>5, 40</td>
<td>0.69</td>
</tr>
<tr>
<td>Carrier Frequency x HPN or CF</td>
<td>5, 40</td>
<td>8.87</td>
</tr>
<tr>
<td>Condition x Carrier Frequency x HPN or CF</td>
<td>5, 40</td>
<td>1.31</td>
</tr>
</tbody>
</table>

* Condition: single vs multiple stimuli. b Carrier Frequency: 500 vs 2000 Hz. c High pass noise cutoff frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, 1.0, and 1.5 octaves from stimulus frequency. d Derived-band center frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, and 1.0 octaves from stimulus frequency. e Huynh-Feldt epsilon correction factor for degrees freedom. f Probability reflects corrected degrees of freedom.

* significant (p <.01)
uncovered that ASSR amplitudes for HPN cutoff frequencies a ½-octave and greater than the carrier frequency were larger than those for HPN cutoff frequencies less than and equal to the carrier frequency.

*Derived-band ASSR.* Means of individual ASSR relative amplitudes for 1-octave-wide derived bands, obtained in ½-octave steps, were compared between single- and multiple-stimulus conditions (Figure 3.8). Amplitude profiles for the 500- and 2000-Hz AM tones were similar between conditions, except that the peaks of the amplitude profile for the 500-Hz AM tone were at derived-band centre frequencies of 0.5 kHz and 0.354 kHz for the single- and multiple-stimulus conditions, respectively. Additionally, there were larger relative amplitudes for the single 500-Hz AM tone at derived-band centre frequencies from 0.5 to 2 kHz compared to the multiple-stimulus condition. For the 2000-Hz AM tone, there were larger relative amplitudes at derived-band centre frequencies from 1.41 to 4 kHz for the single-stimulus condition compared to the multiple-stimulus condition. However, despite these apparent differences in means, none reached significance (Table 3.3). Furthermore, there were no significant interactions involving condition. *Post hoc* analyses of the expected significant main effect of derived-band centre frequency revealed that derived-band ASSR relative amplitudes were significantly larger for derived-band centre frequencies at and ½-octave below the carrier frequency compared to derived-band centre frequencies greater than and equal to a ½-octave above, as well as 1-octave below the carrier frequency (p < .025). There was no carrier frequency effect (Table 3.3). However, there was a significant interaction between carrier frequency and derived-band centre frequency. *Post hoc* analyses revealed significantly larger derived-band ASSRs to the 500-Hz
Figure 3.8. Mean and standard deviation (SD; lower panel) of relative amplitudes (% of "non-masked") for 1-octave-wide derived-band ASSRs to 60 dB SPL AM tones of 500 and 2000 Hz for the single- and multiple-stimulus conditions. Mean estimates of the noise floor (% of "non-masked") with respect to stimulus carrier frequency are designated at the derived-band center frequency of 0.150 kHz.
than 2000-Hz AM tones for derived-band centre frequencies equal to and a \( \frac{1}{2} \)-octave greater than their respective carrier frequencies (p < .002).

For the single-stimulus condition, mean values of BW\(_{6dB}\) were approximately 1-octave-wide and mean CFs were generally within a \( \frac{1}{4} \)-octave of the carrier frequency (see Table 3.4). These results were not different from measures of place specificity for the multiple-stimulus condition, as revealed by 2-way repeated-measures ANOVA. There was no significant difference in Q\(_{6dB}\) or %CF between conditions (single versus multiple), between carrier frequency (500 versus 2000 Hz), and no condition by carrier frequency interactions.

**Discussion**

The frequency specificity of an auditory evoked potential, such as the ASSR, can be subdivided into three aspects: acoustic specificity of the stimulus, cochlear place specificity, and frequency specificity of central auditory neurons. These will be discussed below in greater detail regarding the multiple and single ASSRs.

**Acoustic Specificity of the Stimulus**

A stimulus' acoustic specificity is identified as the amount of spectral splatter around the nominal frequency (Durrant, 1983). The amount of spectral splatter of a stimulus is dependent on duration, rise/fall times, gating, transfer function of the transducer, and resonant properties of the acoustic coupler (Burkard, 1984; Durrant, 1983; Harris, 1978; Nuttall, 1981). It is important when estimating a hearing threshold for a specific frequency to limit the amount of spectral splatter so as to limit activation of the cochlear regions which have characteristic frequencies away from the nominal stimulus frequency. If there is a large amount of spectral splatter,
Table 3.4

Measurements for derived-band single- and multiple-stimulus ASSRs (means and standard deviations)

<table>
<thead>
<tr>
<th>Measure</th>
<th>500 Hz</th>
<th>2000 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SINGLE(^a)</td>
<td>MULTIPLE(^b)</td>
</tr>
<tr>
<td>BW(_{6\text{dB}}) (Hz)</td>
<td>486 ± 193</td>
<td>476 ± 220</td>
</tr>
<tr>
<td></td>
<td>1.20 ± 0.35</td>
<td>1.21 ± 0.30</td>
</tr>
<tr>
<td>CF (Hz)</td>
<td>558 ± 128</td>
<td>555 ± 253</td>
</tr>
<tr>
<td></td>
<td>0.13 ± 0.29</td>
<td>0.05 ± 0.53</td>
</tr>
<tr>
<td>Q(_{6\text{dB}})</td>
<td>1.25 ± 0.35</td>
<td>1.23 ± 0.32</td>
</tr>
<tr>
<td>%CF (%)</td>
<td>112 ± 26</td>
<td>111 ± 51</td>
</tr>
</tbody>
</table>

\(^a\) Single-stimulus condition. \(^b\) Multiple-stimulus condition. \(^c\) Octave scale for BW\(_{6\text{dB}}\). \(^d\) Octaves from carrier frequency.
additional frequencies may be used by the auditory system to produce a response. Thus, thresholds for the frequency of interest would be underestimated.

Because the brief tones required for the ABR need to have rapid onsets and short durations, their spectra show considerable spectral splatter (Hartmann, 1997). Brief tones typically used to evoke ABRs thus have side lobes that may activate cochlear regions away from the frequency of interest. When using high-intensity brief tones to elicit ABRs, it may be necessary to add notched-noise masking to limit side-lobe activation of the cochlea (Picton, 1991; Picton, et al., 1979; Stapells & Oates, 1997; Stapells et al., 1994; Stapells, Picton, Durieux-Smith et al., 1990; Stapells et al., 1985). Unlike brief tones, the spectral splatter for long-duration AM tones is confined to three spectral peaks, one peak at the carrier frequency and two side-peaks at a frequency of plus/minus one modulation frequency from the carrier frequency. The spectral spread for AM tones modulated between 77-101 Hz range from 154-202 Hz at -6 dB from peak amplitude and are centred around the carrier frequency. This suggests that AM tones would be preferable over brief tones for use in estimating hearing thresholds. However, acoustic spectral splatter is only one aspect of frequency specificity for the ASSR. Place specificity and neuronal specificity also play important roles when using evoked potentials to estimate hearing thresholds.

*Cochlear Place Specificity*

Due to basilar membrane mechanics, the frequency components of a stimulus may not activate only discrete regions of the cochlea with characteristic frequencies specific to the stimulus' spectral components. Both upward and downward spread of activation exists in the cochlea. There is greater upward spread of excitation whereby low-frequency stimuli of
moderate-to-high intensities can cause appreciable displacement of the basal regions of the cochlea that have characteristic frequencies above the spectral components in the stimulus (Dallos, 1996). Because regions away from the frequency of interest are being activated, this spread of activation may also contribute to an underestimation of hearing thresholds, as would spectral splatter discussed above. Increasing the intensity of the stimulus results in greater spread of activation within the cochlea due both to upward spread of activation and to more-intense acoustic side lobes that exceed the thresholds at these frequencies. Thus, it is important to identify the extent of the spread of activation or place specificity for moderate-to-high intensity stimuli. A caveat to the present study is that only moderately intense (60 dB SPL) tones were used. Presenting higher intensity AM tones would have required higher levels of masking, which would have exceeded our safety limits.

Place specificity of multiple ASSRs. Results from this study show good place specificity for the multiple-ASSR method. Small but significant reductions in relative amplitudes for HPN cutoff frequencies above a ½-octave from the carrier frequency suggest some upward spread of excitation. However, the largest reduction in ASSR relative amplitudes is when the HPN cutoff frequency is lowered from a ½-octave above the carrier frequency to the carrier frequency. This large differential in masking suggests that there is little contribution of cochlear regions with characteristic frequencies greater than ½-octave above the stimulus frequency. These results are analogous to data reported in a HPN study of tone-evoked ABR and MLR (Oates & Stapells, 1997a). Oates and Stapells (1997a) reported significant decreases in ABR wave V-V' and MLR wave Na-Pa when HPN cutoff frequencies were lowered from a ½-octave above (707 or 2830 Hz) the stimulus frequency to the stimulus frequency (500 or 2000 Hz). Thus, HPN data for
ASSRs show similar place specificity to that of the ABRs and MLRs.

In contrast to HPN data, the derived-band response method delineates both high- and low-frequency sides of the cochlear regions that contribute to ASSRs. The present study's derived-band ASSR results reveal reasonably narrow activation of the cochlea for all carrier frequencies. An upward spread of activation can be seen for the 500- and 4000-Hz mean amplitude profiles (Figure 3.4) in that there is a shallower sloping function for the high-frequency sides of the profiles than the steep-sloping function for the low-frequency side. This asymmetry suggests that the stimulus activates regions somewhat more basal to the characteristic frequency as well as regions with characteristic frequencies equal to the stimulus frequency. Regions more than ½-octave apical to the stimulus frequency are less activated by the stimulus compared to regions more than ½-octave basal to the nominal stimulus frequency. Visual observations may suggest that there is a difference in place specificity between stimuli. However, this difference is neither substantial nor significant, as indicated by the lack of interaction between carrier frequency and derived-band ASSRs. Furthermore, mean BW_{6dB} results demonstrate that ASSRs to AM tones predominantly reflect activation of cochlear regions with characteristic frequencies from approximately a ½-octave below to a ½-octave above the carrier frequency, with no difference between carrier frequencies. This good place specificity of ASSRs is in agreement to that reported by John et al. (1998). Using AM tones of various carrier frequencies to mask ASSRs to a 60 dB SPL, 1000-Hz AM tone modulated at 80.9 Hz, John and colleagues reported significant reductions in ASSR amplitudes when the masker AM tone was within a ½-octave of the 1000-Hz AM tone. Reduction in ASSR amplitudes shown by John et al., however, could be due to a demodulation of the response to the AM tone by the addition of a masking tone, instead of the suggested direct masking, as pointed out by Bernstein (1994). That
is, a pure tone presented simultaneously with an AM tone can significantly reduce the amplitude of the energy at the modulation frequency. Results from the present study, which show that there is a significant masking within a $\frac{1}{2}$-octave of the carrier frequency, however, support the claim of direct masking made by John et al. (1998).

For derived bands centred at 5.66 and 8 kHz, response amplitudes are significantly greater than the noise floor for all stimuli (Figure 3.4). This result was not expected for AM tones of 500 to 2000 Hz because the derived-band amplitude profile dips to non-significant ASSR amplitudes (i.e., to the EEG noise floor for 3.54 and 4.0 kHz) and then rises to significant responses in the derived bands centred at 5.66 and 8.0 kHz. This is inconsistent with cochlear travelling wave envelopes, which do not show a relatively large initial amplitude at the cochlear base and then decrease as the wave travels apically until it begins its increase near the characteristic place (Dallos, 1996). One possible explanation for this result is a possible “release from masking” of responses in these high-frequency derived-band regions as the HPN cutoff frequency is increased. Consider that all frequency stimuli appear to produce a small-amplitude response from cochlear regions above 4 kHz (Figure 3.4). Also, that levels of broad-band noise masking used in this study are sufficient to fully mask out all ASSRs, including the ones in derived bands centred at 5.66 and 8 kHz. When the HPN cutoff frequency is increased (i.e., less masking of the cochlea), there may be some removal of suppression of these higher frequency regions. The HPN masking level may then not be sufficient to now mask response from the 8 kHz region and above as compared to the broadband masker. This effect may be explained by assuming that the broadband masking also involves suppression mechanisms in addition to “line-busy” effects (Delgutte, 1996). Stapells et al. (1985) observed similar phenomena in notched-noised masking of click-ABRs. They revealed a waveform earlier in latency than expected when
a notch of 0.5 kHz was introduced in the broadband masker. Considering its latency, this earlier wave was suggested to originate in the basal portion of the cochlea and was a result of a release from masking when the notched noise was introduced. Although this release from masking is a possible explanation for an increase in ASSR amplitudes for derived-bands at and above 4 kHz, other explanations may exist. Further investigation into this issue is needed.

Grand-mean data considers the phase of the derived-band ASSRs by averaging the time-domain waveforms of all subjects and then transforming the average into the frequency domain; in contrast, mean relative derived-band ASSR amplitudes obtained from individuals do not. The results show that the grand-mean amplitudes (Figs 2, 5, and 6) are somewhat smaller than the mean relative derived-band ASSR amplitudes (Fig 4 and 8). This discrepancy is a result of phase variability between subjects because averaging ASSRs that have different phases will result in deconstruction of the time-domain waveform. Although there is some inconsistency in the magnitude of the mean derived-band ASSRs, the amplitude profiles between grand-mean amplitudes and mean amplitudes of individuals are very similar. Both show peak amplitudes at the stimulus frequency and largely diminished responses at an octave away. Thus, calculating the amplitude profiles by averaging individual amplitudes seems to be a valid method for determining measures of place specificity.

Place specificity of single versus multiple ASSR. Another key issue being tested in this study was the possibility of masking within the multiple-stimulus condition. That is, does the presence of the lower frequency stimuli cause masking of the ASSR to higher frequency stimuli? Results of the present study indicate no significant differences in measures of place specificity of the ASSR whether AM tones are presented separately or simultaneously. When compared across
conditions, HPN data for AM tones of 500 and 2000 Hz show the same decrease in ASSR amplitudes as the HPN cutoff frequency decreases from a \(\frac{1}{2}\)-octave above to the carrier frequency. Comparing between conditions, ASSR amplitudes are greater, on average, for the single-stimulus than the multiple-stimulus condition at HPN cutoff frequencies of 1- to 2-octaves (500 Hz) and 1- to 1.5-octaves above the carrier frequency. These difference may suggest that addition of other AM tones can cause attenuation of response amplitudes. However, differences did not reach significance between single- and multiple-stimulus conditions, suggesting that interactions between stimuli, such as masking, do not appear to occur when simultaneously presenting multiple (four) AM tones that have carrier frequencies an octave apart.

Analyses of derived-band ASSR amplitude profiles between conditions further confirms that place specificity is not significantly different between multiple- and single-ASSR methods. Nevertheless, there were differences, though statistically non-significant, between the peak amplitudes of the derived-band profiles. For the 500-Hz AM tone in the multiple-stimulus condition, the peak amplitude is smaller and shifted somewhat more apically than in the single-stimulus condition. Also, there are smaller derived-band relative amplitudes at the carrier frequency and above for the 2000-Hz AM tone in the multiple-stimulus condition, as compared to the single-stimulus condition. These results may support the hypothesis that there are indeed interactions between stimuli that affect the derived-band profiles. These differences, however, are not substantial.

*General comments regarding place specificity.* Comparison of ASSRs in HPN masking between carrier frequencies showed that amplitudes are significantly diminished for 2000-Hz compared to 500-Hz AM tones. This difference can also be seen in ABR and MLR data reported by Oates and Stapells (1997a). This trend is consistent with behavioural results showing that
detection of a 2000-Hz stimulus is more affected by masking noise than detection of a 500-Hz tone (Reed & Bilger, 1973).

For some carrier frequencies, the derived-band amplitude profiles appear to be centred as much as ½ octave below the stimulus carrier frequency. These observations may suggest that it would be more appropriate to designate the derived-band centre frequency as the geometric mean of the two HPN cutoffs, rather than the lower HPN cutoff frequency in the subtraction procedure. However, this would result in shifts of the profiles for the other stimulus frequencies (e.g., 4000 Hz) by ½-octave. Thus, the centre frequency for the 4000-Hz AM tone (multiple-stimulus condition) would be moved to 5918 Hz (i.e., 1918 Hz from the stimulus frequency) instead of 4185 Hz (i.e., 185 Hz from the stimulus frequency). Most empirical data, however, support the use of the lower HPN cutoff frequency as the derived-band centre frequency (Evans & Elberling, 1982; Nousak & Stapells, 1992; Stapells & So, 1999).

Derived-band ASSR amplitude profiles from this study look similar to derived-band profiles for ABRs and MLRs (Oates & Stapells, 1997b). This comparable place specificity indicates that the high acoustic specificity for AM tones does not translate directly into better place specificity of the ASSRs. For instance, although a 1000-Hz AM tone modulated at 85 Hz has an acoustic bandwidth of only 170 Hz, the corresponding ASSR to the 1000-Hz AM tone reflects responses from a band spanning 737 Hz. This may be caused, in part, by the width of the cochlear filter, which provides a lower bound for the place specificity of a stimulus containing only a single frequency component. For example, at 1000 Hz, the cochlear filter bandwidth for a 60 dB SPL stimulus is approximately 200 Hz (Moore, 1987), thus the 1000-Hz AM tone’s three components (carrier frequency and the two sidebands) would result in a cochlear excitation pattern spanning several hundred hertz.
Average $\text{BW}_{6\text{dB}}$ values for the ASSRs, and for ABRs and MLRs to 500- and 2000-Hz tones (Oates & Stapells, 1997b), shown in Table 3.5, reveal similar degrees of place specificity across the different methods. Several of the statistical comparisons between the ABR/MLR and ASSR results show better specificity for the ASSR technique, with p-values between .01 and .10 (see Table 3.5). These differences would be compatible with the increased acoustic specificity of AM tones over the brief tones. Nevertheless, the differences in bandwidths between ABRs/MLRs and ASSRs are small and may not be that meaningful in clinical situations. Further research is needed in patients with steep-sloping hearing losses.

*Frequency Specificity of Central Auditory Neurons*

In addition to acoustic specificity and cochlear place specificity, the tuning curves of the neurons generating the ASSRs should be considered when discussing the frequency specificity of the auditory evoked potentials. First, recall that the cochlea processes sound somewhat like a bank of filters centred at different frequencies. In a normal cochlea responding to single tones, the narrow tuning of one of these cochlear filters is directly translated to the primary auditory neurons which innervate a particular cochlear place. Thus, the tuning curves of the auditory nerve fibers are essentially the same as the activation patterns of the basilar membrane (Pickles, 1988). Some central neurons preserve the specificity of these primary afferent tuning curves because they are mostly activated by fibers coming from the same cochlear place (i.e., from the same cochlear filter). Other neurons are activated by converging afferent fibers that have a range of characteristic frequencies, thereby rendering broader tuning curves (Rhode & Greenberg, 1992). Our results suggest that the central neurons generating ASSRs at modulation frequencies of 75-105 Hz (believed to be within the brainstem; see Chapter 2) have a frequency specificity broader
Chapter 3: Place Specificity of ASSRs

Table 3.5

Measurements for derived-band ASSRs and ABRs/MLRs (means, standard deviations, and sample size) and t-test comparisons between ASSR and ABR/MLR

<table>
<thead>
<tr>
<th>Measure</th>
<th>500 Hz</th>
<th>2000 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASSR(^a)</td>
<td>ABR(^b)</td>
</tr>
<tr>
<td>BW(_{60%}) (Hz)</td>
<td>481 ± 201</td>
<td>648 ± 182</td>
</tr>
<tr>
<td>sample size</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>t-score (^c)</td>
<td>1.99</td>
<td>2.14</td>
</tr>
<tr>
<td>df</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>p-value</td>
<td>.061</td>
<td>.046</td>
</tr>
</tbody>
</table>

Note. df = degrees of freedom calculated for independent samples (Howell, 1997, pp. 192)

\(^a\) Averaged results across single and multiple-stimulus conditions. \(^b\) Results for 53 and 52 dB nHL brief-tones (exact Blackman gated) of 500 and 2000 Hz, respectively (Oates & Stapells 1997b). \(^c\) comparison of means between ASSR-ABR and ASSR-MLR
than that of primary auditory neurons. This suggests that these central neurons integrate
frequency information over a range of cochlear filters surrounding the carrier frequency of the
stimulus. To use the example already cited, the AM tone at 1000 Hz with a modulation frequency
of 85 Hz has an acoustic specificity of 170 Hz (i.e., between the two sidebands, each 85 Hz away
from the carrier frequency). After the cochlear filter, one should obtain an activation pattern in
the primary afferent fibers spanning about 370 Hz -- the 170 Hz acoustic specificity processed
through a cochlear filter with a bandwidth of approximately 200 Hz (Glasberg and Moore, 1987).
Nonetheless, we measured a broader tuning of 737 Hz for central auditory neurons responding to
a 1000-Hz AM tone. This suggests that afferent fibers with different tuning characteristics (i.e.,
different centre frequencies) are converging on the neural generators of ASSRs. Brainstem
neurons having primary-like tuning curves may also contribute to the ASSRs; however,
contributions seem to be more so from neurons with somewhat wider frequency tuning.

Two further issues concerning central auditory specificity need to be considered. First, in
the case of sensorineural hearing loss, the tuning curves of auditory nerve fibers are distorted,
exhibiting diminished tip-to-tail differences and lower low-frequency tail thresholds (e.g., Dallos
& Harris, 1978). These fibres may respond better to frequencies much lower than their
characteristic frequency (or from what might be expected from their place on the basilar
membrane). In addition to changes in auditory nerve fibres, there may be additional effects within
higher levels of the auditory nervous system caused by the plasticity following deafferentation.
This may change the tonotopic organization of central auditory neurons, and shift the balance
between excitation and inhibition within these neuronal populations (e.g., Harrison, Ibrahim, &
Mount, 1998). A derived-response analysis of the ASSRs might, therefore, show different
response profiles in patients with sensorineural hearing loss.
Second, most studies of frequency specificity do not use multiple simultaneous stimuli. Processes such as suppression and lateral inhibition may alter the neuronal specificity of the responses when multiple stimuli occur together. The results of the present study suggest that these processes do not significantly affect the responses. However, this lack of effect may be related to the one-octave separation of the carrier frequencies and the moderate intensity level. At higher intensities, significant interactions between all stimuli may occur (John et al., 1998). Even at moderate intensities, there may be some attenuation of the lower frequency responses by concomitant high-frequency sounds (John et al., 1998; Dolphin & Mountain, 1993). The effects may be quite complex when multiple stimuli are presented to pathological ears. High characteristic-frequency fibers with pathologically broadened tuning may respond preferentially to the lower frequency stimuli. Thus, in a high-frequency hearing loss, lower frequency (i.e., 500 Hz) AM tones may mask the ASSR to high-frequency (i.e., 4000 Hz) stimuli (Picton et al., 1998). There is also the possibility of a larger ASSR to the 500-Hz AM tone because there would be an increased number of neurons responding to the 500-Hz stimulus. However, the different nerve fiber populations responding to the 500-Hz stimulus may have different phases, due to the travelling wave along the basilar membrane, and this may cause destructive addition of their response waveforms. If these central modifications alter ASSRs, they may or may not affect the ability of the multiple-ASSR method to estimate hearing thresholds in sensorineural hearing patients. Further research is warranted (see Chapter 5).
Conclusions

Multiple- and single-ASSR methods exhibit good place specificity. Results indicate that ASSRs reflect activation of narrow regions of the cochlea by AM tones modulated between 70-110 Hz. This specificity is as good as, or slightly better than, that obtained with the transient evoked potentials (ABRs/MLRs) elicited by brief tones. Such differences would not seem to be clinically significant and thus the ASSR technique might not have the advantage of a more frequency-specific estimate of hearing thresholds than ABR or MLR methods. Both are equally good.

Place specificity is not altered when multiple (four) stimuli are presented simultaneously; multiple AM tones are therefore processed similarly within the cochlea as compared to single AM tones. Additionally, there is no evidence for the masking of high-frequency stimuli by low-frequency tones presented at 60 dB SPL and 1-octave apart, in normal-hearing adults. Given that place specificity is not significantly different between multiple- and single-stimulus conditions, it is clear that use of the multiple ASSR technique has a considerable advantage of using multiple stimuli to substantially reduce recording time.
Chapter 4: Thresholds Determined using the Monotic and Dichotic Multiple Auditory Steady-State Response Technique in Normal-Hearing Subjects
Abstract

Auditory steady-state responses (ASSRs) were elicited by presenting single or multiple, 77-105 Hz amplitude-modulated 0.5, 1, 2, and 4 kHz tones to one or both ears. Objectives of this study were to (i) replicate and extend previous multiple ASSR studies in a quiet double-walled sound booth, and (ii) discover differences (if any) between thresholds assessed in monotic and dichotic conditions, which ranged between 15-22 dB SPL. The present study's behavioural and ASSR thresholds are 0-10 dB lower (better) than results of previous monotic studies. Further, there are no significant differences in ASSR thresholds between dichotic and monotic stimulus conditions. Therefore, dichotic multiple AM tone stimulation does not produce a change in the ASSR that affects threshold estimation in a clinically significant manner. Thus, at least for detecting normal hearing, the dichotic multiple ASSR technique is a feasible method for estimating hearing thresholds that would substantially reduce recording time compared to conventional single-stimulus techniques.
Chapter 4: ASSR Thresholds of Normal-Hearing Subjects

*Introduction*

Auditory steady-state responses (ASSRs) evoked by amplitude-modulated (AM) tones at modulation frequencies (fm) between 70 to 110 Hz have recently been shown to be a useful technique in estimating hearing thresholds in individuals with normal or impaired-hearing (Aoyagi et al., 1994a; Aoyagi et al., 1999; Lins et al., 1995; Lins & Picton, 1995; Lins et al., 1996; Picton et al., 1998; Rance et al., 1998; Rance, Rickards, Cohen, De Vidi, & Clark, 1995; Rickards et al., 1994). Earlier ASSR studies used fm between 35 to 55 Hz to assess hearing thresholds (e.g., (Galambos et al., 1981; Griffiths & Chambers, 1991; Kuwada et al., 1986; Milford & Birchall, 1989; Picton, Vajsar, Rodriguez, & Campbell, 1987b; Plourde et al., 1991; Rodriguez et al., 1986; Stapells et al., 1984; Stapells et al., 1987; Szyfter et al., 1984). At these lower modulation rates, however, ASSRs are difficult to obtain and unreliable in estimating thresholds in infants and young children (Aoyagi et al., 1993; Maurizi et al., 1990; Stapells et al., 1988; Suzuki & Kobayashi, 1984). In contrast, ASSR amplitudes to AM tones at fm between 70-110 Hz are stable for infants and adults, whether sleeping or awake (Aoyagi et al., 1993; Cohen et al., 1991; Levi et al., 1993). Estimating behavioural thresholds using ASSRs to AM tones modulated between 70-110 Hz has been shown to be a reliable technique in testing infants and children with normal or impaired-hearing (Aoyagi et al., 1994b; Lins et al., 1996; Picton et al., 1998; Rance et al., 1995).

Presenting single AM tones at a stimulus level above threshold will result in discrete energy at the fm in the evoked potentials recorded in response to these tones (Aoyagi et al., 1994a; Lins et al., 1995; Lins & Picton, 1995; Picton et al., 1987b; Plourde et al., 1991; Rickards & Clark, 1984; Stapells et al., 1984). These evoked potentials may then be analysed in the frequency domain for response detection (Dobie, 1993; Stapells et al., 1984; Stapells et al.,
Studies presenting single AM tones modulated between 70 and 110 Hz, at varying intensities, indicate that ASSR thresholds can be recorded to within 16 and 30 dB of behavioural thresholds for carrier frequencies of 0.5 and 4 kHz, respectively (Aoyagi et al., 1994b; Lins et al., 1995).

In addition to ASSR results to single AM tones, some studies have investigated ASSRs to multiple AM tones presented to one ear (John et al., 1998; Lins & Picton, 1995). These studies indicated that simultaneously presenting four AM tones to one ear produce ASSRs with energy at each fm of each AM tone. Further, ASSR amplitudes to the simultaneous presentation of four AM tones to one ear were not significantly different from amplitudes when each AM tone was presented alone, provided the carrier frequencies are at least an octave apart (John et al., 1998; Lins & Picton, 1995). Lins and colleagues determined ASSR thresholds by simultaneously presenting four AM tones to one ear and reported the difference between ASSR and behavioural thresholds were 9-11 dB for carrier frequencies of 0.5 to 4 kHz (Lins et al., 1996).

ASSRs to a binaural presentation of 1-kHz AM tones, modulated at 91 Hz, are not significantly different from the summation of ASSRs to monaural presentations of a 1-kHz AM tone to the right and left ears, which suggests no binaural interaction exists for 91-Hz ASSRs (Lins et al., 1995), at least at (60 dB SPL) moderate intensities. Studies have also used dichotic stimuli (i.e., two AM tones with the same carrier frequency but different modulation rates) to investigate binaural interactions produced by non-linear processes in the cochlea and brainstem. Differences between behavioural and ASSRs thresholds for dichotic presentation of two (0.5 and 2-kHz) AM tones per ear, with different fm for each ear, reveal no significant differences between the thresholds for monotic versus dichotic presentations (Lins & Picton, 1995).

Investigations of the ASSRs to dichotic presentation of eight AM tones (four AM tones per ear;
60 dB SPL) have demonstrated no significant differences for amplitudes between dichotic multiple and monotic single presentations of the AM tones (Lins & Picton, 1995). There are few threshold data for dichotic stimuli, however, with threshold results available only for two stimuli per ear condition and none for four stimuli per ear. Whether the dichotic multiple (four AM tones per ear) ASSR technique can reliably estimate behavioural thresholds remains in question.

The behavioural and ASSR thresholds reported in the above-mentioned studies of subjects with normal hearing were relatively high (ranging from 17 to 26 dB SPL for behavioural and 29 to 46 dB SPL for ASSR). The elevated thresholds may be due to the presence of high ambient noise levels in the test booth. For example, Lins and colleagues reported octave-band ambient noise levels of 47, 36, 26, and 31 dB SPL for centre frequencies of 0.5, 1, 2, and 4 kHz (Lins et al., 1996).

The intent of the present study was to replicate and extend previous results by obtaining threshold measures in a quieter test environment (octave-band levels of 10-12 dB SPL). Further, this study investigated the sensitivity of the dichotic multiple (four AM tones per ear) ASSR technique for estimating normal behavioural thresholds. Finally, a fundamental goal of this study was to determine if ASSRs differ between various monotic and dichotic stimulus conditions. We obtained thresholds, amplitudes and phases for ASSRs to presentation of monotic single AM tones, monotic multiple (four) AM tones, and dichotic multiple (four stimuli per ear) AM tones.

**Materials & Methods**

**Subjects**

Ten human volunteers (6 females) participated in this study. Their ages ranged from 21 to 42 years (mean age 28 years). All participants had normal middle-ear function and normal
hearing thresholds, as determined by tympanometry and pure-tone behavioural audiometry, respectively. All participants demonstrated normal middle-ear compliance and reflexes, and all had hearing thresholds at or better than 15 dB HL for octave frequencies between 0.5 and 4 kHz.

**Stimulation & Recordings**

Stimulus and recording parameters are based on those previously reported by Lins et al. (1996). Software was provided by John and Picton (John et al., 1998; John & Picton, 2000b).

Air-conducted stimuli were presented to one or both ears through ER-3A insert earphones. The AM stimuli were calibrated in dB SPL (Quest Electronics model 1800 sound level meter; linear mode; Bruel & Kjaer DB0138 2-cc adapter) and attenuated using a clinical audiometer (Interacoustics model AC 40). Stimuli consisted of sine waves at carrier frequencies of 0.5, 1, 2, and 4 kHz that were 100% amplitude-modulated at frequencies of 77.148, 84.961, 92.773, and 100.586 Hz, respectively, for the left ear (LE), and at 81.055, 88.867, 96.680, 105.469 Hz, respectively, for the right ear (RE). These modulation frequencies were employed so that each EEG recording section (see below) would contain an integer number of fm cycles and each recording sweep would contain an integer number of carrier frequency cycles. Three stimulus conditions were used: (1) Monotic Single (MS): AM tones of 0.5, 1, 2, and 4 kHz were separately presented to the test ear; (2) Monotic Multiple (MM): four AM tones were simultaneously presented to the test ear; and (3) Dichotic Multiple (DM): simultaneous presentation of four AM tones to the test ear along with four AM tones to the other ear.

For ASSR data, recording electrodes were placed at the vertex (Cz) and on the back of the neck, just below the hairline in the mid-sagittal plane. A ground electrode was placed on the forehead. Inter-electrode impedances were less than 3 kOhms at 10 Hz. The EEG was amplified
80,000 times and filtered using a bandpass of 5 to 250 Hz (12 dB/octave). An EEG recording sweep lasted for 16.38 seconds, which contained 16 sections of 1.02 seconds each. Artefact rejection limits were set at ± 40 μV to eliminate potentials due to muscle or movement artefacts. Twelve to 48 EEG recording sweeps were averaged for each stimulus intensity (see Procedure).

Procedure

The study involved three recording sessions, each requiring 2-3 hours, for a total of 6-9 hours. Participants relaxed in a comfortable reclining chair in a double-walled sound-attenuated booth during behavioural and ASSR measures. Background acoustic noise levels were 12, 10, 10 and 12 dB SPL for octave bands centred at 0.5, 1, 2, and 4 kHz, respectively. Most participants slept or relaxed quietly. Three participants, however, read a book or watched closed-caption videos.

Thresholds Evaluation

Behavioural thresholds were determined for each single AM tone for each ear. Threshold levels were obtained using a modified Hughson-Westlake procedure (Carhart & Jerger, 1959). A starting intensity of 40 dB SPL was used, then the intensity was decreased using 10-dB steps for correct response trials, and increased using 5-dB steps for no-response trials. Behavioural thresholds were the lowest intensities for which the participant indicated three correct responses out of five stimulus presentations. Subsequently, one ear was randomly chosen as the “test” ear for ASSR threshold assessment.

ASSR thresholds were also determined using a 10-dB down and 5-dB up search method starting at 30 dB SPL. If, after averaging 12 sweeps, the amplitude at the fm of the AM tone was
indicated to be statistically significant from the background noise (see section: Evoked Potential Analyses), then the stimulus intensity was decreased in 10-dB steps until a no-response was obtained. A no-response, however, could only be determined after a total of 48 sweeps had been collected and averaged together. Ascending steps of 5-dB followed until a response was present. ASSR threshold for a specific carrier frequency was the lowest intensity where a response was detected at the fm and a no-response was obtained at 5 dB below that intensity. False-positive responses were classified as statistically significant responses occurring at levels where a non-significant response was present at both 5 and 10 dB higher. Three ASSRs (of 120 total) were classified as false positive responses.

*Evoked Potential Analyses*

ASSRs were analysed in the frequency domain by Fast Fourier Transform (FFT) of the average time-domain waveforms. The FFT resolution was 0.083 Hz, spanning from 0 to 250 Hz. Amplitudes reported were measured from baseline-to-peak. Cosine onset phases were measured from the FFT in the range of -90 to 270 degrees. Onset phases were converted to phase delays for easier interpretation (i.e., phase delays increase as intensity decreases). First, 90 degrees was added to the onset phase measurements to obtain values between 0 and 360 degrees. Onset phases were then “unwrapped” by adding one cycle (i.e., 360 degrees) to compensate for the circularity of phase measurements. These values were then subtracted from 720 degrees to determine phase delay values (John & Picton, 2000). Phase data were only analysed for those results showing a significant response.

ASSRs were assessed as “present” or “no-response” by an analysis of variance (i.e., the “F-technique”) of the FFT (Dobie, 1993; Dobie & Wilson, 1996; Picton et al., 1987b; Valdes et
This method determines if a response at the fm of an AM tone is significantly different from the background noise in adjacent frequencies. An F-ratio is evaluated between the amplitude of the responses at the fm and an average noise value calculated by averaging the amplitudes of 120 surrounding frequency bins -- 60 bins above and 60 bins below the fm (extending 4.98 Hz on either side of the fm). When four or eight AM tones were presented, the noise value was calculated by averaging the amplitudes of 120 frequency bins centred around the frequency which was the average of the fm of the AM tones. Frequency bins at the fm of AM tones were excluded in the 120 bins used to estimate the noise level. A response was considered present when the F-ratio of the signal to noise was significant at the p< .05 level.

Recording time for threshold evaluation for each condition was estimated by the number of trials needed to obtain thresholds (3.2 minutes per trial).

Statistical comparison of behavioural and ASSR thresholds were assessed using repeated-measures analyses of variance (ANOVA). Greenhouse-Geisser epsilon correction factors for degrees of freedom correction were used when appropriate (Greenhouse & Geisser, 1959). Results of these ANOVAs were considered significant if p< .01. Newman-Keuls post hoc comparisons were performed only for significant main effects and interactions. Results of the post hoc tests were considered significant if p<.05. To test clinical equivalence between conditions for difference scores, confidence intervals of 95% were compared to a practical limit (Altman & Bland, 1983; Hauck & Anderson, 1986). Equivalence between conditions (MS, MM, and DM) was accepted if the upper limit of the confidence interval for difference scores between conditions, averaged across frequency, was within the clinically significant limit of 10 dB.
Chapter 4: ASSR Thresholds of Normal-Hearing Subjects

Results

Thresholds

Figure 4.1 illustrates one participant’s ASSR amplitude spectra for threshold determination in the MS, MM, and DM conditions. Significant ASSRs, designated by the arrows heads, indicate that this participant’s ASSR thresholds for the 4-kHz AM tone modulated at 105 Hz are 15, 20, and 10 dB SPL for condition MS, MM, and DM, respectively. These 4-kHz ASSR thresholds are within 5 dB of the participant’s behavioural thresholds for these stimuli, with the exception of the 4-kHz AM tone in condition MM (which was within 10 dB). Similar results are seen for the other fm.

As shown in Table 4.1, average behavioural thresholds, across all subjects, for condition MS are between 7-11 dB SPL for carrier frequencies of 0.5 to 4 kHz. Mean ASSR thresholds range from 15-25 dB SPL in conditions MS, MM, and DM for carrier frequencies of 0.5 to 4 kHz. Ninety percent of the 120 ASSR thresholds were 30 dB SPL or better. The behavioural thresholds are significantly lower than the ASSR thresholds (F=20.8; df=3,27; ε=0.747; p<.0001). There are no significant differences, however, for ASSR thresholds between the three ASSR stimulus conditions or the four carrier frequencies.

Table 4.1 also shows the difference scores between ASSR and behavioural thresholds. These difference scores demonstrate that the ASSR thresholds, on average, are within 5-15 dB of behavioural thresholds. Eighty-seven percent of the 120 thresholds were within 20 dB of behavioural thresholds. There are no significant differences for difference scores between ASSR stimulus conditions or carrier frequencies.
Figure 4.1. ASSRs for the monotonic-single (MS), monotonic-multiple (MM) and dichotic-multiple (DM) conditions for a single subject. Arrows indicate that responses at the modulation frequency of the AM tones are significantly different from the background noise. For condition MS, only the FFT for responses to a 4-kHz AM tone modulated at 105.469 Hz is shown. For condition MM and DM, closed arrowheads indicate significant responses to 0.5, 1, 2, and 4 kHz AM tones modulated at 81.055, 88.867, 96.680, and 105.469 Hz, respectively. Open arrowheads indicate significant responses to 0.5, 1, 2, and 4 kHz AM tones modulated at 11.148, 84.961, 92.773, and 100.586 Hz, respectively. Stimulus intensities (dB SPL) are indicated on the left. ASSRs are significant down to 15 dB SPL for the 4 kHz AM tones in condition MS. For condition MM, ASSRs were evident at intensities of 10 dB SPL for 0.5 kHz, 15 dB SPL for 1 and 2 kHz, and 20 dB SPL for 4 kHz. For condition DM, responses are significant at intensities of 10 dB SPL for 0.5, 1, and 4 kHz, and 15 dB SPL for 2 kHz.
Table 4.1

Behavioural and ASSR Thresholds and Difference Scores for Subjects with Normal Hearing

<table>
<thead>
<tr>
<th>fc</th>
<th>Behav</th>
<th>ASSR</th>
<th>Difference scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>MS</td>
<td>MM</td>
</tr>
<tr>
<td>0.5</td>
<td>11 ± 3</td>
<td>18 ± 12</td>
<td>22 ± 12</td>
</tr>
<tr>
<td>1</td>
<td>9 ± 4</td>
<td>19 ± 13</td>
<td>19 ± 10</td>
</tr>
<tr>
<td>2</td>
<td>8 ± 4</td>
<td>20 ± 9</td>
<td>18 ± 9</td>
</tr>
<tr>
<td>4</td>
<td>7 ± 5</td>
<td>20 ± 7</td>
<td>20 ± 11</td>
</tr>
</tbody>
</table>

*Note.* fc = carrier frequency. Behav = behavioural thresholds. Difference scores (dB) = ASSR threshold (dB SPL) - behavioural threshold (dB SPL). MS = monotic-single condition. MM = monotic-multiple condition. DM: dichotic-multiple condition. Mean ± one standard deviation are given.
Equivalence testing indicates that the upper limits of the 95% confidence intervals (CI) for difference scores between conditions, averaged over carrier frequency, are within the 10-dB clinical limit (marginal means and standard deviations for MS = 10.5 ± 10.5, MM = 11.1 ± 10.0 and DM 11.1 ± 9.0; CI\textsubscript{MS-MM} = 7.8, CI\textsubscript{MS-DM} = 7.4, CI\textsubscript{MM-DM} = 7.8). The small differences between conditions MS, MM and DM are thus neither statistically significant nor clinically significant.

**ASSR Amplitude and Phase**

The adaptive nature of the threshold search resulted in not all conditions and frequencies having significant responses. In order to obtain amplitude and phase data for all participants at both stimulus intensities of 60 and 30 dB SPL, 13 amplitudes were used where a significant response was not present at 30 dB SPL and 13 phases were predicted for 30 dB SPL from neighbouring intensities of an individual’s phase-intensity function.

The left side of Figure 4.2 ("A") shows mean ASSR amplitudes for carrier frequencies of 0.5 to 4 kHz presented at 60 and 30 dB SPL. Analysis of variance of the ASSR amplitudes indicates no significant differences in amplitude between the different stimulus conditions or carrier frequencies. However, there is a significant main effect for stimulus intensity, such that ASSR amplitudes are significantly larger to 60 dB SPL compared to 30 dB SPL stimuli (F=190.0, df=1,9, p<.000001).

The right side of Figure 4.2 ("B") presents the mean phase delays of the ASSRs to AM tones presented at 30 and 60 dB SPL. There are no significant phase differences between the stimulus conditions or carrier frequencies. Phase delays, however, are significantly smaller for ASSRs to 60 compared to 30 dB SPL (F=237.6; df=1,9; p<.000001).
Figure 4.2. (A) ASSR amplitudes for carrier frequencies of 0.5, 1, 2, and 4 kHz in condition MS, MM, and DM at intensities of 60 and 30 dB SPL. (B) ASSR phases for carrier frequencies of 0.5, 1, 2, and 4 kHz in condition MS, MM, and DM at intensities of 60 and 30 dB SPL. Error bars represent one standard deviation.
ASSR Recording Time

For condition MS, the average (± standard deviation) recording time is 164 ± 22 minutes, whereas the recording times for conditions MM and DM are 86 ± 16 and 83 ± 19 minutes, respectively.

Discussion

ASSR Thresholds

The ASSR thresholds obtained in the present study are similar to, or better than, those previously reported in the literature, with average ASSR thresholds for monotic single AM tones (0.5 to 4 kHz) in normal-hearing adults ranging from 18-20 dB SPL. For example, Lins and colleagues reported ASSR thresholds for 1-kHz AM tones to be 18.5 dB SPL (value corrected to insert earphones; Lins et al., 1995). Picton et al. reported ASSR thresholds of 27 and 29 dB SPL (corrected for insert earphones) for 1- and 4-kHz AM tones, respectively (Picton et al., 1998). In the present study, ASSR thresholds for monotic-multiple AM tones (0.5 to 4 kHz) ranged from 18 to 22 dB SPL. Other reports have shown ASSR thresholds for this stimulus condition to range from 21.5 to 31 dB SPL (corrected for insert earphones; Lins et al., 1996; Picton et al., 1998). Finally, threshold results for the dichotic condition (four AM tones per ear) in the present study range between 15 to 25 dB SPL. These thresholds are 10 dB lower (better) than those reported by Lins and Picton (1995) for simultaneous presentation of two AM tones to both ears. Overall, the present study’s results suggest ASSR threshold sensitivity is equal to, or in most cases, 5 to 10 dB better than previously reported data. This improvement is most likely due to the lower ambient acoustic noise levels of the test environment used in the current study. Our results also
show that 89% of the ASSR thresholds (107 of 120) are 30 dB SPL or better, indicating good threshold sensitivity for the ASSR technique.

The mean difference scores between behavioural and ASSR thresholds range from 7 to 14 dB SPL for monotic-single and monotic-multiple AM tones. These scores are very close to those previously reported, which range from 8 to 17.5 dB (Lins & Picton, 1995; Lins et al., 1995; Lins et al., 1996), with the exception of the difference scores reported by Aoyagi and associates (Aoyagi et al., 1994) of 28.5 and 30 dB for 1 and 2-kHz AM tones, respectively. Also, some previous studies show somewhat higher differences scores for 500-Hz stimuli compared to other carrier frequencies. The present study shows elevated thresholds for 500-Hz compared to 1000- and 2000-Hz tones, albeit these differences are not significant. The present study’s difference scores for the dichotic-multiple AM tones range between 8 and 15 dB, similar to those reported by Lins and Picton (1995). Importantly, ASSRs estimated behavioural thresholds within 20 dB for 87% of thresholds obtained (104 of 120). Thus, our results confirm that ASSRs can reliably assess behavioural thresholds in normal-hearing adults for both monotic and dichotic stimulus conditions.

An important objective of this study was to determine if an interaction between responses to AM tones simultaneously presented to both ears would significantly alter ASSR thresholds. We found no significant differences for ASSR thresholds between conditions where single AM tones were presented to one ear, multiple (four) AM tones were presented to one ear, and multiple (four per ear) AM tones were presented to both ears. The difference scores may also be considered clinically equivalent (i.e., within 10 dB) between condition MS, MM, and DM. Thus, presenting multiple stimuli dichotically does not affect ASSR thresholds in a clinically significant manner.
ASSR Amplitudes and Phases

John and colleagues presented two or four AM tones at 75 dB SPL, which produced a significant attenuation of ASSR amplitudes to low-frequency AM tones (i.e., 0.5 kHz) by the addition of higher-frequency AM tones (John et al., 1998). At 60 dB SPL and below, however, they reported ASSRs amplitudes for multiple-stimulus conditions were not significantly different from the single-stimulus condition (John et al., 1998; Lins & Picton, 1995). The present study's results confirm this, indicating ASSR amplitudes are not significantly different between conditions MS and MM, at least for 60 dB SPL and lower. Also, simultaneously presenting AM tones (four per ear) to both ears does not produce any significant differences in ASSR amplitudes compared to presenting AM tones (single or multiple) to one ear. Similar to the amplitude results, the present study's phase delay data show no effect of binaural (dichotic) presentation, at least for 60 dB SPL and lower (Figure 4.2).

ASSR Recording Time

In the present study, the average time to obtain thresholds for four carrier frequencies one at a time (condition MS) is 164 minutes, almost twice that required to obtain the same number of thresholds for the multiple-stimulus conditions (MM: 86 minutes, DM: 83 minutes). It should be noted, however, that most threshold searches for condition DM also allowed for identification of thresholds for the “non-test” ear (except for 6 of 40). Given this, eight ASSR thresholds can be recorded in the same amount of time as four thresholds. Condition DM is, therefore, up to four times more efficient for threshold evaluation than condition MS.

Recording times for condition MM and DM have the potential to be up to four and eight times more efficient, respectively, than for condition MS. The present study's recording times are
half their theoretical efficiency, likely due to all carrier frequencies having the same intensity for each trial. Changing intensity levels for each carrier frequency independently and adaptively for each trial would allow for fast bracketing of a single carrier frequency’s threshold, resulting in a more efficient threshold search. The combination of AM tones at different intensities, however, could result in masking of the response to one tone by another tone due to upward spread of excitation. That is, lower frequency AM tones may affect thresholds for higher frequency stimuli. Such findings have already been reported for the multiple ASSR technique (Picton et al., 1998). Research into the frequency specificity of ASSRs to multiple AM tones is, therefore, required.

Conclusions

ASSR amplitudes, phase delays, and thresholds are not different between simultaneously presenting multiple AM tones to both ears compared to single or multiple AM tones presented to just one ear. Thus, the dichotic-multiple ASSR technique allows for substantially reduced recording time for assessment of hearing thresholds, at least for normal-hearing adult subjects. The principal clinical application for this technique, however, is in testing infants, especially those with hearing loss. Preliminary work has shown promising results for the monotic-multiple ASSR technique in adolescents with hearing loss (Lins et al., 1996), children with hearing aids (Picton et al., 1998), as well as infants with normal birth histories (Lins et al., 1996). Research is currently underway in several labs into the ability of the dichotic-multiple ASSR technique to estimate hearing thresholds in the paediatric population.
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Abstract

Four issues were examined in this study of subjects with sensorineural hearing impairments: (1) the utility of multiple auditory steady-state responses (ASSRs) to monotic presentation of multiple amplitude-modulated (between 77-105 Hz) tones (500, 1000, 2000 and 4000 Hz) in estimating the degree and configuration of behavioural audiograms; (2) the place specificity of the multiple-ASSR method; (3) the possible masking effects when presenting multiple stimuli at the same intensity; and (4) the amount of time needed to record four thresholds using the multiple-ASSR method. (1) Results show that, on average, multiple-ASSR thresholds were 14 ± 13, 8 ± 9, 10 ± 10 and 3 ± 10 dB above behavioural thresholds for 500, 1000, 2000 and 4000 Hz, respectively. Behavioural and multiple-ASSR thresholds for 1000, 2000, and 4000 Hz were significantly correlated (r= .75 to .89). Within subjects, correlations and standardized difference vectors revealed no significant difference between behavioural or multiple-ASSR measures of the audiogram configuration. (2) In subjects with steep-sloping (≥30 dB/octave) hearing losses, multiple-ASSR thresholds did not underestimate behavioural thresholds. This suggests that spread of cochlear activation away from the frequency of interest is not significant. (3) For subjects with moderate-to-severe hearing loss, subtracting behavioural thresholds from single- and multiple-ASSR thresholds resulted in differences scores of 5 ± 12 and 6 ± 13 dB, respectively. Thus, there was no significant difference in thresholds when presenting AM tones separately or simultaneously. This suggests that the inclusion of lower frequency stimuli in the multiple-stimulus condition does not mask ASSRs to the higher frequency stimuli. (4) Recording times to obtain thresholds for four frequencies using the multiple-ASSR technique was 47 minutes, on average. Together, these results reveal that the multiple-ASSR method provides good estimates of the degree and configuration of hearing in individuals with mild-to-severe sensorineural hearing impairments and shallow- to steep-sloping audiograms, within a reasonable period of time.
Introduction

Several studies have found that ASSRs to single AM tones accurately estimate hearing thresholds in individuals with sensorineural hearing impairments, with differences between behavioural and ASSR thresholds ranging from 4 to 8 dB (Aoyagi et al., 1993; Rance et al., 1998; Rance et al., 1995). Rance and colleagues (1998) report correlations of .96 to .99 between ASSR and behavioural thresholds for AM tones between 500 and 4000 Hz. Aoyagi et al. (1999) report a correlation of .88 for a 1000-Hz AM tone modulated at 80 Hz. These results indicate that the single-ASSR method can accurately estimate hearing loss. However, a key advantage of using ASSRs to evaluate hearing thresholds is that ASSRs may be evoked by simultaneously presenting at least four separate AM tones per ear (John et al., 1998; Lins et al., 1995; Lins et al., 1996; Chapter 4).

A few studies have investigated the multiple-ASSR method's ability to estimate hearing thresholds of subjects with hearing impairments. Picton and associates, in two separate studies, tested young children with hearing impairments (range 20-75 dB HL) and showed that multiple-ASSR thresholds are within 9 to 17 dB of behavioural thresholds (Lins et al., 1996; Picton et al., 1998). Correlations between behavioural and multiple-ASSR thresholds range from .54 to .91 for octave frequencies between 0.5 and 4.0 kHz (Lins et al., 1996; Picton et al., 1998). However, these studies' results were obtained in high ambient noise environments, which elevated their absolute threshold estimations. Behavioural thresholds in the study by Lins et al. (1996), also show a restriction of range and clustering around the mean. Because there were only 4 subjects with hearing losses greater than 65 dB HL and none greater than 80 dB HL, it may be misleading to conclude that the multiple-ASSR method is useful for estimating hearing thresholds in patients with severe-to-profound hearing losses. Additionally, a postulated masking effect (Picton et al.,...
1998) of low-frequency (e.g., 500 Hz) AM tones masking ASSRs to high frequency (e.g., 4000 Hz) AM tones when simultaneously presenting multiple stimuli may be greater for cases of severe-to-profound sensorineural hearing loss. Therefore, the moderate-to-good correlations between behavioural and multiple-ASSRs thresholds may not be consistent for greater degrees of hearing impairments. Thus, it was an objective of the current study to replicate and extend previous results by obtaining, in a quiet environment, multiple- and single-ASSR thresholds from a sample of subjects with a wide range of hearing impairments (from 20 to 90 dB HL).

Another objective of the present study was to determine whether or not inclusion of low-frequency stimuli (e.g, 500-Hz) in the multiple-ASSR method will mask ASSRs to high-frequency AM tones (e.g., 4000 Hz). For example, if multiple-ASSR thresholds for 4000 Hz are significantly higher compared to those for the single-ASSR method, then it may be assumed that in the multiple-stimulus condition the lower frequency stimuli are masking/altering the response to the 4 kHz stimulus (Picton et al., 1998). Picton and colleagues (Dimitrijevic et al., in press; Picton et al., 1998) report results from a few subjects with hearing impairments that suggest multiple-ASSRs underestimate behavioural thresholds, as compared to the single-ASSR method. The current study provides more conclusive data by obtaining results from a greater number of subjects.

To date, only one-study has objectively assessed how well multiple-ASSR thresholds match the configuration of behavioural audiograms (Perez-Abalo et al., 2001). Therefore, further evaluation of this is being conducted in the present study and will add to the limited data previously reported.

There is little information regarding multiple-ASSR threshold estimates in subjects with steep-sloping hearing losses. Subjects' audiograms in the study by Perez-Abalo et al. (2001) have
relatively flat configurations and there is little information regarding the audiogram configurations for the studies by Picton and colleagues. The present study objectively evaluates the multiple-ASSR method for its threshold sensitivity and ability to match audiogram configurations of subjects with steep-sloping, as well as with flat/shallow-sloping hearing impairments.

ASSRs to single and multiple AM tones (500 to 4000 Hz) have been shown to primarily reflect activation of approximately 1-octave-wide regions centred within ¼-octave of the carrier frequency, at least in subjects with normal-hearing (see Chapter 3). If a subject has a steep-sloping hearing loss, adjacent cochlear regions that have lower thresholds may respond and cause an underestimation of the threshold at the frequency of interest. Underestimation of behavioural thresholds may occur when using brief-tone ABRs (without notched-noise masking) to estimate hearing thresholds in individuals with steep-sloping hearing losses (Picton et al., 1979; Stapells, Picton, & Durieux-Smith, 1994; Stapells et al., 1985). Therefore, it was an objective of the present study to determine if this occurs when multiple-ASSRs are used to evaluate thresholds in such individuals.

The current study investigates the ASSR thresholds to single and multiple AM tones in order to determine the threshold sensitivity as well as the ability of the multiple-ASSRs method to match the configuration of the behavioural audiogram. Additionally, this paper investigates ASSR thresholds in individual’s with steep-sloping hearing loss to evaluate the place specificity of the multiple-ASSR technique. Finally, ASSR thresholds are compared between single- and multiple-stimulus conditions to determine if there is any masking due to inclusion of lower frequency AM tones.
Methods

Subjects

Thirty-one adults (27 male) with sensorineural hearing impairments participated in this study. Their ages ranged from 25 to 94 years (mean = 63 years). Participants were selected based on their behavioural pure-tone audiograms in order to fill a wide range of hearing impairments across four frequencies (0.5, 1, 2, and 4 kHz). Twenty-six participants were tested in the sound-attenuated booth at the Worker’s Compensation Board of British Columbia. Sensorineural hearing impairments for these 26 individuals were confirmed by behavioural bone-conducted thresholds being within 10 dB of air-conducted thresholds. Behavioural (air- and bone-conduction) and ASSR thresholds were evaluated on the same day. Five other participants were tested in the sound-attenuated booth at the Human Auditory Physiology Laboratory (University of British Columbia). Air-conduction thresholds for these five participants were obtained on the same day as ASSR testing; each subject had confirmed sensorineural hearing impairment by previous audiological assessment at other clinics. Acoustic immittance measures confirmed normal middle-ear function for all participants on the day(s) of testing. A participant’s audiological results were obtained and used for analysis only after consent was obtained.

For a recording session to be within a practical period of time, only one ear from each subject was tested. Selecting the test ear was based on three selection criteria. First, because of their infrequent occurrence, impairments sloping towards the low frequencies (i.e., “reverse” slope) were chosen over losses sloping towards the high frequencies (N=1). Second, the ear which had a greater sloping impairment between octave frequencies was selected next (N=27). Third, the ear with a greater impairment was selected (N=3). Pure-tone behavioural thresholds for all subjects are presented in the Results section (see Figure 5.2).
ASSR Stimuli

Stimulus and recording parameters were based on those previously reported by Lins et al., (1996).

Air-conducted stimuli were presented through Eartone 3A insert earphones. Stimuli consisted of sine waves at carrier frequencies of 500, 1000, 2000, and 4000 Hz that were 100% amplitude-modulated (AM) at frequencies of 77.148, 84.961, 92.773, and 100.586 Hz, respectively. To obtain the desired presentation level, AM stimuli were presented through a clinical audiometer. Stimulus intensities were calibrated in dB SPL for each carrier frequency (Quest Electronics model 1800 sound level meter; linear mode; Bruel & Kjaer DB0138 2-cc adapter) and adjusted to obtain dB normal hearing levels (nHL) from the audiometer. Adjusted 0 dB nHL for AM tones of 500, 1000, 2000, and 4000 Hz were 11, 9, 8, and 7 dB SPL, respectively (see Chapter 4).

Two stimulus conditions were used: (1) Multiple: simultaneous presentation of four AM tones (500, 1000, 2000, and 4000 Hz); (2) Single: either 500, 1000, 2000, or 4000 Hz AM tones were presented separately, depending on the frequency of interest. To minimize recording time, one “frequency of interest” for the single-stimulus condition was designated. This was the frequency within the steepest-sloping portion of the audiogram with the greater behavioural threshold.

For the multiple-stimulus condition, all carrier frequencies were presented at the same intensity, and stimulus energy at frequencies with better hearing, could result in temporary or permanent threshold shifts. To ensure this would not happen, the following precautions were taken. First, intensity levels did not exceed 90 dB nHL, because the recording time needed to obtain a reasonable electroencephalographic (EEG) noise level (see below) would exceed safety
limits if higher stimulus levels were assessed. Second, at 90 dB nHL, stimulation time was limited to three trials of 3 minutes with two inter-trial, no-stimulus periods of 3 minutes (i.e., a 50% duty cycle).

Procedure

Behavioural and ASSR measures were obtained in one session lasting approximately 1.5 hours at the Worker’s Compensation Board of British Columbia (N=26) or at the Human Auditory Physiology Laboratory on the campus of the University of British Columbia (N=5). Of the five subjects tested at the Human Auditory Physiology Laboratory, three subjects returned for an additional session of 2 hours to obtain single-stimulus results. During behavioural measures, participants relaxed in a comfortable reclining chair in a double-walled sound-attenuated booth. During ASSR measures, participants slept or relaxed.

Background acoustic noise levels for one-octave-wide bands centred at 0.5, 1, 2, and 4 kHz were 13, 9, 9, and 10 dB SPL, respectively, in the sound-attenuated booth at the Worker’s Compensation Board, and 12, 10, 10 and 12 dB SPL, respectively, in the sound-attenuated booth at the Human Auditory Physiology Laboratory.

Recording electrodes were placed at the vertex (Cz) and on the back of the neck, just below the hairline in the mid-sagittal plane. A ground electrode was placed on the forehead. Inter-electrode impedances were less than 3 kOhms at 10 Hz. The EEG was amplified 80,000 times and filtered using a bandpass of 30 to 250 Hz (12 dB/octave). An EEG recording sweep lasted for 16.384 seconds that contained 16 sections of 1.024 seconds each. ASSRs were analysed in the frequency domain by Fast Fourier Transform (FFT) of the average time-domain waveforms. The FFT resolution was 0.061 Hz, spanning from 0 to 250 Hz. In order to determine
If a response at the modulation frequency was different from the background EEG noise, an analysis of variance (i.e., the “F-technique”; Dobie, 1993; Picton et al., 1987b; Valdes et al., 1997; Zurek, 1992) compared the FFT components at the modulation frequency to the 120 adjacent frequency bins (60 above and 60 below the modulation frequency, or ± 3.7 Hz). A response was considered “present” when the F-ratio of the signal to noise was significant if $p < .05$. A “no response” was accepted after the EEG background noise amplitude around the frequency of interest was less than 10 nanovolts (nV) and $p > .20$. Approximately two percent (11 of 660) of response assessments missed the noise criteria for a “no response” by only 2 nV. A “no response” was still accepted for these recordings because the p-values were greater than .50, indicating a low chance of obtaining a response with a few more averages, and the EEG noise level was reasonably low (i.e. ≤ 12 nV).

**Behavioural and ASSR Threshold Evaluation**

Behavioural thresholds were obtained using a Hughson-Westlake procedure (Carhart & Jerger, 1959) for pure tones at ½-octave intervals ranging from 0.25 to 8 kHz. One ear was chosen for ASSR testing, based on behavioural audiogram configurations, as stated above. Starting intensities for ASSR testing were 40 or 60 dB nHL (randomized between subjects). ASSR thresholds for the multiple-stimulus technique were bracketed using 20-dB steps and then 10-dB up/down steps. If, after averaging at least five sweeps, a response was indicated to be significantly present, then the stimulus intensity was decreased in 20-dB steps until a no-response was obtained for at least three out of four carrier frequencies. Intensity was then increased to a level that would provide estimation of the greatest number of thresholds. Remaining levels were then tested to fill in the gaps. Stimulus intensities did not go below 0 dB nHL or exceed 90 dB.
ASSR thresholds were defined as the lowest intensity where a response was present and a no-response was obtained at 10 dB lower. False-positive responses were classified as statistically significant responses occurring at levels where a non-significant response was present at both 10 and 20 dB higher. False-negative responses were classified as non-significant responses where a significant response was identified at both 10 dB lower and 10 dB higher. False-positive and false-negative responses were determined to be present in 13 of 660 assessments (2.0%). In three recordings (two subjects), significant responses (one at 2000 Hz and two at 4000 Hz) could not be obtained at any of the test levels (0 to 90 dB nHL). Therefore, thresholds were arbitrarily defined as 100 dB nHL (i.e., 10 dB above the highest intensity tested). If there were significant responses down to 0 dB nHL, threshold was considered to be 0 dB nHL. Excluding these arbitrarily set thresholds of 0 and 100 dB nHL did not change the statistical results. Therefore, they were included in the analysis.

Statistical Analysis

Based on their audiogram configurations, participants’ results were placed in either group: (A) steep-sloping (≥30 dB per octave) hearing impairments (N=18), or (B) flat/shallow-sloping (<30 dB per octave) hearing impairments (N=13). Steep-sloping impairments ranged from 30 to 65 dB/octave (mean 43 ± 11 dB/octave) and shallow-sloping impairments ranged from 0 to 25 dB/octave (mean 15 ± 9 dB/octave).

Results were statistically analysed to examine four important issues: (1) behavioural audiogram estimation using multiple-ASSRs thresholds; (2) place specificity of the multiple-ASSR method; (3) possible masking effects when presenting iso-intense multiple-stimuli; and (4)
recording time for the monotic multiple-ASSR method in estimating thresholds for hearing-impaired subjects.

Analyses of estimating the behavioural threshold. Similar to previous studies (e.g., Lins et al., 1996; Stapells, Gravel, & Martin, 1995), the relationship of multiple-ASSR and behavioural thresholds as well as the accuracy of multiple-ASSRs to estimate behavioural thresholds were assessed.

First, difference scores (multiple-ASSR thresholds minus pure-tone behavioural thresholds) were calculated for each group (A and B) and each carrier frequency (500, 1000, 2000, and 4000 Hz). A two-way repeated-measures analysis of variance (ANOVA) compared difference scores to evaluate the accuracy of the multiple-ASSR method in estimating behavioural thresholds. Huynh-Feldt epsilon correction factors for degrees of freedom were used to evaluate significant ANOVA results (Huynh & Feldt, 1976). Results from the ANOVA were considered significant if \( p < .01 \). Newman-Keuls post hoc comparisons were performed only for significant main effects and interactions. Post hoc comparisons were considered significant if \( p < .05 \).

Second, Pearson product-moment correlation coefficients assessed the relationship between behavioural and multiple-ASSR thresholds at each carrier frequency, as well as for results for all frequencies combined. Results from these tests were considered significant if \( p < .01 \).

Analysis of estimating the audiogram configuration. In addition to considering each frequency separately, it is also important to assess how well multiple-ASSRs estimate the overall
shape (i.e., configuration) of the audiogram. Two statistical methods presented previously by Pérez-Abalo et al. (2001), as well as an additional method, were used to assess the how well multiple-ASSR thresholds matched the configuration of the behavioural audiogram.

First, a within-subject Pearson product-moment correlation coefficient was determined for each individual. The X and Y values were the multiple-ASSR and behavioural thresholds for each carrier frequency (500, 1000, 2000, and 4000 Hz). Only subjects' data with ASSR thresholds at three or more frequencies were used to calculate an individual subject's correlation. Individual subject's correlation coefficients were separately assessed for significance. If multiple-ASSRs thresholds change across frequency to the same degree as behavioural thresholds, then an individual subject's correlation will be high and positive.

Second, individual subject's correlation coefficients (see paragraph above) were used as dependent variables in a Student's t-test and tested for significance against a mean of zero. If, across all subjects, the mean correlation is small and/or if there is large variability between subjects, then the t-test will be non-significant and would indicate that multiple-ASSR thresholds do not match the behavioural audiogram configuration.

Third, to compensate for the systematic elevation of multiple-ASSR thresholds over behavioural thresholds (Pérez-Abalo et al., 2001), z-scores for multiple-ASSRs and behavioural thresholds ($Z_R$ and $Z_B$) for each carrier frequency (500, 1000, 2000 and 4000 Hz) were calculated using a Z transform, as follows:

$$z\text{-score} = \frac{\text{individual threshold} - \text{mean threshold}}{\text{standard deviation}} \quad \text{(Equation 1)}$$

This normalized the data so that ASSR thresholds could be compared to the behavioural thresholds. Subtracting the z-scores ($Z_R$ minus $Z_B$), for each subject at each frequency yielded a Z-score difference value. By comparing Z-score differences across carrier frequency using a
one-way repeated-measures ANOVA, we were able to assess how well multiple-ASSRs match the configuration of the behavioural audiogram. ANOVA results were considered significant if $p<.01$.

**Analysis of place specificity.** To assess place specificity, difference scores (multiple-ASSRs thresholds minus behavioural thresholds) were calculated for frequencies within the steepest-sloping portion of the audiogram with the greater behavioural threshold (i.e., “frequency of interest”, see above). For example, if behavioural thresholds were 10, 20, 60, 70 dB HL for respective frequencies of 500, 1000, 2000, and 4000 Hz, then a difference score was calculated at 2000 Hz. For each group, individual difference scores were combined across different frequencies because different subjects had audiograms where the steepest slope occurred at different frequencies. A student’s t-test for independent samples was used to compare these difference scores between group A and B. Results were considered significant if $p<.01$.

**Analyses of masking issues using multiple iso-intense AM tones.** The possibility of masking of multiple ASSRs to high-frequency AM tones (e.g., 4000 Hz) by simultaneously presenting lower frequency stimuli (e.g., 500 Hz) was assessed by comparing multiple- and single-ASSR thresholds for high-frequencies with moderate-to-severe hearing impairments. Subjects with moderate-to-severe hearing impairments were chosen for this analysis because they would theoretically have the most masking due to their poorer cochlear tuning. ASSR thresholds were combined over 2000 Hz ($N=3$) and 4000 Hz ($N=7$). Additionally, the relationship between multiple and single-ASSR thresholds was determined from a Pearson product-moment correlation coefficient and considered significant if $p<.01$. 
Analyses of recording time. Total recording times were estimated from the total number of sweeps that were recorded to obtain thresholds for four frequencies in one ear using the multiple-ASSR method. The total number of sweeps was multiplied by the time per sweep (16.384 sec/sweep) to give a total recording time per subject. Only subject data that had thresholds for all four frequencies were included in the average of total recording times. Because steep-sloping hearing impairments may require more time to obtain ASSR thresholds than flat/shallow-sloping audiograms, recording times between group A and B were assessed using a Student’s t-test for independent samples. Results were considered significant if p<.01.
Results

*Multiple-ASSRs Estimation of Behavioural Thresholds*

Figure 5.1 shows the single and multiple ASSRs used to assess hearing thresholds in an individual (subject 1) with a steep-sloping severe hearing impairment. Mean amplitude spectra at various stimulus intensities are shown for the multiple-stimulus condition, for the 1000-Hz single AM tone, and for the 2000-Hz AM tone. Significant ASSRs occur at the modulation frequencies of 77, 85, 93, and 101 Hz for AM tones of 500, 1000, 2000, and 4000 Hz, respectively. Four significant ASSRs can be seen for the multiple-stimulus condition at 80 dB nHL. At 70 dB nHL, there is no significant response for the 4000-Hz AM tone. Thus, multiple-ASSR threshold for the 4000-Hz AM tone is determined to be 80 dB nHL. This is equal to the subject's behavioural pure-tone threshold. For the 2000-Hz AM tone in the multiple-stimulus condition, ASSRs are significant down to 70 dB nHL and non-significant at 60 dB nHL. Threshold is, therefore, 70 dB nHL and is at the same level measured behaviourally. There are significant ASSRs for the 1000-Hz AM tone in the multiple-ASSR condition from 80 to 10 dB nHL with a non-significant response at 0 dB nHL. As for the 500-Hz AM tone in the multiple-stimulus condition, significant ASSRs are recorded down to 0 dB nHL. Threshold is, therefore, considered to be 0 dB nHL.

Single AM tone thresholds for 1000 and 2000-Hz are 10 and 80 dB nHL, respectively. Behavioural, multiple-ASSR, and single ASSR thresholds for subject S1 are tabulated at the bottom of Figure 5.1 and graphically presented in Figure 5.2.

Figure 5.2 depicts behavioural, multiple-ASSR, and single-ASSR thresholds for each subject. They are grouped according to the slopes of their behavioural hearing impairments. Thresholds for subjects in group A, who have steep-sloping (>30 dB/octave) impairments, are shown in the first 18 audiograms, whereas thresholds for subjects in group B, who have
Figure 5.1. ASSR amplitude spectra from subject S1 for the monotic multiple-ASSR (left panel) and single-ASSR (right panel) methods. Spectra are only plotted for 70 to 110 Hz. Stimulus intensities (dB nHL) are specified to the left of the amplitude spectra. Closed arrowheads designate significant ASSRs at modulation frequencies of 77, 85, 93, and 101 for carrier frequencies of 500, 1000, 2000 and 4000 Hz, respectively. ASSR thresholds were determined to be at the level with a significant response and a no response at 10 dB lower. Behavioural (dB HL) and ASSR (dB nHL) thresholds are tabulated at the bottom.
Chapter 5: ASSRs Thresholds of Hearing-Impaired Subjects

Figure 5.2. Behavioural, multiple-ASSR, and single-ASSR thresholds at 500, 1000, 2000, and 4000 Hz are graphed for each subject. Based on their audiograms, subjects are divided into group A (>30 dB/octave slope) and B (<30 dB/octave slope). Subject identifiers are in the top right-hand corner of each graph.
flat/shallow-sloping (<30 dB/octave) impairments, are shown in the lower 13 audiograms. Mean behavioural thresholds, multiple-ASSR thresholds, and difference scores (multiple-ASSR threshold minus behavioural threshold) are listed in Table 5.1 for group A and B, as well as for groups combined.

Multiple-ASSR thresholds are within 20 dB of behavioural thresholds in 81%, 93%, 93%, and 100% of the subjects for frequencies of 500, 1000, 2000, and 4000 Hz, respectively (Table 5.2). A two-way ANOVA (group x frequency) of difference scores reveals no significant differences between group A and B when averaged across frequency (F = 0.12; df = 1,21; p=.729), with no significant interaction between group and frequency (F = 1.87; df = 3,63; p=.144). ANOVA results reveal a significant effect of frequency, averaged over group A and B (F= 5.59; df = 3,63; € = 1.00; p = .002). Post hoc analysis shows that the difference score for 4000 Hz is significantly (p<.05) smaller than those for 500, 1000, and 2000 Hz.

Pearson product-moment correlations show significant (p<.001) relationships (r = .75 to .89) between multiple-ASSR thresholds and behavioural thresholds for each carrier frequency and for all carrier frequencies combined. Figure 5.3 depicts the relationship between behavioural and multiple-ASSR thresholds. Regression equations, sample size (N), and correlation coefficients (r) are presented in Figure 5.3.

To provide an indication of how well the configurations of the multiple-ASSR and behavioural audiogram match, correlations between multiple-ASSR and behavioural thresholds were determined across frequency for each individual. The mean correlations, averaged across subjects, is r = .83 ± 0.28. A Student’s t-test of the average individual correlations, testing the null hypothesis that thresholds are unrelated (i.e., a mean of zero), shows a significant relationship between behavioural and multiple-ASSR thresholds (t = 4.05, df = 24, p < .001).
Table 5.1

Mean Behavioural Thresholds, Multiple-ASSR Thresholds, and Difference Scores by Frequency for Group A, Group B, and Both Groups Combined

<table>
<thead>
<tr>
<th>Measure</th>
<th>500 Hz</th>
<th>1000 Hz</th>
<th>2000 Hz</th>
<th>4000 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M±SD</td>
<td>n</td>
<td>M±SD</td>
<td>n</td>
</tr>
<tr>
<td>Group A: steep-sloping hearing impairment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural(a)</td>
<td>14 ± 8</td>
<td>18</td>
<td>23 ± 17</td>
<td>18</td>
</tr>
<tr>
<td>Multiple ASSR(b)</td>
<td>28 ± 15</td>
<td>13</td>
<td>33 ± 18</td>
<td>16</td>
</tr>
<tr>
<td>Difference Score(c)</td>
<td>13 ± 13</td>
<td>13</td>
<td>8 ± 10</td>
<td>16</td>
</tr>
<tr>
<td>Group B: flat/shallow-sloping hearing impairments</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural</td>
<td>32 ± 23</td>
<td>13</td>
<td>35 ± 22</td>
<td>13</td>
</tr>
<tr>
<td>Multiple ASSR</td>
<td>46 ± 17</td>
<td>13</td>
<td>42 ± 20</td>
<td>13</td>
</tr>
<tr>
<td>Difference Score</td>
<td>15 ± 13</td>
<td>13</td>
<td>7 ± 8</td>
<td>13</td>
</tr>
<tr>
<td>Groups A and B Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behavioural</td>
<td>21 ± 18</td>
<td>31</td>
<td>28 ± 20</td>
<td>31</td>
</tr>
<tr>
<td>Multiple ASSR</td>
<td>37 ± 22</td>
<td>26</td>
<td>37 ± 21</td>
<td>29</td>
</tr>
<tr>
<td>Difference Score</td>
<td>14 ± 13</td>
<td>26</td>
<td>8 ± 9</td>
<td>29</td>
</tr>
</tbody>
</table>

Note. M = mean. SD = one standard deviation. n= sample size.

\(a\) measured in dB HL. \(b\) measured in dB nHL. \(c\) calculated in dB.
Table 5.2

Percent of Subjects' Difference Scores by Frequency

<table>
<thead>
<tr>
<th>Range</th>
<th>500 Hz&lt;sup&gt;a&lt;/sup&gt;</th>
<th>1000 Hz&lt;sup&gt;b&lt;/sup&gt;</th>
<th>2000 Hz&lt;sup&gt;c&lt;/sup&gt;</th>
<th>4000 Hz&lt;sup&gt;d&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>20 &lt; Diff ≤ -10</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>-10 &lt; Diff ≤ 0</td>
<td>19</td>
<td>31</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>0 &lt; Diff ≤ 10</td>
<td>23</td>
<td>45</td>
<td>41</td>
<td>32</td>
</tr>
<tr>
<td>10 &lt; Diff ≤ 20</td>
<td>35</td>
<td>14</td>
<td>30</td>
<td>18</td>
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<tr>
<td>20 &lt; Diff ≤ 30</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>30 &lt; Diff ≤ 40</td>
<td>12</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Note. Diff = difference score (multiple-ASSR minus behavioural thresholds).

<sup>a</sup> N = 26. <sup>b</sup> N = 29. <sup>c</sup> N = 27. <sup>d</sup> N = 28.
Figure 5.3. Graphical representation of linear regression analysis comparing multiple-ASSR thresholds with behavioural pure-tone thresholds for frequencies of 500, 1000, 2000, and 4000 Hz, as well as for data combined across all carrier frequency (middle plot). Regression equations, sample size (N) and correlation coefficient (r) are given in the upper left hand corner of each graph. Overlapping data have adjusted by ±1 dB in both directions to resolve all points in the plots. Arrows designate thresholds that were set at 10 dB above maximum testing levels. The regression equation is as follows: \( y = mx + b \), where \( y \) is the behavioural threshold, \( m \) is the slope of the regression, \( x \) is the ASSR threshold, and \( b \) is the \( y \)-intercept.
Moreover, 42\% (11/26) of the individual correlations are greater than .99 and have probabilities less than <.01 of being different from a mean of zero; 73 \% (19/26) are greater than .83 and have probabilities less than .05; 81\% (21/26) are greater than .78 and have probabilities less than .10; and 85\% (22/26) are greater than .66 and have probabilities less than .15.

Comparing across carrier frequency, the $z$-score differences ($Z_R$ minus $Z_B$) is another statistical method used to indicate the correspondence of multiple-ASSR and behavioural audiogram configurations (Perez-Abalo et al., 2001). Mean $z$-score differences are $-0.022 \pm 0.597$, $-0.016 \pm 0.477$, $0.058 \pm 0.407$, $0.036 \pm 0.497$ standard deviations for carrier frequencies of 500, 1000, 2000, and 4000 Hz, respectively. Thus, $Z$-score differences are small, with none exceeding $\pm 1.23$ standard deviations. Results from the ANOVA show no significant difference between $z$-scores differences compared across carrier frequency ($F = 0.167$; $df = 3,69$; $p = .918$).

**Place Specificity of the Multiple-ASSR Method**

Place specificity of the multiple-ASSR method is assessed by comparing difference thresholds (multiple-ASSR minus behavioural) at the frequency with the highest behavioural threshold and the greatest slope between group A ($\geq 30$ dB/octave slopes) and B ($<30$ dB/octave slopes). Mean difference threshold for group A is $2.5 \pm 10.5$ dB ($N = 18$) and for group B is $5.0 \pm 5.4$ dB ($N = 13$). Group A shows a 2.5 dB smaller difference between behavioural and multiple-ASSR thresholds compared to group B. However, statistical comparison using a t-test for independent samples reveals this slightly smaller difference is not significant ($t = -0.786$; $df = 26$; $p = .438$).
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Masking Issues using Multiple Iso-Intense AM tones

Simultaneously presenting multiple iso-intense AM tones may cause ASSRs to high-frequency stimuli (e.g., 4000 Hz) to be masked by low-frequency stimuli (e.g., 500 Hz). This hypothesis is tested by comparing single- and multiple-ASSR thresholds for moderate-to-severe hearing impairments at high frequencies, combined across 2000 Hz (N = 3) and 4000 Hz (N = 7). For the single- and multiple-stimulus conditions, mean thresholds are 63 ± 9 and 64 ± 14 dB nHL, respectively. A repeated-measures student’s t-test reveals no significant difference between stimulus conditions (t = -.318; df = 9; p = .758). Furthermore, the Pearson product-moment correlation between these single- and multiple-ASSR thresholds is .72, which nearly reaches statistical significance (F = 8.652; df = 1, 8; p = .016). Subtracting behavioural thresholds from single-ASSR and multiple-ASSR thresholds yields mean difference scores equalling 6 ± 11 dB and 5 ± 12 dB, respectively.

Recording Time

Recording times to obtain four thresholds (500, 1000, 2000, and 4000 Hz) using the multiple-ASSR method are estimated from the total number of sweeps recorded. Mean total recording times for group A and B are 49 ± 13 and 44 ± 14 minutes, respectively. There is no significant difference for recording times between group A and B (t = 0.935; df = 21; p = .360). Distribution of recording times are shown in Table 5.3. For 78% of the subjects, thresholds for four frequencies (in one ear) are obtained within 60 minutes.
Table 5.3

Percent of Subjects’ Recording Times by Group

<table>
<thead>
<tr>
<th>Recording Time (t) in minutes</th>
<th>Group A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Group B&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 &lt; t ≤ 30</td>
<td>8</td>
<td>20</td>
</tr>
<tr>
<td>30 &lt; t ≤ 40</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>40 &lt; t ≤ 50</td>
<td>15</td>
<td>30</td>
</tr>
<tr>
<td>50 &lt; t ≤ 60</td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td>60 &lt; t ≤ 70</td>
<td>23</td>
<td>20</td>
</tr>
</tbody>
</table>

Note. t = recording time needed to obtain thresholds for all four frequencies (500, 1000, 2000, and 4000 Hz).

<sup>a</sup> N = 13. <sup>b</sup> N = 10.
Discussion

Multiple-ASSRs Estimation of Behavioural Thresholds

Audiograms in Figure 5.2 suggest that the multiple-ASSR method can accurately predict both the degree and configuration of the behavioural audiogram. Similar conclusions can be made from single-ASSR results reported by Aoyagi et al., (1999) and from multiple-ASSR results reported by Lins et al. (1996). Quantitative analyses from the present study confirm this impression.

Results from the present study are similar to those reported from previous investigations assessing the sensitivity of either single- or multiple-ASSR methods in estimating behavioural thresholds in subjects with sensorineural hearing impairments (Table 5.4). ASSR thresholds are, on average, between 3 to 17 dB higher than behavioural thresholds, which indicates good sensitivity for ASSR method. Whether presenting stimuli separately to one ear (i.e., monotic single-stimulus condition) or multiple-stimuli simultaneously to one (i.e., monotic multiple-stimulus condition) or both ears (i.e., dichotic multiple-stimulus condition) does not seem to make a difference in estimating hearing thresholds. Results from the present study confirms this by revealing that differences in difference scores of 6 and 5 dB between the single-stimulus and multiple-stimulus conditions are neither statistically nor clinically significant.

Table 5.4 also presents grand means, standard errors of the means, and 95% percent confidence limits for the difference scores from a meta-analysis performed on results from the seven studies presented in Table 5.4. All calculations within the meta-analysis are appropriately weighted for each study's sample size (Howell, 1997). Results from the meta-analysis show that ASSR thresholds are 6 to 10 dB higher than behavioural thresholds and indicate that ASSRs provide accurate estimates of behavioural thresholds. Moreover, these small difference scores
Table 5.4
Summary of Difference Scores from the Present Study, Previous Literature and a Meta-analysis

<table>
<thead>
<tr>
<th>Study and ASSR method</th>
<th>500 Hz</th>
<th>1000 Hz</th>
<th>2000 Hz</th>
<th>4000 Hz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diff r N</td>
<td>Diff r N</td>
<td>Diff r N</td>
<td>Diff r N</td>
</tr>
<tr>
<td><strong>Present Study</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monotic multiple</td>
<td>14 ± 13 .75 26</td>
<td>8 ± 9 .89 29</td>
<td>10 ± 10 .88 27</td>
<td>3 ± 10 .85 28</td>
</tr>
<tr>
<td>monotic single</td>
<td>– .73 34</td>
<td>– .86 169</td>
<td>– .88 30</td>
<td>– .92 13</td>
</tr>
<tr>
<td>Dimitijevic et al., in press</td>
<td>13 ± 11 .85 31</td>
<td>5 ± 8 .94 31</td>
<td>5 ± 9 .95 31</td>
<td>8 ± 11 .95 31</td>
</tr>
<tr>
<td>dichotic multiple</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lins et al., 1996*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monotic multiple</td>
<td>9 ± 9 .72 10</td>
<td>13 ± 12 .70 10</td>
<td>11 ± 10 .76 10</td>
<td>12 ± 13 .91 10</td>
</tr>
<tr>
<td>Perez-Abalo et al., 2001*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>dichotic multiple</td>
<td>13 ± 15 .70 80</td>
<td>7 ± 15 .79 80</td>
<td>5 ± 15 .83 80</td>
<td>5 ± 16 .78 80</td>
</tr>
<tr>
<td>Picton et al., 1998*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sound-field multiple</td>
<td>17 ± 8 .68 32</td>
<td>13 ± 8 .54 32</td>
<td>14 ± 8 .63 32</td>
<td>17 ± 13 .60 31</td>
</tr>
<tr>
<td>Rance et al., 1998*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>monotic single</td>
<td>6 ± 7 .97 129</td>
<td>4 ± 6 .98 108</td>
<td>3 ± 6 .99 47</td>
<td>6 ± 7 .99 32</td>
</tr>
<tr>
<td><strong>Meta-Analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All methods combined</td>
<td>10 ± 0.6</td>
<td>6 ± 0.5</td>
<td>7 ± 0.7</td>
<td>7 ± 0.9</td>
</tr>
<tr>
<td><em>(95% confidence interval)</em></td>
<td>(9.2-11.6)</td>
<td>(4.6-6.7)</td>
<td>(5.3-8.2)</td>
<td>(5.7-9.2)</td>
</tr>
<tr>
<td><em>(N)</em></td>
<td>308</td>
<td>459</td>
<td>7</td>
<td>212</td>
</tr>
</tbody>
</table>

*Note.* Dashes indicate data was not reported or calculated. Carrier frequencies are given in Hz. Diff = mean ± one standard deviation for difference scores (ASSR minus behavioural thresholds). r = correlations. *a* includes data from children. *b* grand means ± standard error of the mean and 95% confidence intervals given in parentheses for difference scores appropriately averaged over the seven studies presented above.
support that ASSRs can be useful for audiometric evaluation of hearing thresholds in subjects with sensorineural hearing impairments.

There is some concern regarding the sensitivity of ASSRs at 500 Hz (Lins et al., 1996; Perez-Abalo et al., 2001). Lins et al. (1996) revealed that ASSR thresholds for 500 Hz were significantly elevated compared to thresholds at frequencies of 1000 to 4000 Hz in subjects with normal hearing. This pattern of results is similar to that for tone-evoked ABRs (Stapells, 2000b). Perez-Abalo et al., (2001) also revealed that the elevated 500-Hz threshold was age dependent, with infants having greater thresholds. Perez-Abalo et al. (2001) showed similar results with higher ASSR thresholds at 500 Hz than at other frequencies, but this was also the case for behavioural thresholds. An ANOVA comparing difference scores across frequencies was not performed by Perez-Abalo et al. (2001); however, our post hoc analysis of their results reveals that the difference score at 500 Hz is statistically greater than that at 4000 Hz ($t = 3.26; df = 78; p = .002$). The 500-Hz grand mean difference scores from the meta-analysis are 3 to 4 dB higher than at any for the other carrier frequencies (Table 5.4). Additionally, the 95% confidence intervals for the difference scores for the 1000- to 4000-Hz carrier frequencies overlap with each other but do not overlap with the confidence interval for 500-Hz. The 4000-Hz and 500-Hz confidence intervals are remarkably close. These results suggest that there is a lower sensitivity for ASSRs to 500-Hz AM tones compared to ASSRs evoked by high-frequency stimuli.

Although these differences are statistically significant, a 3-4 dB difference in sensitivity is not clinically relevant. Most importantly, grand-mean differences scores for all carrier frequencies have standard errors that are quite low ($\pm 1$ dB) and 95% confidence intervals that are quite narrow (ranging within $\pm 3.5$ dB) This indicates reasonably consistent threshold evaluations across a large number of subjects. Furthermore, results from the present study and Lins et al.
(1996) show that difference scores are not significantly different between carrier frequencies for
subjects with hearing impairments. This is also the case for subjects with normal hearing (see
Chapter 4).

While their results show no significant differences in difference scores across carrier
frequency, Lins et al. (1996) speculated that elevated absolute ASSR thresholds at 500 Hz may
result from a greater jitter in the neural synchrony in response to a 500-Hz AM tone compared to
higher frequency stimuli. Although this may be the case, it is also possible that optimal stimulus
parameters, such as modulation frequency, have not yet been found for lower frequency stimuli,
such as 500 Hz.

Even though statistical results conflict between studies (Dimitrijevic et al., in press; Lins
et al., 1996; Perez-Abalo et al., 2001), most results show that difference scores are not
substantially different between carrier frequencies and that there are respectable threshold
sensitivities for ASSRs to carrier frequencies between 500 to 4000 Hz. These results indicate that
there is little concern for using ASSRs, evoked by AM tones of 500 to 4000 Hz, to clinically
assess air-conduction hearing thresholds of subjects with normal or impaired hearing.

Correlations from the present study show significant relationships between multiple-
ASSR and behavioural thresholds for all carrier frequencies. Similar correlations, listed in Table
5.4, have been reported by other studies. (Aoyagi et al., 1999; Dimitrijevic et al., in press; Lins
et al., 1996; Perez-Abalo et al., 2001). There are notable inconsistencies, such as the low
correlations (.54 to .68) in the Picton et al. (1998) study and the very high correlations (.97 to
.99) in the Rance et al. (1998) study. Such discrepancies could be a result of different stimulus
techniques. For example, a monotic single-stimulus condition was used in the Rance et al. (1998)
study, whereas a binaural (sound field) presentation of multiple AM tones was used in the Picton
et al. (1998) study. Most other investigations have reported correlations between .70 and .95, which indicate a good relationship between ASSR and behavioural thresholds.

Along with providing good sensitivity and moderate-to-high correlations across subjects, the multiple-ASSR technique must accurately estimate the configuration of the behavioural audiogram for individuals. By testing the difference between standardized vectors for behavioural and multiple-ASSR thresholds, Perez-Abalo et al. (2001) show that differences in audiogram configuration are not statistically different between behavioural and multiple-ASSR methods. However, most of their subjects had flat configurations of their audiograms. We, therefore, tested subjects with a variety of audiogram configurations to objectively assess (using the same statistical methods) the ability for multiple-ASSR thresholds to match behavioural audiograms. The present study's results show the difference in z-scores are near zero; thus, not significantly different and indicating that there are no differences in audiogram configurations between behavioural and ASSR methods. To further confirm this, individual correlations were calculated and again show that the differences between audiogram estimates are not significant. These results indicate that multiple-ASSRs can accurately predict the configuration of the behavioural audiogram.

**Place Specificity of the Multiple-ASSR Method**

Place specificity of the multiple-ASSR method has been recently shown for normal-hearing subjects (John et al., 1998; Chapter 3). Results from Chapter 3 of this thesis show that bandwidths for multiple ASSRs to 60 dB SPL AM tones (500 to 4000 Hz) are approximately 1-octave-wide and centred within ¼-octave of the stimulus frequency. Although there is reasonable place specificity for subjects with normal hearing, subjects with a steep-sloping hearing
impairment (≥30 dB/octave) may have adjacent frequency regions undesirably contributing to the ASSR. In the present study, an indication of the place specificity for the multiple-ASSR method was determined by investigating whether there is an underestimation of the highest threshold at a frequency within the steepest-sloping part of the audiogram. For example, Picton et al., (1979) and Stapells et al., (1985) reported that brief-tone ABRs underestimate behavioural thresholds in subjects with steep-sloping hearing impairments because of the spectral splatter of the brief tones stimulating regions with better hearing sensitivity. They showed that this underestimation can be reduced if “notched” noise is used to mask the regions responding to this splatter. Purdy and Abbas (in press) investigated the place specificity of the tone-ABR in subject’s with sensorineural hearing impairment and reported that for most subjects with steep-sloping hearing losses, the tone-evoked ABR did not underestimate behavioural thresholds. Results from the present study similarly show that for all subjects with steep-sloping hearing losses, the multiple-ASSRs to AM tones do not underestimate behavioural thresholds, as indicated by ASSR thresholds being 2.5 dB greater than behavioural thresholds. There are no differences in thresholds between groups A and B, which indicates that multiple-ASSRs are able to accurately predict thresholds in subjects whether or not they had steep-sloping hearing impairments. Moreover, for subject S1, who has a very steep-sloping loss (45 dB drop between 1500 and 2000 Hz), there is no underestimation of the behavioural threshold using the multiple-ASSR method. This is in contrast to results for one subject, in the study by Purdy and Abbas (in press), who had a very steep-sloping (45 dB drop between 3000 and 4000 Hz) hearing loss showing that the behavioural threshold at 4000 Hz is largely underestimated by brief-tone ABRs because of better hearing at 3000 Hz. Although both multiple-ASSRs and tone-evoked ABRs do not underestimate hearing thresholds in subjects with steep-sloping hearing losses, there may be a
difference for testing subjects with very steep-sloping impairments. Results from subject S1 in the current study might indicate that the multiple-ASSR method has an advantage, compared to the brief-tone ABR technique, of not requiring masking procedures to obtain frequency-specific thresholds for subjects with very steep-sloping hearing impairments. However, there are data from only a few subjects in the ASSR and ABR literature (including this thesis), thus no conclusion can be drawn. Overall, the results from the present study confirm that there is good place specificity for ASSRs in subjects with sensorineural hearing impairments and that they are consistent with results presented for normal-hearing listeners (see Chapter 3).

*Masking Issues using Multiple Iso-Intense AM tones*

The concern of masking high-frequency (e.g., 4000 Hz) ASSRs by simultaneously presenting a lower frequency stimulus (e.g., 500 Hz), is not supported by the present data. There is no significant difference in thresholds (63 versus 64 dB nHL) between the single- and multiple-ASSR method for subjects with moderate-to-severe hearing impairments. This is contrary to results for a few subjects reported by Picton and associates (Dimitrijevic et al., in press; Picton et al., 1998). Picton et al., (1998) proposed this masking problem because a few subjects showed more accurate threshold estimates at 2000 and 4000 Hz using the single- versus multiple-stimulus method. Dimitrijevic et al. (in press) also provided some evidence for possible masking from a limited number of subjects (N=5), showing that mean difference scores (ASSR minus behavioural thresholds) for the single-ASSR method of 9 dB was lower than for the multiple-ASSR method of 21 dB. Their difference score of 21 dB for the multiple-ASSR method is quite elevated compared to those reported in the present study and other studies with larger sample sizes (see Table 5.4). For a sub-population of 10 subjects in the current study used to
assess the possibility of masking, difference scores are 6 and 5 dB for the single- and multiple-ASSR method, respectively. It may also be that the small sample size (N=5) in the study by Dimitrijevic et al. (in press) resulted in an erroneous significant difference because the data was not normally distributed, thus violating statistical assumptions. More importantly, results in the present study of a larger sample of subjects (N=10) with moderate-to-severe hearing impairments, indicate that inclusions of low-frequency (i.e., 500 or 1000 Hz) AM tones in the multiple-stimulus method do not mask ASSRs to higher frequency stimuli (i.e., 2000 or 4000 Hz).

In order to reduce recording time, the current practice of presenting multiple-stimuli at the same intensity for recording ASSRs may be modified by simultaneously presenting carrier frequencies at different intensities. Thus, concerns of masking may arise for this multiple-intensity (MINT) method when testing subjects with hearing impairments, especially for those with reverse-sloping audiograms. At least for subjects with normal hearing, John, Purcell, Dimitrijevic, and Picton (in press) showed that presenting 500- and 4000- Hz AM tones at 10 to 20 dB higher than the 1000- and 2000-Hz AM tones did not significantly change response amplitudes to the 1000- and 2000-Hz stimuli. The MINT technique may be even faster than the current iso-intensity method of recording multiple-ASSRs, thus adding to the overall efficiency of ASSR to assess hearing thresholds.
Recording Time

Recording times estimated from the total number of sweeps revealed that thresholds for four frequencies could be obtained within 60 minutes for 78% (18/23) of the subjects. The present study’s mean recording time of 47 minutes for obtaining four frequency-specific thresholds from subjects with varying degrees of hearing impairments, is within practical limits for assessing hearing in hard-to-test patients. This mean recording time is substantially longer than the 21 minutes reported by Perez-Abalo et al. (2001). However, this may be a result of a lesser number of intensities needed bracket the flat audiograms of most subjects tested in the study by Perez-Abalo et al. (2001). Additionally, this discrepancy in recording times may be further compounded by the fact that the present study uses a more-strict noise criteria for determining a “no response”, which required averaging until the surrounding EEG noise was less than 10 nV. In the study by Perez-Abalo et al. (2001), averaging stopped after a maximum of 24 sweeps of 12.6 seconds (i.e., after 5 minutes). Stopping after 24 sweeps may have reduced recording time, but some recordings may have substantial EEG noise that may conceal a significant response, thereby elevating threshold. Nevertheless, the less-strict stopping criteria used by Perez-Abalo et al. (2001) did not dramatically affect sensitivity of the multiple-ASSR threshold in predicting behavioural thresholds, as indicated by the difference scores (see Table 5.4).

Recording times were not presented in Dimitrijevic et al. (in press). However, using initial noise estimates and stopping criteria from Dimitrijevic et al. (in press), John and colleagues (in press) predicted the total recording time to be 83.5 minutes to obtain multiple-ASSR thresholds (four frequencies) from subjects with an arbitrarily designated shallow-sloping hearing-impairment. This prediction of recording time considers the same noise criteria as the
current study, but it is almost double that of the real measurements of recording times in the present study. The present study calculated the actual recording time across subjects, thereby accounting for changes in subject state within each subject and between subjects. It is, therefore, a better estimate of recording time as compared to that predicted by John et al., (in press). These results demonstrate the multiple-ASSR method can be used to measure thresholds in individuals with hearing impairments within a realistic amount of time.

**Conclusion**

Results from this study confirm previous reports showing that the multiple-ASSR method is an accurate and sensitive predictor of the behavioural audiogram in patients with a wide range of sensorineural hearing impairments. Furthermore, an objective analysis of the threshold data revealed that the configuration of an individual's behavioural audiogram can be matched using the multiple-ASSR technique. Given that ASSR thresholds did not underestimate the elevated behavioural thresholds at the frequency edge of the steep-sloping impairment, ASSR thresholds for one frequency do not appear to be affected by better hearing at other frequencies. Results from the current study indicate no masking of high-frequency ASSRs by concomitant presentation of lower frequencies. In summary, these results provide good evidence for the usefulness of the multiple-ASSR technique for predicting behavioural thresholds to air-conducted stimuli in patients with sensorineural hearing impairments.
Chapter 6: Summary and Future Directions of ASSRs
Previous chapters have focused on different topics pertaining to the ASSRs. The following discussion summarizes each chapter and attempts to provide a greater understanding of how each study contributes to our knowledge of ASSRs and their usefulness in objective audiometry.

**Generators**

Chapter 2 identified the generators for ASSRs to different modulation rates of AM tones. Estimated latencies from the modelled brainstem generators are very similar to apparent latencies of scalp-recorded ASSRs previously reported (Cohen et al., 1991; John & Picton, 2000; Kuwada et al., 1986). This suggests that our model is valid and provides further support for the theory that the brainstem is the primary generator site for ASSRs to AM tones modulated near 80 Hz. For ASSRs to AM tones modulated near 40 Hz, bilateral auditory cortices predominantly contributed to the scalp-recorded responses. Again, estimated latencies for the dipole sources within the cortex are in agreement with apparent latencies for the 40 Hz ASSR recorded from the scalp (Cohen et al., 1991; John & Picton, 2000; Kuwada et al., 1986; Stapells et al., 1987). Results from animal studies suggest subcortical origins for the 40-Hz response (Hori et al., 1993; Karmos et al., 1993; Kiren et al., 1994). Few studies in humans (Harada et al., 1994), however, have been able to corroborate these results from animals. It is most likely that the auditory cortices are the primary generator sites for the 40-Hz ASSRs in humans.

Identifying the generators of ASSR is meaningful for clinicians. It is very important for us to understand that ASSRs to AM tones modulated at a specific modulation frequency reflects an intact auditory pathway only up to the level where these responses are generated. Impairments at higher levels may still exist. For example, obtaining normal thresholds to 80-Hz ASSRs tells the
clinician that the patient’s brain normally processes the stimuli at least up to the level of the brainstem. It does not indicate possible abnormalities in the cortex that could produce a hearing deficit, albeit these cases are rare in infants with no other significant history of abnormalities. Ignoring where ASSRs are generated, however may lead to a mis-diagnosis of normal hearing in a patient with abnormal hearing.

Generation of the 80-Hz ASSR within the human brainstem is intriguing because it may suggest that they are akin to the 80-100 Hz ASSRs invasively recorded from the brainstem nuclei in animals. This assumed similarity between humans and animals for brainstem processing of AM stimuli may help to solve the ongoing controversy between the “overlap theory” and the “intrinsic-rate theory”. If one presumes that the human brainstem is quite similar to the rat brainstem, then it may be suggested that humans have neurons that respond best to specific modulation rates, as discovered in the rat as periodotopic maps (Langer, 1992). This would support the “intrinsic-rate theory” more so than the “overlap theory”. Also, the lack of interaction between stimuli when presented simultaneously as compared to separately (shown in Chapter 3, 4, and 5) suggests that neural populations respond independently to the different modulation frequencies. The overlap theory contends that ASSRs result from the overlap of MLRs and ABRs because the amplitude enhancement of ASSRs at modulation frequencies around 40- and 80-Hz seems to correspond to the latencies of the MLR wave Pa and ABR wave V, respectively.

Assume that ASSRs are a result of overlapping of responses. One possible explanation for the distinctly generated multiple ASSRs is that as transient responses overlap, some neurons respond to one modulation frequency, whereas other neurons respond to a different modulation frequency. This could very much be true, but there is the question of the underlying mechanisms of why some neurons respond to one modulation frequency while other neurons respond to a
different modulation frequency? The answer to this question may transcend the gap between the two theories. For example, some brainstem neurons may have intrinsic firing rates at (i.e., most sensitive to) modulation frequencies around 75 Hz, whereas other brainstem neurons (within the same nucleus) may have intrinsic firing rates at modulation frequencies near 85 Hz. These functionally separate neural populations may then be driven by the rate of input to cause overlap of their responses. It seems that there needs to be some sort of design to separate neural populations rather than a haphazard assignment of some neurons responding to one modulation frequency and other neurons responding to a different modulation frequency. Although data from Chapter 2 can not resolve the controversy between the “overlap theory” and the “intrinsic-rate theory”, it seems plausible that both theories may be true, in some respects. Further investigation is required.

Frequency Specificity

Dominant issues regarding the place specificity for ASSRs, which the current thesis investigated, are: (1) the extent of cochlear excitation reflected by ASSRs to AM tones; (2) the effect on place specificity by presenting multiple AM tones simultaneously; (3) whether AM tones excite adjacent cochlear regions with better hearing sensitivity, which may cause a significant underestimation of hearing thresholds in individuals with steep-sloping hearing impairments; and (4) the potential advantage of the ASSR method using more acoustically specific AM tones to assess hearing thresholds, as compared to the ABR technique of using brief tones.

The HPN/DR technique was used to evaluate the spread of activation along the normal functioning cochlea that is responsible for producing ASSRs to single or multiple AM tones.
Results of the study in Chapter 3 show that ASSRs to 60 dB SPL AM tones reflect narrow contributions from the cochlea centred around the stimulus frequency, as indicated by approximately 1-octave-wide bandwidths centred within ¼-octave of the carrier frequency. There is no difference in place specificity between carrier frequencies when stimuli are presented separately or simultaneously. This indicates that significant interactions between stimuli do not occur for the ASSRs to moderately-intense multiple AM tones that are separated by at least 1-octave. These results are also similar to place-specificity results for the ABR and MLR to brief tones (Oates & Stapells, 1997a&b). It is important to note that the relatively narrow bandwidths broaden as stimulus intensity increases. This may result in underestimation of hearing thresholds when using ASSR to assess severe-to-profound hearing loss in individuals with steep-sloping impairments because of the spread of activity into adjacent regions with better hearing sensitivity.

Results from the study in Chapter 5, however, conclusively show that multiple-ASSRs do not underestimate hearing thresholds of subjects with steep-sloping (≥30 dB per octave) severe hearing loss. This indicates that multiple-ASSRs to AM tones are sufficiently place specific and that AM tones can be presented at high intensities (60-90 dB nHL) for clinical evaluation of individuals with steep-sloping severe hearing impairments.

Results from the study in Chapter 3, showing comparable bandwidths between ASSR and ABR measures, do not seem to support the notion that ASSRs have a potential advantage due to AM tones being more acoustically specific compared to brief tones used to evoke ABRs (Lins et al., 1996). The greater acoustic specificity for AM tones does not translate into remarkably better ASSR place specificity compared to the ABR to brief tones. Similarly, ASSRs and ABRs are not different in their ability to accurately estimate behavioural hearing thresholds in general (meta-
analysis in Table 5.4; Stapells, 2000b) or in subjects with steep-sloping hearing loss (Purdy & Abbas, in press; Chapter 5), which indicates good place specificity for ASSRs to AM tones and ABRs to brief tones.

Although ASSRs and ABRs have reasonable place-specificity for steep-sloping hearing impairments, ABR results for a single subject (Purdy & Abbas, in press) with a very steep-sloping loss (i.e., 45 dB between 1/2-octave frequencies) have shown that ABRs to brief tones (without notched-noise masking) significantly underestimate the behavioural threshold at the frequency with the greatest loss. Underestimation of behavioural hearing threshold by the tone-evoked ABR is also reported by Stapells, Picton, Durieux-Smith, Edwards, and Moran (1990) for one subject with a very steep-sloping hearing impairment. Contrary to these findings for the ABR, ASSR results from subject (S1) presented in Chapter 5, who has a very steep-sloping hearing loss of 45 dB between 1500 Hz and 2000 Hz, did not show an underestimation of the 2000 Hz behavioural thresholds. Thus, the multiple-ASSR method may have an advantage of being able to assess very steep-sloping hearing losses without requiring masking procedures to limit excitation of adjacent cochlear regions, as compared to the tone-evoked ABR technique. However, this is simply conjecture at this point because there are no repeated-measures studies that have directly compared ASSR and ABR thresholds in subjects with very steep-sloping hearing loss.

Clinical Utility of ASSRs

In order to provide appropriate intervention for infants who likely have a significant hearing impairment, it is important obtain accurate estimation of the audiogram. Because infants less than six months of age are unable to reliably respond behaviourally, objective methods must
be used to evaluate their hearing. Current ABR methods using brief tones provide accurate and reliable measures of hearing sensitivity (Stapells, 2000b). However, there are some drawbacks to using ABRs in testing infants. For example, babies may not to sleep for the required period of time needed to obtain complete assessment of their hearing thresholds. Because the multiple-ASSR method is able to simultaneously evaluate frequency-specific cochlear regions in both ears simultaneously, it may provide a faster means to assess hearing thresholds in infants. Before using this technique in clinical settings, the multiple-ASSR method needs to be validated for assessing hearing thresholds in a large sample of infants with normal and impaired hearing.

**Threshold Detection**

Results from the current thesis show that 70-110 Hz multiple-ASSRs accurately and reliably assesses hearing thresholds in individuals with normal hearing or with sensorineural hearing impairments (Chapter 4 & 5) and are comparable to results previously reported (Aoyagi et al., 1999; Dimitrijevic et al., in press; Lins et al., 1996; Perez-Abalo et al., 2001; Picton et al., 1998; Rance, Rickards, Cohen, De Vidi, & Clark, 1995; Rickards et al., 1994). ASSR thresholds are generally 6-10 dB above behavioural thresholds (see meta-analysis in Table 5.4), with better sensitivity for determining thresholds in subjects with sensorineural hearing losses (compare Table 4.1 to 5.4). Furthermore, results from Chapter 4 and 5 show little difference in multiple-versus single-ASSR thresholds, demonstrating that there is no significant cost to presenting multiple-stimuli simultaneously in order to benefit from the decreased recording time that the multiple-stimulus method offers.

Moderate-to-high correlations (.54 to .99; .75 to .89 for this thesis) between ASSR and behavioural thresholds indicate a good relationship between these two measures (Aoyagi et al.,
1999; Dimitrijevic et al., in press; Lins & Picton, 1995; Perez-Abalo et al., 2001; Picton et al., 1998; Rance et al., 1998; Chapter 5). More importantly, there is a good correspondence between audiogram configurations for multiple-ASSR and behavioural measures in subjects with a variety of types and degrees of hearing impairments (Perez-Abalo et al., 2001; Chapter 5).

Additionally, results from Chapter 5 alleviate the concern of masking of ASSR to high-frequency stimuli by including lower frequency AM tones in the multiple-stimulus method.

**Advantages of the ASSRs**

The following sub-sections discuss some potential advantages that the multiple-ASSR method may have over conventional objective audiometric methods, such as the ABR.

**Response detection.** Currently, tone-evoked ABR waveforms for threshold evaluation (i.e., wave V) are typically identified to be "present" or "absent" by visually determining the replicability between two average waveforms (Stapells, 2000a). This requires a highly trained individual to judge the waveforms and to make sure that there is sufficient averaging to reduce the EEG noise floor to reasonable levels in order to make accurate judgements regarding replicability. Inexperience in judging waveforms and lack of sufficient averaging to reduce EEG noise are common issues that can lead to making response detection difficult for the ABR (Stapells, 2000a). Compared to the ABR response detection, identification of an ASSR is likely more reliable because responses are objectively determined using robust statistical analyses (e.g., F-technique; (Dobie & Wilson, 1996). Thus, the ASSRs have the advantage of objectively identifying responses to within a certain probability.
Dynamic range. A greater dynamic range of intensities may be used for the ASSR methods because behavioural thresholds for AM tones are 9 to 11 dB SPL, whereas for the brief tones (used in ABR testing) behavioural thresholds are 22 to 29 dB SPL. This potentially extends the upper limit of intensities that can be tested. Using maximum stimulus intensities of 100 dB nHL for ABRs and 120 dB nHL for ASSRs, Rance et al. (1998) showed that 8 to 21% of the subjects with a minimal degree of residual hearing had absent ASSR, whereas 27 to 78% had absent ABRs. This suggests that the 20 dB difference in maximum intensities could allow for more subjects to be identified as having some degree of residual hearing. This may have implications for selecting cochlear implant candidates. Although the greater dynamic range seems promising, the amount of time required to average enough trials to obtain a reasonable EEG noise floor for response detection is approximately 3 minutes (in a quiet/sleeping subject) and would exceed safety limits if the stimulus intensity is greater than 95 dB nHL (or 106 dB SPL). Moreover, there is even greater concern when using the multiple-ASSR method to evaluate subjects with a hearing loss. For example, inclusion of high-intensity (i.e., 95 dB nHL) low-frequency AM tones within the multiple-stimulus method would damage hearing in subjects with residual hearing in the low frequencies while evaluating their profound losses in the high frequencies. The concern of exceeding safety limits may be lessened if recording times for individual trials could be reduced (as discussed below).

Recording time. The advantage of being able to assess multiple frequencies simultaneously using ASSRs can dramatically reduce recording time as compared to single-stimulus methods, such as the ABR (see Chapter 4 & 5). By using the multiple-ASSR method, a recording time of approximately 47 minutes is quite reasonable for determining four frequency-
specific thresholds in individuals with impaired hearing. These results are fairly consistent with the results from other studies (Dimitrijevic et al., in press; Perez-Abalo et al., 2001) and indicate that they are within practical limits for using ASSRs to test infant hearing thresholds. Recording times may be even further decreased. For example, an adaptive procedure might be used that would automatically decrease the intensity at one frequency once a response is determined to be significant while averaging continues for the other frequencies. Other recording methods, such as weighted averaging of ASSRs (John, Dimitrijevic, & Picton, 2001), or use of phase-weighting for response detection (Picton, Dimitrijevic, John, & Van Roon, 2000) may further reduce recording times.

**Future Directions and Issues**

Several aspects of using the multiple-ASSR technique as a useful clinical tool still need to be investigated. For example, large scale clinical trials using the multiple-ASSR method to evaluate hearing thresholds in infants would clearly establish its effectiveness as an objective audiometric measure.

Recording ASSRs to bone-conducted stimuli requires examination to determine if it can provide reliable and accurate assessments of normal cochlear function in subjects with conductive or mixed hearing impairments. Although some bone-conducted ASSR studies have been published (Dimitrijevic et al., in press; Lins et al., 1996), preliminary studies in our lab indicate that presenting AM tones through a bone oscillator produces substantial stimulus artefact at the modulation frequency that may be mistaken for a “present” ASSR (S. Small & D.R. Stapells, personal communication, January, 2002).
Although current hearing screening practices reasonably detect most infants with hearing impairments (Fujikawa & Yoshinaga-Itano, 2000), the 70-110 Hz multiple-ASSR method may have some advantages compared to click-ABR screening or otoacoustic-emission screening. For example, using the multiple-ASSR method, both ears may be simultaneously screened, whereas only one ear can be assessed at a time using the click-ABR method. Compared to otoacoustic emissions, 70-110 Hz ASSRs evaluate the auditory system up to the level of the brainstem (Chapter 2), whereas otoacoustic emissions only evaluate outer hair cell function (Lonsbury-Martin et al., 1991). Therefore, ASSR may be less likely to, theoretically, miss (i.e., pass) infants with auditory neuropathies or brainstem lesions. Although there are no data on the rate of false-positives for hearing screening using the multiple-ASSR method (i.e., normal hearing infants failing a hearing screen), threshold results showing that ASSRs can differentiate between normal and mild hearing loss suggests that, for screening purposes, these individuals will not be referred for further testing. This might translate into a low false-positive rate for ASSR hearing screening, unlike that for otoacoustic emissions (Thompson et al., 2001). Investigating the use of multiple-ASSRs as a method for hearing screening is, therefore, encouraged.
References
References


Appendix A: Dipole Source Analysis
Dipole Source Modelling

As previously described by Picton et al. (1995), general principles for dipole source modelling are depicted in Figure A1, which shows an example of sources for ASSRs to a 500-Hz AM tone modulated at 81 Hz. In order to project the source waveforms onto the scalp, we first postulate a reasonable head model based on the anatomy of the head. We then speculate on the number of dipole sources \((n = 1, \ldots, N)\) with a specific location and orientation that may account for the surface recorded waveforms. Source activity from each dipole can be projected onto the scalp at each electrode position \((k = 1, \ldots, K)\) by using transfer coefficients \((C_{nk})\) that take into account the location and orientation of the each dipole, as well as the geometry and impedance of the head model. The resulting source waveform \((U_k)\) at one electrode is thus the summation of the projected scalp potentials from each of the dipole sources. The difference between the scalp-projected waveforms and the actual recorded waveforms can be used to determine how well the model fits the recorded data. One way to measure this is to calculate the residual variance between the two sets of waveforms (i.e., predicted versus actual). The magnitude, orientation, and/or location of each dipole can then be iteratively changed to provide different scalp-projected waveforms \((U_k)\) that minimizes this residual variance; thereby improving the fit of the model.
Appendix A: Dipole Source Modelling

Figure A1. Basic principles of dipole source modelling. Three dipole sources (S1, S2, and S3) are shown in response to the 500-Hz AM tone. Activity from these sources will produce electrical potentials \( U^* \) that sum at each surface electrode (numbered 1-5), which depends on factors such as the location and orientation of the sources, as well as the geometry and impedance of the head. These factors are integrated into one coefficient \( C_{nk} \) for each source and then used to calculate the projected scalp waveforms at a specific electrode.

\[
U_4 = C_{14}S_1 + C_{24}S_2 + C_{34}S_3
\]
Appendix B: Data and Statistical Results for Chapter 2
### Table B1

Amplitudes (µVeff) for source waveforms for each subject by modulation frequency

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## Table B2
Onset phases (degrees) for source waveforms for each subject by modulation frequency

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Table B3
Amplitudes (μVeff) for source waveforms for each subject by modulation frequency for Test data

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Table B5

Residual variances for source models fitting individual data

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*Note.* fm = modulation frequency.
Table B6

Results from a three-way repeated-measures ANOVA: 2(ear) x 3(fm) x 6 (sources) for source amplitudes

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<th>Effect</th>
<th>df</th>
<th>F</th>
<th>ε&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
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<td>–</td>
<td>.02183</td>
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<td>20.74311*</td>
<td>1.0</td>
<td>.00013*</td>
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<tr>
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<td>19.80776*</td>
<td>0.35</td>
<td>.00023*</td>
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<tr>
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<td>3.28021</td>
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<td>.07304</td>
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<td>4.98071*</td>
<td>–</td>
<td>.00003*</td>
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<td>1.19282</td>
<td>–</td>
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*Note. fm = modulation frequency.*

<sup>a</sup> Huynh-Feldt epsilon correction factor for degrees of freedom. <sup>b</sup> Probability reflects corrected degrees of freedom. <sup>c</sup> Ear Stimulation.

* significant (p<.01)
Table B7

Results from a three-way repeated-measures ANOVA: 2(ear) x 3(fm) x 6 (sources) for estimated latencies of source waveforms

<table>
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<th>p  $^c$</th>
</tr>
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<tr>
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<td>478.3711*</td>
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<td>57.3224*</td>
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* significant (p<.01)

Note. fm = modulation frequency.

$^a$ Huynh-Feldt epsilon correction factor for degrees of freedom. $^b$ Probability reflects corrected degrees of freedom. $^c$ Ear Stimulation.
Table C1

ASSR amplitudes (nV) for multiple presentations of AM tones (500, 1000, 2000, and 4000 Hz) with ipsilateral high-pass noise at cutoff frequencies ranging from 0.250 to 16.0 kHz

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</tr>
<tr>
<td>S8</td>
<td>9</td>
</tr>
<tr>
<td>S9</td>
<td>8</td>
</tr>
</tbody>
</table>

Multiple-Stimulus Condition: 500 Hz AM tone

Multiple-Stimulus Condition: 1000 Hz AM tone

S1     | 7     | 7     | 6     | 6     | 24    | 49    | 57    | 70    | 71    | 72    | 62    | 76    | 110   |
S2     | 7     | 8     | 5     | 7     | 6     | 62    | 79    | 86    | 91    | 84    | 97    | 83    | 96    |
S3     | 6     | 7     | 7     | 7     | 6     | 23    | 44    | 33    | 36    | 31    | 46    | 50    | 32    |
S4     | 7     | 5     | 6     | 6     | 19    | 44    | 53    | 52    | 45    | 58    | 42    | 57    | 54    |
S5     | 5     | 6     | 7     | 7     | 23    | 43    | 56    | 43    | 53    | 70    | 62    | 84    | 75    |
S6     | 9     | 4     | 7     | 6     | 7     | 48    | 45    | 48    | 44    | 48    | 49    | 46    | 62    |
S7     | 7     | 8     | 8     | 7     | 17    | 69    | 52    | 61    | 54    | 41    | 66    | 76    | 75    |
S8     | 7     | 7     | 5     | 6     | 14    | 49    | 47    | 50    | 37    | 40    | 37    | 50    | 55    |
S9     | 7     | 5     | 5     | 8     | 6     | 40    | 46    | 41    | 43    | 54    | 54    | 62    | 54    |

(table continues)
### HPN cutoff frequencies (kHz)

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Table C2

ASSR amplitudes (nV) for single presentations of AM tones (500 and 2000 Hz) with ipsilateral high-pass noise at cutoff frequencies ranging from 0.250 to 16.0 kHz

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Table C3

Derived-ASSR amplitudes (nV) for multiple presentation of AM tones (500, 1000, 2000 and 4000 Hz) in 1-octave-wide derived bands at \( \sqrt{2} \)-octave intervals between 0.25 and 8.0 kHz.

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Multiple-Stimulus Condition: 500 Hz AM tone

Multiple-Stimulus Condition: 1000 Hz AM tone

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## Appendix C: Data and Statistical Results for Chapter 3

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Table C4

Derived-ASSR amplitudes (nV) for single presentations of AM tones (5000 and 2000 Hz) in 1-octave-wide derived bands at ½-octave intervals between 0.250 and 2.83 kHz

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Table C5

Measurements for derived-band multiple-stimulus ASSRs

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<td>2482</td>
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<td>S5</td>
<td>2535</td>
<td>6618</td>
<td>4083</td>
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<td>S7</td>
<td>4521</td>
<td>7177</td>
<td>2656</td>
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<td>S8</td>
<td>3142</td>
<td>7626</td>
<td>4484</td>
<td>4895</td>
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<td>S9</td>
<td>3043</td>
<td>5357</td>
<td>2314</td>
<td>4038</td>
</tr>
</tbody>
</table>

*Note. BW<sub>6dB</sub> = bandwidths at 50 % of the maximal derived-band ASSR for each subject by subtracting the lower frequency edge (LH) of the profile from the higher frequency edge (HF). CF = centre frequencies calculated as the geometric mean between LF and HF.*
### Table C6

Measurements for derived-band single-stimulus ASSRs

<table>
<thead>
<tr>
<th>Subject</th>
<th>LF (Hz)</th>
<th>HF (Hz)</th>
<th>$BW_{6\text{dB}}$ (Hz)</th>
<th>CF (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single-Stimulus Condition: 500 Hz</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>S1</td>
<td>309</td>
<td>637</td>
<td>327</td>
<td>444</td>
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<td>S2</td>
<td>307</td>
<td>1127</td>
<td>820</td>
<td>588</td>
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<td>S3</td>
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<td>468</td>
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<td>S5</td>
<td>295</td>
<td>883</td>
<td>588</td>
<td>511</td>
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<tr>
<td>S6</td>
<td>389</td>
<td>946</td>
<td>557</td>
<td>607</td>
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<td>S7</td>
<td>401</td>
<td>746</td>
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<td>547</td>
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<td>S8</td>
<td>584</td>
<td>1294</td>
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<td>869</td>
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<td>S9</td>
<td>312</td>
<td>744</td>
<td>431</td>
<td>482</td>
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<tr>
<td><strong>Single-Stimulus Condition: 2000 Hz</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>S1</td>
<td>1124</td>
<td>2564</td>
<td>1440</td>
<td>1698</td>
</tr>
<tr>
<td>S2</td>
<td>1153</td>
<td>2423</td>
<td>1270</td>
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<tr>
<td>S3</td>
<td>1117</td>
<td>2552</td>
<td>1435</td>
<td>1688</td>
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<tr>
<td>S4</td>
<td>1051</td>
<td>1926</td>
<td>875</td>
<td>1423</td>
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<td>S5</td>
<td>1134</td>
<td>2564</td>
<td>1430</td>
<td>1705</td>
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<tr>
<td>S6</td>
<td>1075</td>
<td>1908</td>
<td>833</td>
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<tr>
<td>S7</td>
<td>1133</td>
<td>2221</td>
<td>1089</td>
<td>1586</td>
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<tr>
<td>S8</td>
<td>1079</td>
<td>3657</td>
<td>2578</td>
<td>1986</td>
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<td>S9</td>
<td>1452</td>
<td>2839</td>
<td>1387</td>
<td>2031</td>
</tr>
</tbody>
</table>

*Note.* $BW_{6\text{dB}}$ = bandwidths at 50% of the maximal derived-band ASSR for each subject by subtracting the lower frequency edge (LH) of the profile from the higher frequency edge (HF).

$CF =$ centre frequencies calculated as the geometric mean between LF and HF.
Table C7

Results of 2-way repeated measures ANOVAs of ASSRs in HPN for the multiple-stimulus condition

<table>
<thead>
<tr>
<th>Effects</th>
<th>df</th>
<th>F</th>
<th>( \varepsilon )^{c}</th>
<th>p^{d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier Frequency (^a)</td>
<td>3, 24</td>
<td>1.92</td>
<td>0.8</td>
<td>.168</td>
</tr>
<tr>
<td>HPN (^b)</td>
<td>5, 40</td>
<td>109</td>
<td>0.5</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Carrier Frequency x HPN</td>
<td>15, 120</td>
<td>3.86</td>
<td>0.4</td>
<td>.004*</td>
</tr>
</tbody>
</table>

*Note.* HPN = high pass noise.

\(^a\) Carrier Frequency: 500, 1000, 2000, and 4000 Hz. \(^b\) High pass noise cutoff frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, 1.0, and 1.5 octaves from stimulus frequency.

\(^c\) Huynh-Feldt epsilon correction factor for degrees freedom. \(^d\) Probability reflects corrected degrees of freedom.

* significant (p <.01)
### Table C8

Results of a 2-way repeated measures ANOVA of derived-band ASSRs for the multiple-stimulus condition

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>$\varepsilon^c$</th>
<th>p $^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carrier Frequency $^a$</td>
<td>3, 24</td>
<td>2.65</td>
<td>0.42</td>
<td>.130</td>
</tr>
<tr>
<td>CF $^b$</td>
<td>4, 32</td>
<td>30.5</td>
<td>1.0</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Carrier Frequency x CF</td>
<td>12, 96</td>
<td>2.19</td>
<td>0.5</td>
<td>.061</td>
</tr>
</tbody>
</table>

*Note. CF = centre frequency of derived bands.*

$^a$ Carrier frequency: 500, 1000, 2000, and 4000 Hz. $^b$ Derived-band centre frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, and 1.0 octaves from stimulus frequency. $^c$ Huynh-Feldt epsilon correction factor for degrees freedom. $^d$ Probability reflects corrected degrees of freedom.

* significant (p <.01)
### Table C9

Results of a 3-way repeated measures ANOVA of ASSRs in HPN for multiple-stimulus versus single-stimulus conditions

<table>
<thead>
<tr>
<th>Effects</th>
<th>df</th>
<th>F</th>
<th>ε</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition (^a)</td>
<td>1, 8</td>
<td>1.05</td>
<td>1</td>
<td>.336</td>
</tr>
<tr>
<td>Carrier Frequency (^b)</td>
<td>1, 8</td>
<td>2.83</td>
<td>1</td>
<td>.131</td>
</tr>
<tr>
<td>HPN (^c)</td>
<td>5, 40</td>
<td>243.5</td>
<td>0.67</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>1, 8</td>
<td>0.02</td>
<td>1</td>
<td>.884</td>
</tr>
<tr>
<td>Condition x HPN</td>
<td>5, 40</td>
<td>0.69</td>
<td>0.53</td>
<td>.553</td>
</tr>
<tr>
<td>Carrier Frequency x HPN</td>
<td>5, 40</td>
<td>8.87</td>
<td>0.68</td>
<td>&lt;.001*</td>
</tr>
<tr>
<td>Condition x Carrier Frequency xHPN</td>
<td>5, 40</td>
<td>1.31</td>
<td>0.71</td>
<td>.291</td>
</tr>
</tbody>
</table>

*Note.* HPN = high pass noise.

\(^a\) Condition: single vs multiple stimuli. \(^b\) Carrier Frequency: 500 vs 2000 Hz. \(^c\) High pass noise cutoff frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, 1.0, and 1.5 octaves from stimulus frequency. \(^d\) Huynh-Feldt epsilon correction factor for degrees freedom. \(^e\) Probability reflects corrected degrees of freedom.

* *significant (p <.01)
Table C10

Results of a 3-way repeated measures ANOVA of derived-band ASSRs for multiple-stimulus versus single-stimulus conditions

<table>
<thead>
<tr>
<th>Effects</th>
<th>df</th>
<th>F</th>
<th>( \epsilon )^d</th>
<th>p</th>
<th>e</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition ^a</td>
<td>1, 8</td>
<td>3.24</td>
<td>1</td>
<td>.11</td>
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</tr>
<tr>
<td>Carrier Frequency ^b</td>
<td>1, 8</td>
<td>2.81</td>
<td>1</td>
<td>.132</td>
<td></td>
</tr>
<tr>
<td>CF ^c</td>
<td>4, 32</td>
<td>35.09</td>
<td>0.415</td>
<td>&lt;.001*</td>
<td></td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>1, 8</td>
<td>0.09</td>
<td>1</td>
<td>.768</td>
<td></td>
</tr>
<tr>
<td>Condition x CF</td>
<td>4, 32</td>
<td>2.69</td>
<td>0.523</td>
<td>.095</td>
<td></td>
</tr>
<tr>
<td>Carrier Frequency x CF</td>
<td>4, 32</td>
<td>4</td>
<td>1</td>
<td>.010*</td>
<td></td>
</tr>
<tr>
<td>Condition x Carrier Frequency x CF</td>
<td>4, 32</td>
<td>0.82</td>
<td>0.547</td>
<td>.468</td>
<td></td>
</tr>
</tbody>
</table>

*Note. CF = centre frequency.

^a Condition: single vs multiple stimuli. ^b Carrier Frequency: 500 vs 2000 Hz. ^c Derived-band centre frequency normalized to carrier frequency: -1.0, -0.5, 0, 0.5, and 1.0 octaves from stimulus frequency. ^d Huynh-Feldt epsilon correction factor for degrees freedom. ^e Probability reflects corrected degrees of freedom.

* significant (p <.01)
Table C11

Results of a 1-way repeated measures ANOVA of $Q_{6\text{dB}}$ and normalized centre frequency ($\% \text{ CF}$) for the multiple-stimulus condition

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>$F$</th>
<th>$\varepsilon^a$</th>
<th>$p^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Q_{6\text{dB}}$</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Carrier Frequency</td>
<td>3, 24</td>
<td>1.37</td>
<td>.938</td>
<td>.275</td>
</tr>
<tr>
<td>$% \text{ CF}$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>3, 24</td>
<td>2.64</td>
<td>.480</td>
<td>.130</td>
</tr>
</tbody>
</table>

$^a$ Huynh-Feldt epsilon correction factor for degrees freedom. $^b$ Probability reflects corrected degrees of freedom.

* significant ($p < .01$)
Table C12

Results of a 2-way repeated measures ANOVA of $Q_{6dB}$ and normalized centre frequency (% CF) for the single-stimulus condition

<table>
<thead>
<tr>
<th>Effect</th>
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<th>F</th>
<th>$\epsilon$</th>
<th>p</th>
</tr>
</thead>
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<tr>
<td>$Q_{6dB}$</td>
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</tr>
<tr>
<td>Condition $^a$</td>
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<td>--</td>
<td>.655</td>
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<tr>
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<td>1, 8</td>
<td>1.916</td>
<td>--</td>
<td>.204</td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>1, 8</td>
<td>.621</td>
<td>--</td>
<td>.453</td>
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<tr>
<td>% CF</td>
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</tr>
<tr>
<td>Condition $^a$</td>
<td>1, 8</td>
<td>.058</td>
<td>--</td>
<td>.816</td>
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<tr>
<td>Carrier Frequency $^b$</td>
<td>1, 8</td>
<td>10.861</td>
<td>--</td>
<td>.011</td>
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<tr>
<td>Condition x Carrier Frequency</td>
<td>1, 8</td>
<td>.037</td>
<td>--</td>
<td>.852</td>
</tr>
</tbody>
</table>

$^a$ Condition: single vs multiple stimuli. $^b$ Carrier Frequency: 500 vs 2000 Hz. $^c$ Huynh-Feldt epsilon correction factor for degrees freedom. $^d$ Probability reflects corrected degrees of freedom.

* significant (p <.01)
Table D1

Behavioural and ASSR thresholds, from subjects with normal hearing, for conditions monotonic single (MS), monotic multiple (MM) and dichotic multiple (DM) across frequencies of 500, 1000, 2000 and 4000 Hz. Thresholds are listed in dB SPL. Test ear is designated for each subject as right (RE) and left (LE) ear. Averages and standard deviations (St.Dev.) are also given.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test Ear</th>
<th>Behavioural</th>
<th>Condition MS</th>
<th>Condition MM</th>
<th>Condition DM</th>
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<tr>
<td></td>
<td></td>
<td>500 1000 2000 4000</td>
<td>500 1000 2000 4000</td>
<td>500 1000 2000 4000</td>
<td>500 1000 2000 4000</td>
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<td>S1</td>
<td>RE</td>
<td>10 10 5 5</td>
<td>20 10 10 15</td>
<td>20 0 15 25</td>
<td>25 10 5 30</td>
</tr>
<tr>
<td>S2</td>
<td>LE</td>
<td>5 5 5 5</td>
<td>25 15 25 10</td>
<td>10 15 25 15</td>
<td>20 10 20 5</td>
</tr>
<tr>
<td>S3</td>
<td>RE</td>
<td>10 10 5 10</td>
<td>20 40 35 35</td>
<td>15 35 30 0</td>
<td>35 30 30 25</td>
</tr>
<tr>
<td>S4</td>
<td>RE</td>
<td>10 10 5 5</td>
<td>0 15 30 20</td>
<td>20 20 20 20</td>
<td>10 15 15 30</td>
</tr>
<tr>
<td>S5</td>
<td>RE</td>
<td>10 10 15 15</td>
<td>30 5 20 30</td>
<td>30 20 30 35</td>
<td>35 15 15 30</td>
</tr>
<tr>
<td>S6</td>
<td>LE</td>
<td>10 5 5 5</td>
<td>20 35 15 20</td>
<td>40 30 10 30</td>
<td>30 20 20 20</td>
</tr>
<tr>
<td>S7</td>
<td>LE</td>
<td>15 10 5 10</td>
<td>10 20 15 20</td>
<td>20 25 15 30</td>
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<td>15 15 10 0</td>
<td>35 30 5 15</td>
<td>40 15 20 15</td>
<td>35 25 10 20</td>
</tr>
<tr>
<td>S10</td>
<td>RE</td>
<td>10 0 10 0</td>
<td>15 0 20 20</td>
<td>10 10 0 10</td>
<td>25 5 10 20</td>
</tr>
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</table>
### Table D2

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test</th>
<th>Condition: MM</th>
<th>Condition: DM</th>
<th>Condition: Single (MS)</th>
<th>Condition: Single (DS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 dB SPL</td>
<td>30 dB SPL</td>
<td>500 Hz, 1000 Hz, 2000 Hz, 4000 Hz</td>
<td>500 Hz, 1000 Hz, 2000 Hz, 4000 Hz</td>
<td>500 Hz, 1000 Hz, 2000 Hz, 4000 Hz</td>
</tr>
<tr>
<td>S1</td>
<td>RE</td>
<td>0.026</td>
<td>0.029</td>
<td>0.015</td>
<td>0.028</td>
</tr>
<tr>
<td>S2</td>
<td>LE</td>
<td>0.055</td>
<td>0.043</td>
<td>0.045</td>
<td>0.025</td>
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<tr>
<td>S3</td>
<td>RE</td>
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<td>0.019</td>
<td>0.007</td>
<td>0.003</td>
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<td>RE</td>
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<td>0.015</td>
<td>0.016</td>
<td>0.022</td>
</tr>
<tr>
<td>S5</td>
<td>RE</td>
<td>0.029</td>
<td>0.016</td>
<td>0.016</td>
<td>0.026</td>
</tr>
<tr>
<td>S6</td>
<td>LE</td>
<td>0.026</td>
<td>0.026</td>
<td>0.039</td>
<td>0.034</td>
</tr>
<tr>
<td>S7</td>
<td>RE</td>
<td>0.010</td>
<td>0.024</td>
<td>0.022</td>
<td>0.026</td>
</tr>
<tr>
<td>S8</td>
<td>LE</td>
<td>0.007</td>
<td>0.030</td>
<td>0.037</td>
<td>0.020</td>
</tr>
<tr>
<td>S9</td>
<td>RE</td>
<td>0.022</td>
<td>0.030</td>
<td>0.022</td>
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<td>S10</td>
<td>RE</td>
<td>0.065</td>
<td>0.042</td>
<td>0.101</td>
<td>0.062</td>
</tr>
</tbody>
</table>

ASR amplitudes (microVolts) for 30 and 60 dB SPL AM tones (carrier frequencies of 500, 1000, 2000, and 4000 Hz) across conditions mononic single (MS), mononic multiple (MM), and dichotic multiple (DM).
Table D3
ASSR phase delays (degrees) for 30 and 60 dB SPL AM tones (carrier frequencies of 500, 1000, 2000, and 4000 Hz) across conditions monotonic single (MS), monotonic multiple (MM), and dichotic multiple (DM)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test</th>
<th>Condition: MS</th>
<th>Condition: MM</th>
<th>Condition: DM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 Hz</td>
<td>1000 Hz</td>
<td>2000 Hz</td>
</tr>
<tr>
<td>S1</td>
<td>RE</td>
<td>366</td>
<td>263</td>
<td>201</td>
</tr>
<tr>
<td>S2</td>
<td>LE</td>
<td>201</td>
<td>195</td>
<td>135</td>
</tr>
<tr>
<td>S3</td>
<td>RE</td>
<td>66</td>
<td>290</td>
<td>236</td>
</tr>
<tr>
<td>S4</td>
<td>RE</td>
<td>222</td>
<td>205</td>
<td>167</td>
</tr>
<tr>
<td>S5</td>
<td>RE</td>
<td>184</td>
<td>250</td>
<td>190</td>
</tr>
<tr>
<td>S6</td>
<td>LE</td>
<td>402</td>
<td>232</td>
<td>208</td>
</tr>
<tr>
<td>S7</td>
<td>LE</td>
<td>92</td>
<td>195</td>
<td>175</td>
</tr>
<tr>
<td>S8</td>
<td>RE</td>
<td>292</td>
<td>277</td>
<td>276</td>
</tr>
<tr>
<td>S9</td>
<td>LE</td>
<td>720</td>
<td>282</td>
<td>173</td>
</tr>
<tr>
<td>S10</td>
<td>RE</td>
<td>158</td>
<td>318</td>
<td>233</td>
</tr>
</tbody>
</table>

30 dB SPL

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test</th>
<th>Condition: MS</th>
<th>Condition: MM</th>
<th>Condition: DM</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>500 Hz</td>
<td>1000 Hz</td>
<td>2000 Hz</td>
</tr>
<tr>
<td>S1</td>
<td>RE</td>
<td>256</td>
<td>-68</td>
<td>161</td>
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<tr>
<td>S2</td>
<td>LE</td>
<td>34</td>
<td>99</td>
<td>118</td>
</tr>
<tr>
<td>S3</td>
<td>RE</td>
<td>113</td>
<td>73</td>
<td>146</td>
</tr>
<tr>
<td>S4</td>
<td>RE</td>
<td>123</td>
<td>133</td>
<td>142</td>
</tr>
<tr>
<td>S5</td>
<td>RE</td>
<td>107</td>
<td>201</td>
<td>150</td>
</tr>
<tr>
<td>S6</td>
<td>LE</td>
<td>80</td>
<td>106</td>
<td>105</td>
</tr>
<tr>
<td>S7</td>
<td>LE</td>
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<td>98</td>
<td>120</td>
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<tr>
<td>S8</td>
<td>RE</td>
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<td>187</td>
<td>192</td>
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<tr>
<td>S10</td>
<td>RE</td>
<td>112</td>
<td>147</td>
<td>178</td>
</tr>
</tbody>
</table>

60 dB SPL
Table D4

Number of sweeps required to estimate threshold for conditions monotic single (MS), monotic multiple (MM), and dichotic multiple (DM)

<table>
<thead>
<tr>
<th>Subject</th>
<th>MS</th>
<th>MM</th>
<th>DM</th>
<th>Estimated recording time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>38</td>
<td>34</td>
<td>28</td>
<td>124.5 111.4 91.7</td>
</tr>
<tr>
<td>S2</td>
<td>53</td>
<td>21</td>
<td>21</td>
<td>173.6 68.8 68.8</td>
</tr>
<tr>
<td>S3</td>
<td>45</td>
<td>25</td>
<td>17</td>
<td>147.4 81.9 55.7</td>
</tr>
<tr>
<td>S4</td>
<td>48</td>
<td>22</td>
<td>37</td>
<td>157.2 72.1 121.2</td>
</tr>
<tr>
<td>S5</td>
<td>47</td>
<td>25</td>
<td>28</td>
<td>154.0 81.9 91.7</td>
</tr>
<tr>
<td>S6</td>
<td>52</td>
<td>35</td>
<td>25</td>
<td>170.4 114.7 81.9</td>
</tr>
<tr>
<td>S7</td>
<td>64</td>
<td>22</td>
<td>23</td>
<td>209.7 72.1 75.3</td>
</tr>
<tr>
<td>S8</td>
<td>49</td>
<td>24</td>
<td>20</td>
<td>160.5 78.6 65.5</td>
</tr>
<tr>
<td>S9</td>
<td>52</td>
<td>29</td>
<td>29</td>
<td>170.4 95.0 95.0</td>
</tr>
<tr>
<td>S10</td>
<td>54</td>
<td>27</td>
<td>27</td>
<td>176.9 88.5 88.5</td>
</tr>
</tbody>
</table>
Table D5

Two-way ANOVA results comparing thresholds between four conditions (behavioural, MS, MM, and DM) and across four frequencies (500, 1000, 2000, and 4000 Hz)

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>ε&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>3, 27</td>
<td>20.79</td>
<td>.75</td>
<td>&lt;.00001*</td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>3, 27</td>
<td>.91</td>
<td>.88</td>
<td>.440</td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>9, 81</td>
<td>1.36</td>
<td></td>
<td>.218</td>
</tr>
</tbody>
</table>

<sup>a</sup> Greenhouse-Geisser epsilon correction factor for degrees of freedom. <sup>b</sup> Probability reflects corrected degrees of freedom.

* significant (p<.01)
Table D6

Two-way ANOVA results comparing difference scores (ASSR minus behavioural thresholds) between three conditions (MS, MM, and DM) and across four frequencies (500, 1000, 2000, and 4000 Hz)

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>$\varepsilon^a$</th>
<th>P $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>2, 18</td>
<td>.106</td>
<td>.68</td>
<td>.822</td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>3, 27</td>
<td>.752</td>
<td>.77</td>
<td>.501</td>
</tr>
<tr>
<td>Condition x</td>
<td>6, 54</td>
<td>1.691</td>
<td>-</td>
<td>.141</td>
</tr>
</tbody>
</table>

$^a$ Greenhouse-Geisser epsilon correction factor for degrees of freedom. $^b$ Probability reflects corrected degrees of freedom.

* significant (p<.01)
Table D7

Three-way ANOVA results comparing amplitudes for three conditions (MS, MM, and DM), four frequencies (500, 1000, 2000, and 4000 Hz), and two intensities (30 and 60 dB SPL)

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>$\varepsilon^a$</th>
<th>p  $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>2, 18</td>
<td>1.113</td>
<td>.95</td>
<td>.348</td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>3, 27</td>
<td>3.709</td>
<td>.829</td>
<td>.033</td>
</tr>
<tr>
<td>Intensity</td>
<td>1, 9</td>
<td>189.969</td>
<td>–</td>
<td>&lt;.00001*</td>
</tr>
<tr>
<td>Condition x Carrier Frequency</td>
<td>6, 54</td>
<td>1.190</td>
<td>–</td>
<td>.326</td>
</tr>
<tr>
<td>Condition x Intensity</td>
<td>2, 18</td>
<td>.083</td>
<td>–</td>
<td>.921</td>
</tr>
<tr>
<td>Carrier Frequency x Intensity</td>
<td>3, 27</td>
<td>2.056</td>
<td>–</td>
<td>.130</td>
</tr>
<tr>
<td></td>
<td>Condition x Carrier frequency x Intensity</td>
<td>6, 54</td>
<td>1.108</td>
<td>–</td>
</tr>
</tbody>
</table>

* Greenhouse-Geisser epsilon correction factor for degrees of freedom. $^b$ Probability reflects corrected degrees of freedom.

* significant (p<.01)
Table D8

Three-way ANOVA results comparing phase delays for three conditions (MS, MM, and DM), four frequencies (500, 1000, 2000, and 4000 Hz), and two intensities (30 and 60 dB SPL)

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>ε^a</th>
<th>p^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Condition</td>
<td>1, 9</td>
<td>237.634</td>
<td>-</td>
<td>&lt;.00001</td>
</tr>
<tr>
<td>Carrier Frequency</td>
<td>2, 18</td>
<td>.454</td>
<td>-</td>
<td>.642</td>
</tr>
<tr>
<td>Intensity</td>
<td>3, 27</td>
<td>1.310</td>
<td>-</td>
<td>.291</td>
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<tr>
<td>Condition x Carrier Frequency</td>
<td>2, 18</td>
<td>5.386</td>
<td>-</td>
<td>.015</td>
</tr>
<tr>
<td>Condition x Intensity</td>
<td>3, 27</td>
<td>3.709</td>
<td>-</td>
<td>.024</td>
</tr>
<tr>
<td>Carrier Frequency x Intensity</td>
<td>6, 54</td>
<td>.712</td>
<td>-</td>
<td>.642</td>
</tr>
<tr>
<td>Condition x Carrier frequency x</td>
<td>6, 54</td>
<td>1.322</td>
<td>-</td>
<td>.264</td>
</tr>
</tbody>
</table>

^a Greenhouse-Geisser epsilon correction factor for degrees of freedom. ^b Probability reflects corrected degrees of freedom.

* significant (p<.01)
Appendix E: Data and Statistical Results for Chapter 5
Table E1

Behavioural and ASSR thresholds, from subjects with hearing-impairments, for conditions monotic single (MS) and monotic multiple (MM) across frequencies of 500, 1000, 2000 and 4000 Hz. Thresholds are listed in dB nHL. Test ear is designated for each subject as right (RE) and left (LE) ear. Averages and standard deviations (St.Dev.) are also given.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Test Ear</th>
<th>Behavioural</th>
<th>Condition MM</th>
<th>Condition MS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>500 1000 2000 4000</td>
<td>500 1000 2000 4000</td>
<td>500 1000 2000 4000</td>
</tr>
<tr>
<td>S1</td>
<td>RE</td>
<td>10 10 15 60</td>
<td>40 20 30 60</td>
<td>-- -- -- 60</td>
</tr>
<tr>
<td>S2</td>
<td>LE</td>
<td>10 20 45 65</td>
<td>50 30 -- 60</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S3</td>
<td>RE</td>
<td>5 10 40 70</td>
<td>-- -- 70</td>
<td>-- -- -- 80</td>
</tr>
<tr>
<td>S4</td>
<td>LE</td>
<td>20 20 15 80</td>
<td>10 20 30 60</td>
<td>-- 30 70</td>
</tr>
<tr>
<td>S5</td>
<td>RE</td>
<td>45 50 50 65</td>
<td>40 50 50 --</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S6</td>
<td>LE</td>
<td>20 50 90 105</td>
<td>40 40 100 100</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S7</td>
<td>LE</td>
<td>20 30 60 60</td>
<td>30 30 80 60</td>
<td>-- 80 --</td>
</tr>
<tr>
<td>S8</td>
<td>LE</td>
<td>10 40 35 50</td>
<td>10 50 50 50</td>
<td>-- 50 -- --</td>
</tr>
<tr>
<td>S9</td>
<td>RE</td>
<td>40 30 20 35</td>
<td>50 30 40 40</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S10</td>
<td>RE</td>
<td>10 5 15 65</td>
<td>30 20 40 50</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S11</td>
<td>LE</td>
<td>30 40 45 85</td>
<td>50 70 50 90</td>
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<tr>
<td>S12</td>
<td>RE</td>
<td>70 75 105 105</td>
<td>70 80 -- --</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S13</td>
<td>RE</td>
<td>10 5 0 35</td>
<td>-- -- -- 50</td>
<td>-- -- -- 40</td>
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<td>S14</td>
<td>LE</td>
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<td>20 30 90 80</td>
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</tr>
<tr>
<td>S15</td>
<td>RE</td>
<td>5 15 60 60</td>
<td>-- 10 70 80</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S16</td>
<td>LE</td>
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<td>80 80 80 70</td>
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</tr>
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<td>S17</td>
<td>RE</td>
<td>5 5 70 80</td>
<td>0 10 70 80</td>
<td>10 80 --</td>
</tr>
<tr>
<td>S18</td>
<td>LE</td>
<td>30 65 65 70</td>
<td>-- 70 70 --</td>
<td>70 -- --</td>
</tr>
<tr>
<td>S19</td>
<td>LE</td>
<td>15 20 60 70</td>
<td>20 20 60 70</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S20</td>
<td>LE</td>
<td>10 10 60 65</td>
<td>30 20 70 70</td>
<td>-- 20 50 --</td>
</tr>
<tr>
<td>S21</td>
<td>LE</td>
<td>15 20 45 85</td>
<td>50 40 80 80</td>
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</tr>
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<td>S22</td>
<td>LE</td>
<td>15 20 40 40</td>
<td>30 30 60 60</td>
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<td>S23</td>
<td>LE</td>
<td>5 30 70 55</td>
<td>-- 40 70 60</td>
<td>-- -- -- --</td>
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<tr>
<td>S24</td>
<td>RE</td>
<td>15 20 35 60</td>
<td>30 30 40 60</td>
<td>-- 30 40 70</td>
</tr>
<tr>
<td>S25</td>
<td>LE</td>
<td>45 50 40 60</td>
<td>60 50 60 70</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S26</td>
<td>LE</td>
<td>20 35 55 80</td>
<td>50 50 40 80</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S27</td>
<td>LE</td>
<td>15 10 5 45</td>
<td>30 30 10 50</td>
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</tr>
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<td>S28</td>
<td>RE</td>
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<td>40 40 40 30</td>
<td>-- -- -- --</td>
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<td>S29</td>
<td>RE</td>
<td>5 15 40 65</td>
<td>40 40 40 70</td>
<td>-- -- -- --</td>
</tr>
<tr>
<td>S30</td>
<td>LE</td>
<td>25 15 10 15</td>
<td>40 10 20 20</td>
<td>30 -- -- --</td>
</tr>
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<td>S31</td>
<td>LE</td>
<td>10 20 40 40</td>
<td>20 30 50 60</td>
<td>40 30 50 60</td>
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</table>
Table E2

Estimated recording times from number of sweeps required to determine threshold for the monotic multiple condition

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Total # of sweeps</th>
<th>Recording time (min)</th>
<th># thresholds</th>
<th>Time/threshold (min)</th>
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</thead>
<tbody>
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<td>S1</td>
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<td>14</td>
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<td>S2</td>
<td>139</td>
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<td>3</td>
<td>13</td>
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<tr>
<td>S3</td>
<td>91</td>
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<td>1</td>
<td>25</td>
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<tr>
<td>S4</td>
<td>87</td>
<td>24</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>S5</td>
<td>63</td>
<td>17</td>
<td>3</td>
<td>6</td>
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<td>S6</td>
<td>247</td>
<td>67</td>
<td>2</td>
<td>34</td>
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<td>S7</td>
<td>215</td>
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<td>4</td>
<td>15</td>
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<td>134</td>
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<td>4</td>
<td>9</td>
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<td>6</td>
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<td>13</td>
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<td>4</td>
<td>9</td>
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<td>S12</td>
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<td>2</td>
<td>10</td>
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<tr>
<td>S13</td>
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<td>1</td>
<td>50</td>
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<tr>
<td>S14</td>
<td>217</td>
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<td>15</td>
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<td>S15</td>
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<td>22</td>
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<tr>
<td>S16</td>
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<td>4</td>
<td>10</td>
</tr>
<tr>
<td>S17</td>
<td>224</td>
<td>61</td>
<td>4</td>
<td>15</td>
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<td>S19</td>
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<td>4</td>
<td>12</td>
</tr>
<tr>
<td>S20</td>
<td>174</td>
<td>48</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>S21</td>
<td>227</td>
<td>62</td>
<td>4</td>
<td>15</td>
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<tr>
<td>S22</td>
<td>197</td>
<td>54</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>S23</td>
<td>238</td>
<td>65</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>S24</td>
<td>110</td>
<td>30</td>
<td>4</td>
<td>8</td>
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<tr>
<td>S25</td>
<td>193</td>
<td>53</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>S26</td>
<td>227</td>
<td>62</td>
<td>4</td>
<td>15</td>
</tr>
<tr>
<td>S27</td>
<td>123</td>
<td>34</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>S28</td>
<td>232</td>
<td>63</td>
<td>4</td>
<td>16</td>
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<tr>
<td>S29</td>
<td>153</td>
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<td>S30</td>
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<tr>
<td>S31</td>
<td>93</td>
<td>25</td>
<td>4</td>
<td>6</td>
</tr>
</tbody>
</table>
Table E3

Results from a two-way repeated-measures ANOVA: 2 (Group) x 4(Frequency) for difference scores (multiple-ASSR threshold minus behavioural threshold) for the multiple-stimulus condition

<table>
<thead>
<tr>
<th>Effect</th>
<th>df</th>
<th>F</th>
<th>ε</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1, 21</td>
<td>0.12</td>
<td>-</td>
<td>0.729</td>
</tr>
<tr>
<td>Frequency</td>
<td>3, 63</td>
<td>5.59</td>
<td>1.0</td>
<td>0.002*</td>
</tr>
<tr>
<td>Group x Frequency</td>
<td>3, 63</td>
<td>1.87</td>
<td>-</td>
<td>0.144</td>
</tr>
</tbody>
</table>

*a Huynh-Feldt epsilon correction factor for degrees of freedom.  
b Probability reflects corrected degrees of freedom.

* significant (p<.01)