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The Auditory Steady State Response in Individuals with Neurological Insult of the Central Auditory Nervous System

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Abstract

The auditory steady state response (ASSR) has recently gained attention with respect to estimates of hearing sensitivity and configuration of hearing loss. The present investigation compared behavioral thresholds to estimated ASSR thresholds in subjects with confirmed CANS lesions to determine if this population can be accurately evaluated with ASSR techniques. Comparisons were made between the experimental group and a normal control group matched for age and hearing sensitivity. ASSR thresholds were obtained for the carrier frequencies of 500 and 2000 Hz with a 46 Hz modulation rate and compared to behavioral thresholds. Within and between group comparisons were made. The control group demonstrated strong correlation between their behavioral and estimated ASSR thresholds which significantly contrasted the neurological group. Additionally, individuals with neurological impairment of the CANS exhibited elevated thresholds that were on average 24 dB greater at 2000 Hz than their behavioral thresholds. These results suggest that individuals with neurological insult may appear as hearing impaired or having greater hearing loss than is actually present. As a result, the ASSR may demonstrate the potential to assist in the detection of CANS dysfunction.

Key Words: Auditory steady state response, central auditory nervous system, lesion, brainstem, cortex, auditory processing, electrophysiology

Abbreviations: ABR = auditory brainstem response; AM = amplitude modulation; APD = auditory processing disorder; ASSR = auditory steady state response; CANS = central auditory nervous system; CPA = cerebello-pontine angle; DPOAE = distortion product otoacoustic emissions; FM = frequency modulation; IRATE = Index of Relative Approximation of Threshold Estimates; MLR = middle latency response

Sumario

Las respuestas auditivas de estado estable (ASSR) han ganado atención recientemente con respecto a la estimación de la sensibilidad auditiva y la configuración de la pérdida auditiva. La presente investigación comparó los umbrales conductuales con umbrales estimados por ASSR en sujetos con

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lesiones CANS confirmadas para determinar si esta población podía ser evaluada con exactitud por medio de técnicas de ASSR. Las comparaciones se realizaron entre el grupo experimental y un grupo control normal ordenados por edad y sensibilidad auditiva. Los umbrales de los ASSR se obtuvieron por medio de frecuencias portadoras de 500 y 2000 Hz, con una tasa de modulación de 46 Hz y se compararon con los umbrales conductuales. Se realizaron comparaciones entre los grupos y dentro de un mismo grupo. El grupo de control mostró una fuerte correlación entre sus umbrales conductuales y los estimados por ASSR, que contrastó significativamente con el grupo neurológico. Adicionalmente, los individuos con un trastorno neurológico de CANS exhibieron umbrales elevados que fueron en promedio 24 dB más alto en 2000 Hz que sus umbrales conductuales. Estos resultados sugieren que los individuos con alteraciones neurológicas pueden lucir como alterados auditivamente o teniendo una pérdida auditiva mayor de la realidad. Como resultados, los ASSR puede demostrar el potencial para ayudar en la detección de la disfunción por CANS.

Palabras Clave: Respuestas auditivas de estado estable, sistema nervioso auditivo central, lesión, tallo cerebral, corteza, procesamiento auditivo, electrofisiología

Abreviaturas: ABR = respuestas auditivas del tallo cerebral; AM = modulación de la amplitud; APD = trastorno de procesamiento auditivo; ASSR = respuesta auditiva de estado estable; CANS = sistema nervioso auditivo central; CPA = ángulo ponto-cerebeloso; DPOAE = emisiones otoacústicas por productos de distorsión; FM = modulación de la frecuencia; IRATE = Índice de Aproximación Relativa de Estimado de Umbrales; MLR = respuestas de latencia media

Human auditory steady state responses (ASSRs), also termed "amplitude modulation following responses," were first introduced more than 25 years ago with a number of follow up investigations shortly thereafter (Campbell, 1977; Hall, 1979; Rickards and Clark, 1984; Kuwada et al., 1986). The ASSR is an electrophysiological neural response of the auditory system to frequency and/or amplitude modulated tones (Picton et al., 2003). The ASSR is recorded using the same montage as the auditory brainstem response (ABR); however, its recording and analysis are performed in a different manner. The ASSR relies not only on precise neural synchrony, but on the ability of the auditory system to phase lock over time.

First recorded in the visual system (Regan, 1966), steady state evoked potentials (steady state responses) have recently received considerable attention in the auditory sciences. The recent attention is a function of their ability to objectively determine hearing sensitivity through the use of frequency specific stimuli in both pediatric and adult populations (Cohen, Rickards & Clark, 1991; Chambers and Meyer, 1993; Rance et al., 1995; Cone-Wesson et al., 2002a; Cone-Wesson et al., 2002b; Cone-Wesson et al., 2002c; Luts & Wouters, 2005; Johnson & Brown, 2005; Scherf et al., 2006; Sturzebecher et al., 2006). The ASSR has followed a long line of evoked potentials, which have been well established, accepted and integrated into diagnostic audiology. Perhaps the most widely utilized is the ABR. For the past 35 years the ABR has demonstrated excellent validity and reliability in the objective measurement of hearing sensitivity (Hecox and Galambos, 1974; Kileny and Magathan, 1987) and neurodiagnostic audiology (Starr and Achor, 1975; Selters and Brackman, 1977; Musiek and Lee, 1995). Specifically, it has been established as both a sensitive and reliable tool in the detection of retrocochlear lesions of the auditory nerve and auditory brainstem pathways. However, the ABR has met with some criticism regarding its ability to obtain accurate estimates of frequency specific threshold information. In fact, it has been proposed that ASSRs yield better correlations to behavioral thresholds than do low frequency tone-burst ABRs (Cone-Wesson et al., 2002 a). Although the concept of the ASSR has been around for an extended period of time, its implementation in clinical practice has only recently emerged. There are several factors that contribute to the rationale for the use of the

ASSR as opposed to the ABR in clinical practice, specifically in the diagnosis of hearing loss. Unlike the ASSR, traditional ABR measurements are obtained using a stimulus such as a click or tone burst. In contrast, the ASSR uses steady state stimuli which do not have to be turned on and off. This prevents spectral splatter and allows for the use of frequency specific stimuli in order to obtain a frequency specific response, especially at the low frequencies.

There has been extensive research over the past decade regarding the clinical utility of the ASSR in both the pediatric and adult populations. It appears that in cases of cochlear impairment, the ASSR presents as a reliable and effective tool in the estimation of both sensitivity and configuration of hearing loss for both the pediatric and adult populations (Rance et al, 1995; Cohen et al., 2002 a, b; Rance, 2005) In fact, it has been demonstrated by Rance and colleagues (1995) that the greater the degree of hearing impairment, the more accurate the estimation of hearing sensitivity.

ASSR has emerged as a clinical tool in the assessment of hearing sensitivity. Similar to the ABR, it may have clinical application with respect to the detection and diagnosis of central auditory disorders. Although the ASSR has been established as a useful tool in the detection and diagnosis of hearing impairment, later in this paper it will be viewed as a possible test for central auditory dysfunction. Before this can happen, several considerations must be taken into account in the development of diagnostic assessment tools in this auditory arena. In order for a test to be integrated into the clinical arena for the detection of central auditory nervous system (CANS) and/or neurological lesions, it should first be evaluated on three populations of subjects (Lusted, 1978). Initially, the measure should be evaluated on those subjects with normal peripheral hearing sensitivity who are free of any neurological pathology in order to obtain normative data. Secondly, a test should be administered on those subjects who present with peripheral hearing loss. Finally, before a test should be implemented into clinical use, its sensitivity and specificity should be determined. This can only be accomplished by evaluating test performance on subjects with known lesions of the CANS. However, to date, there is a paucity of investigations into the effects of neurological lesions of the CANS on ASSR results.

There are some concerns regarding the ability of the ASSR to accurately evaluate hearing sensitivity in individuals with neurological compromise of the CANS. Discussions with manufacturers indicate that in the near future it will be proposed that the ASSR be used in adult populations and a wider range of pediatric populations. Specifically, it has been suggested that the ASSR would be a useful tool in institutions such as the Veterans Administration. Additionally, its use has been recommended for neonates and infants who present with high risk for hearing loss. Diagnostic evaluations in these aforementioned populations often become complicated because they are at higher risk than the "normal" population for neurological involvement. Presently, it remains unclear as to the effects of neurological lesions on ASSR results. The primary concern is that perhaps in cases where patients present with neurological pathology that the elevated electrophysiological thresholds noted may not be an accurate reflection of hearing acuity. Rather they may be a result of the inability of a compromised CANS to phase lock onto the stimulus presented, thus mimicking a hearing impairment which may not be present or may not be as severe as is reflected on the ASSR results. In turn, the ASSR is an evoked potential generated by neurological mechanisms, and involves both brainstem and auditory cortical structures (Kuwada et al., 2002). As a result, the ASSR may demonstrate the potential to assist in the detection of CANS lesions. Therefore, before the ASSR is further implemented in practice, it is critical that it be evaluated on individuals with neurological involvement.

As the literature has historically suggested, the ASSR has demonstrated a strong ability to accurately predict hearing sensitivity in both pediatric and adult populations (Rance et al, 1995; Cohen et al., 2002 a, b; Rance, 2005). It has been well established that when neurological involvement is present, traditional electrophysiological tests such as the ABR and middle latency response (MLR) demonstrate abnormal responses (Starr and Achor, 1975; Musiek and Lee, 1995; Musiek et al., 1999; Japaridze, Shakarishvili and Karanishvilie, 2002). Additionally, there have been several investigations which have demonstrated that in

cases of retrocochlear involvement, ABR thresholds correlate poorly with actual behavioral thresholds (Warren, 1989; Marangos, Schipper and Richter, 1999). Warren (1989) investigated the correlation between ABR and pure-tone thresholds in the pediatric population. He recognized that the ABR threshold can be influenced by retrocochlear involvement. Subsequently, Marangos and colleagues (1999) performed a large scale retrospective study in order to examine the correlation between ABR and subjective pure-tone thresholds in cases of cerebellopontine angle (CPA) tumors. They found that in the control group, there was a discrepancy between ABR and pure-tone thresholds of approximately 3.6 dB. However, in the cases with CPA tumors, the ABR thresholds were significantly elevated compared to the pure-tone thresholds, with mean group differential of 31.2 dB. They concluded that an ABR threshold discrepancy greater than 30 dB may provide an additional indicator of retrocochlear pathology. This leads one to consider that similar abnormalities may be observed for the ASSR in cases of a neurological impairment. If this is the case, perhaps the ASSR can be used as a diagnostic tool for the detection and differentiation of neurological lesions of the CANS.

Few studies have investigated the effects of ASSR in individuals with auditory nerve or CANS impairment. Rance and colleagues (1999, 2002) have examined the ASSR in cases of auditory neuropathy. They investigated infants and young children who were diagnosed with auditory neuropathy based on the findings of repeatable cochlear microphonic potentials in the presence of absent click-evoked ABRs. Both behavioral and ASSR thresholds were established for all subjects. This investigation revealed weak correlations between behavioral results and ASSR thresholds, suggesting that in cases of neurological insult, the ASSR is unable to accurately predict hearing sensitivity.

There are two main purposes of this study, both of which were related to the examination of the effect of neurological involvement on the ASSR. The first is to evaluate the impact of neurological involvement on ASSR results with respect to their ability to accurately and reliably estimate hearing sensitivity. If it is proven that ASSR demonstrates difficulty determining hearing sensitivity in the presence of neurological insult, then it may be that it is a tool that can be used in the assessment of central auditory processing deficits. Therefore, this study also aimed to determine whether or not ASSRs could be feasibly utilized in the detection and diagnosis of lesions of the CANS.

METHODOLOGY

Subjects

Twenty-two individuals recruited from the University of Connecticut in Storrs, Connecticut, as well as the National Hospital for Neurology and Neurosurgery in London, England, participated in the study. Subjects ranged in age from 18 to 80 years. All subjects volunteered for this study and met the Institutional Review Boards' criteria for the enrollment of human subjects at the University of Connecticut and the National Hospital for Neurology and Neurosurgery.

Subjects were divided into two groups of 11 subjects. The first group of subjects, identified as the control group, was composed of individuals who were matched to a neurological group for age and behavioral hearing sensitivity. These individuals were free of learning disabilities, otologic disorder or neurological involvement based on their reported histories. Individuals in the control group were matched for age to within 10 years of the neurological group. Hearing sensitivity was symmetrical between ears for each subject with pure-tone thresholds within 10 dB across the frequencies of 500 through 4000 Hz. Subjects were individually matched based on their pure-tone average (PTA) for the frequencies of 500 and 2000 Hz (the frequencies evaluated for the estimated ASSR thresholds). They were required to demonstrate hearing sensitivity within ± 10 dB HL of the PTA for each ear.

The second, or the neurological group, was comprised of subjects with lesions of the CANS. Subjects in the neurological group consisted of individuals with confirmed brainstem, sub-cortical and/or cortical lesions (Table 1). The neurological group was defined as having lesions within but not limited to the CANS. These lesions were delineated using the anatomical boundaries set forth by Galaburda and Sanides (1980). Each subject underwent either a T1 or T2 weighted Magnetic Resonance Imaging (MRI) study which was interpreted by both neurologists

and radiologists. Neurological subjects were included regardless of level of hearing acuity. A detailed description of the neurological subjects can be found in Table 1.

Procedures

All subjects demonstrated a normal otoscopic examination as defined by non-occluding cerumen, no tympanic membrane dullness and an obvious cone of light. Mean values and standard deviations for the two groups for ages and PTA's are shown in Table 2.

Prior to participating in the experimental protocols, each subject was asked to report on their audiologic, otologic and neurologic histories. Any control subject who reported a recent history of otologic pathology (within one year) or positive neurological history was excluded from the study. Handedness was not considered as an inclusion/exclusion factor.

The GSI Audera™ system, used for this study, has two default protocols which can be used on the adult population. The use of these protocols allows for the assessment of two different regions of the CANS and two different subject states. The protocol utilized in the present investigation is referred to by manufacturers of the GSI Audera™ as the "Awake" protocol. For the purposes of the present investigation, the "Awake" protocol will be referred to as the low rate protocol. This specific protocol was designed to be used with awake adults older than 10 years of age. It has a fixed modulation frequency of 46 Hz regardless of the frequency tested, thus likely eliciting a response from the auditory cortex. Stimuli used in this protocol were sinusoidal in nature and used a combined amplitude modulation (AM) of 100% and frequency modulation (FM) of 10% of the carrier frequency. The intensity of the stimuli is discussed in the procedures. The noise criterion, or sensitivity, was set to -134.7 dBV, where -140.4 is equal to 0.1 microvolts.

In order to understand the test procedures, a basic knowledge of response types which can be obtained via the GSI Audera™ is necessary. Three response types: 1) phase locked, 2) random and 3) noise are possible. A phase locked response is indicative of a response above the subject's threshold of hearing. The phase locked response occurs when the probability curve reaches 97% ($p < .03$). In order for this to occur, there must be a response which is recognizable above the ongoing EEG activity. In contrast, a random response is one in which the response does not reach probability thresholds and the RMS value, and the response does not exceed

Table 1. Description of neurological subjects' site of lesion and disorder.

Subject	Site of Lesion	Disorder
1	Pons	Infarct
2	Pons	Infarct
3	Pons	Infarct
4	Pons	Unknown
5	Temporal Lobe Internal Capsule	Infarct
6	Internal Capsule	Infarct
7	Striatocapsular	Infarct
8	Insula	Infarct
9	Capsulo-Thalamus	Infarct
10	Internal Capsule	Infarct
11	Parietal - Temporal Parietal Junction	Tumor

Table 2. Means and standard deviations (in parentheses) for age, thresholds (in dB HL) at 500 Hz and 2000 Hz, and PTAs.

Group	Age	500 Hz	2000 Hz	PTA Left Ear	PTA Right Ear
Control	54.91 (15.3)	10.2 (10.9)	17.9 (15.8)	14.1 (12.1)	14.1 (14.7)
Neurological	53.7 (15.9)	12.5 (7.9)	24.3 (15.5)	18.4 (10.1)	18.4 (8.9)

the noise threshold limits. In other words, inadequate phase locking occurs. This is considered to be a "no response." It is therefore assumed that the subject is unable to physiologically detect that particular intensity and frequency. Finally, a noise response is when the ASSR does not reach probability thresholds and the RMS value exceeds the noise thresholds limits. This may be the result of excessive internal or external noise activity.

All testing was completed in a sound-treated room or quiet listening environment in order to reduce ambient noise levels. Subjects underwent conventional audiometric evaluations using TDH 49 supra-aural headphones. All subjects were administered a full audiometric evaluation using conventional clinical procedures. Normal hearing sensitivity was defined as audiometric thresholds ≤ 25 dB HL bilaterally. Pure-tone air-conduction thresholds were established using a modified Hughson Westlake technique. Thresholds for the octave frequencies from 250 and 8000 Hz were established using a calibrated GSI 61™ audiometer. Subjects who demonstrated hearing thresholds greater than 20 dB HL between the frequencies of 2000 and 4000 Hz and 4000 and 8000 Hz were evaluated at the inter-octave frequencies of 3000 and/or 6000 Hz, respectively. Subjects with air-conduction thresholds greater than 15 dB also underwent bone-conduction testing to rule out conductive involvement. Any subject who presented with an air-bone gap greater than 15 dB HL was excluded from the study.

Distortion Product Otoacoustic Emissions (DPOAEs) were performed on both groups of subjects to assess outer hair cell integrity. DPOAEs were recorded using the GSI™ 60 system. The two primary stimulus tones used to obtain the responses were 70 dB SPL with an f2/f1 ratio of 1.2 across the frequencies tested. A total of 5 octaves (1000 to 5000 Hz) were tested with obtaining 3 points per octave, resulting in a total of 15 DPOAEs. Normative values were those based on Dartmouth Hitchcock Medical center norms (Musiek and Baran, 1997). The internal default criterion was set for a maximum of 150 frames. DPOAEs were repeated to insure test-retest reliability. Results were required to be consistent with pure-tone audiometric results (i.e., present in cases of normal peripheral hearing sensitivity, and abnormal in cases of hearing loss).

The GSI Audera™ was used as the laboratory instrumentation for the present study to obtain and analyze ASSR responses. It was chosen due to the significant body of research behind its development and its widespread clinical use. Subjects were seated in a reclining chair in a comfortable position. The skin was prepared for electrode placement by cleaning the electrode site with Nuprep™ skin gel and an alcohol pad. Snap electrodes were placed on the subject with the non-inverting electrode placed on the high forehead (Fz), the inverting electrodes at each mastoid (A1, A2). An electrode at the mid forehead served as the ground. Impedances were maintained at less than 10 kilo-ohms across the electrode array for all subjects and conditions. The stimuli were delivered through TIP-50 insert earphones which were placed snugly in the ear canal of each subject.

Before electrophysiological recordings were initiated, behavioral thresholds for the ASSR stimuli were established using the same modified Hughson-Westlake procedure (see below) as used for the pure-tone testing. Subjects were presented with and responses were obtained for the steady state stimuli generated by the Audera™ for the octave frequencies of 500, 1000, 2000 and 4000 Hz. Stimuli were presented for approximately 0.5 to 1 second. Subjects were asked to indicate either verbally or manually when they detected a tone. The threshold was considered to be the lowest intensity level at which a response was detected for 3 out of 5 presentations.

All ASSR testing was pseudo-randomized between ears and across order of test presentation. This was accomplished by counterbalancing the order of protocol, by ear presentation and frequency presentation. Additionally, all subjects were awake throughout the entire test session.

ASSR thresholds were determined at the frequencies of 500 and 2000 Hz using a 97% response criterion. These frequencies were chosen because they provided both a low frequency and high frequency measurement. Additionally, they reflected those frequencies generally tested when tone-burst ABRs are implemented. Threshold testing was initiated at 50 dB HL. Stimuli intensity were either increased or decreased depending on the presence or absence of a response. If a response was present, the intensity level was decreased by 20 dB HL; if it was absent it

was increased 10 dB HL. Once phase locked and random responses were recorded within 10 dB HL of each other, the final stimulus was presented at 5 dB HL above the highest random response and 5 dB HL below the lowest phase locked response. The electrophysiological threshold was considered to be the lowest level at which a phase locked response could be recorded. In addition, the estimated threshold was also determined. The estimated threshold is based on an algorithm that provides the predicted behavioral thresholds which are extrapolated from the ASSR electrophysiological threshold data. The extrapolated algorithm was derived from research conducted at the University of Melbourne School of Audiology (Rance et al., 1995).

Following data collection, the Index of Relative Approximation Threshold Estimates (IRATE) was calculated. The IRATE was calculated by determining the difference between the pure-tone audiometric thresholds and the estimated ASSR thresholds at both 500 and 2000 Hz. In other words, the equation would be: IRATE = $[\text{Threshold}_{\text{behavioral}} - \text{Threshold}_{\text{estimated ASSR}}]_{500}$ or $_{2000}$ Hz. This index was designed to evaluate how closely the estimated ASSR thresholds correlated to the actual behavioral pure-tone audiometric thresholds.

The methodology for the present investigation was developed in order to provide measures to determine the ability of ASSR to accurately and reliably estimate hearing sensitivity in individuals with lesions of the CANS. As will be discussed later, the measurements were designed in order to determine correlations between behavioral and estimated ASSR thresholds, the strength of a new index (IRATE), as well as the sensitivity and specificity of the ASSR in cases of CANS compromise.

RESULTS

Pearson product-moment correlations were performed to evaluate the relationship between the behavioral audiometric thresholds as reflected on the pure-tone audiogram and the estimated ASSR threshold (both in dB HL). Note that the pure-tone audiometric thresholds were utilized to reflect what the authors believe the general population of audiologists would use for comparative purposes. Table 3 provides the correlation coefficient comparisons between the two groups for each ear at both 500 and 2000 Hz, along with their associated significance values. Results for the control group demonstrated that there was a strong and statistically significant ($p < 0.01$) positive correlation between the pure-tone audiometric thresholds and the estimated ASSR thresholds at both 500 and 2000 Hz for each ear. However, the analysis for the neurological group revealed poor and statistically non-significant correlations for the same comparisons. These results suggest that control subjects exhibited a good relationship between their pure-tone (behavioral) thresholds and their estimated ASSR thresholds, whereas the neurological subjects demonstrated a poor relationship between the same measures. Moreover, the data shows that the size of the correlations noted for the control group comparisons were in general approximately twice those of the neurological group.

Figures 1a, b provide individual data points to demonstrate the correlations between the behavioral pure-tone thresholds and the ASSR-estimated thresholds. Interestingly, as shown in other studies, an inspection of the individual subject data suggests that control subjects with greater degrees of hearing loss may demonstrate a closer relationship between their behavioral and estimated ASSR thresholds than the control group. The neurological group did not demonstrate this same trend. Rather, with greater degrees of hearing loss, the behavioral thresholds appear to exhibit poorer correlations with the estimated ASSR thresholds.

The IRATE index was designed to deter-

Table 3. Correlations between behavioral and estimated ASSR thresholds for each group. Note that * indicates statistical significance beyond the .01 level.

	Left Ear		Right Ear	
	500 Hz	2000 Hz	500 Hz	2000 Hz
Control	.74 *p = .009	.80 *p = .003	.75 *p = .008	.77 *p = .006
Neurological	.30 p = .365	.57 p = .066	.43 p = .182	.30 p = .369

mine the difference between the actual behavioral threshold as obtained by a pure-tone audiometric evaluation (behavioral) and the estimated ASSR threshold at two frequencies (500 Hz and at 2000 Hz). Figure 2 provides the descriptive data with respect to the behavioral and estimated ASSR thresholds at these test frequencies. As a reminder, the IRATE is an absolute value, which is used to provide a measure of the accuracy of the estimated ASSR threshold when compared to the actual pure-tone threshold. The mean value was calculated by obtaining the average difference in threshold measures derived by the two test procedures (pure-tone and ASSR) for each ear at 500 and 2000 Hz. The analysis was performed in this manner because no clear laterality effect has been determined for the ASSR (Herdman et al., 2002).

Statistical analysis using independent sample t-tests demonstrated that there was not a significant difference for the IRATE index between the means of the two groups at 500 Hz. However, at 2000 Hz, the control group exhibited an IRATE index of only 11.8 dB HL, whereas the neurological group presented with an IRATE index of almost 23.9 dB HL. This yielded a mean difference of 12.1 dB HL between the two groups. The results suggest that the estimated ASSR thresholds

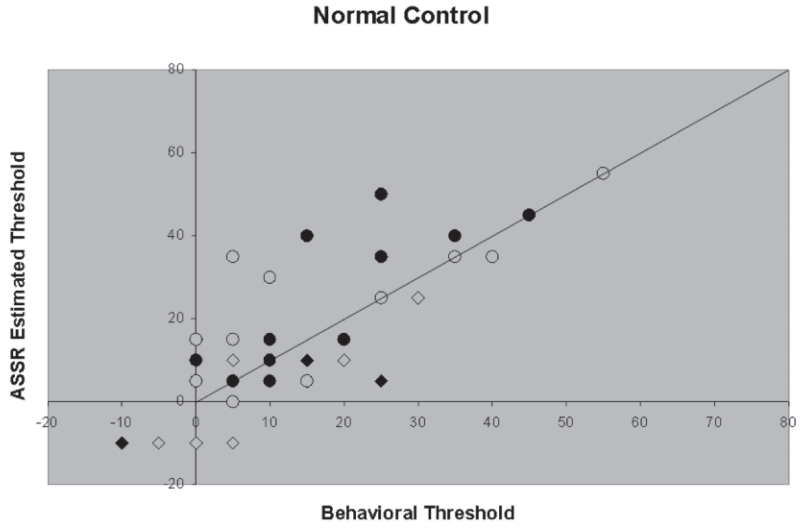

Figure 1. Comparisons between behavioral versus estimated ASSR thresholds for the left (filled) and right (open) ears at both 500 Hz (diamonds) and 2000 Hz (circles). Measurements were made in dB HL. Comparisons were made for both the normal control (upper panel) and neurological group (lower panel). The diagonal line represents a perfect correlation in each of the two panels.

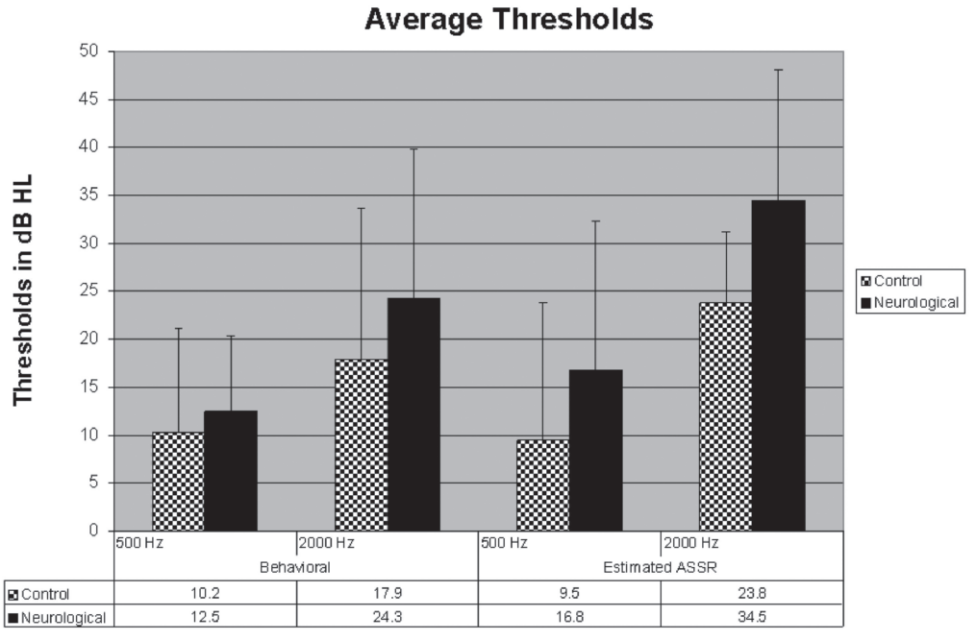

Figure 2. Mean behavioral and estimated thresholds for the control and neurological groups at both 500 and 2000 Hz. Error bars represent group standard deviations.

for patients with neurological damage will tend to overestimate the severity of a co-morbid hearing loss at 2000 Hz. For example, if a subject with CANS compromise presents with a mild hearing loss on pure-tone testing, it is likely that his/her estimated ASSR threshold testing would indicate the presence of a moderate hearing loss.

A Student's t-test was used to determine if there were any statistically significant differences between the normal control and the neurological group at either 500 or 2000 Hz (Figure 3). Results indicate that although there was no significant difference between the two groups at 500 Hz ($p = 0.39$), there was a statistically significant difference at 2000 Hz ($p = 0.02$). This suggests that, for measurements at 2000 Hz, there was a greater differential between the behavioral and estimated ASSR thresholds for individuals with neurological impairment of the CANS than for subjects with preserved neural integrity.

In addition, paired t-tests were performed to determine if there were any within group differences between 500 and 2000 Hz. Results indicated that both the neurologically impaired ($p = 0.02$) and the control group

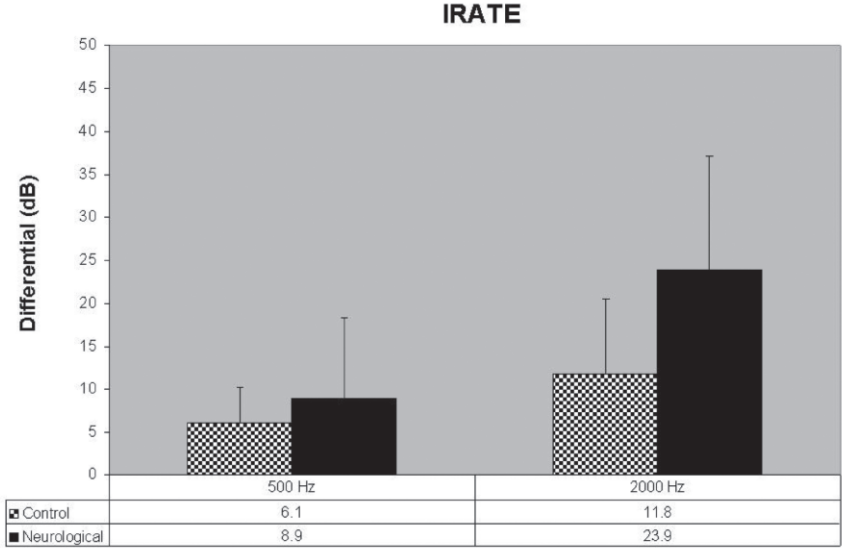

Figure 3. Mean IRATE values for both the normal control and neurological groups at 500 and 2000 Hz. Error bars represent group standard deviations.

($p = 0.03$) showed a statistically significant difference between these two tested frequencies. Finally, paired t-tests were performed to determine if there were any within group ear differences for the IRATE at both 500 and 2000 Hz. Results indicated that the control group did not demonstrate a statistically significant ear difference at either 500 Hz ($p = 0.88$) or 2000 Hz ($p = 0.84$). The neurological group also failed to demonstrate any significant ear differences at 500 Hz or ($p = 0.16$) at 2000 Hz ($p = 0.40$).

Sensitivity and specificity data were derived in order to determine if the ASSR would be a useful tool in the detection of compromise associated with lesions of the CANS. Sensitivity and specificity was analyzed for the IRATE at both 500 and 2000 Hz. From this point forward, the IRATE index calculated at these frequencies will be referred to as the $IRATE_{500}$ or $IRATE_{2000}$ respectively.

Figure 4 presents the sensitivity and specificity data for the $IRATE_{2000}$. The $IRATE_{2000}$ was the only index for which sensitivity and specificity was determined as a result of the fact that it was the only index that yielded statistically significant different results. Results were analyzed using both 1 and 2 standard deviations around the mean as the cut-off criteria in an attempt to determine which criteria would demonstrate the maximum sensitivity and specificity. The criterion used for 1 standard deviation was a 20 dB differential between the behavioral and estimated ASSR thresholds, and 2 standard deviations was considered to be a 28 dB differential.

Finally, efficiency of the test is the number of true findings (true positives and true negatives) divided by the total number of subjects. A high overall efficiency would indicate that the test is very good at detecting the presence and absence of a disorder. Results from data on the 22 subjects indicated that using a 1 standard deviation (20 dB) criterion resulted in a sensitivity measure of 64% and a specificity rating of 81%. Increasing the cut-off criteria to 2 standard deviations (28 dB) decreased the sensitivity to 45%; however, the specificity increased to 91%. Test efficiency, or overall accuracy, was also calculated. The overall accuracy of the ASSR is found in Figure 5. There was little difference in overall test efficiency between the two different cut-off criteria. Overall test efficiency for one standard deviation was 73% and for two standard deviations was 68%. The criterion used ranged from the minimum to maximum of the differentials between the behavioral and estimated ASSR thresholds. This ranged from an IRATE criterion of 0 dB up to 40 dB. The results indicated that the best combination of sensitivity and specificity measures were achieved when a criterion of 17.5 dB was used as the cut-off between normal and abnormal performance. Using this value yielded a sensitivity of 64% and a specificity of 82%, which resulted in essentially the same findings as when using one standard deviation as the cut-off criteria.

The area under the ROC (receiver operating characteristic) curve may be interpreted

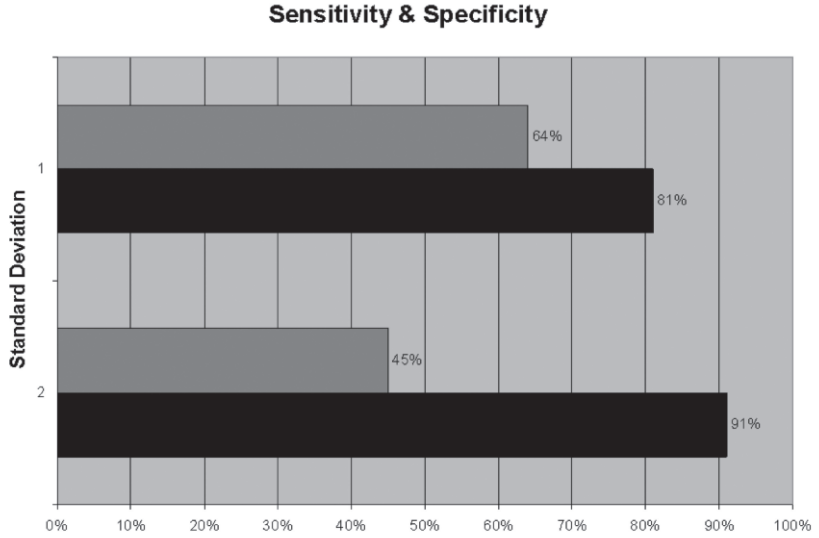

Figure 4. Sensitivity (grey) and specificity (black) using the $IRATE_{2000}$ for both one (top) and two (bottom) standard deviations.

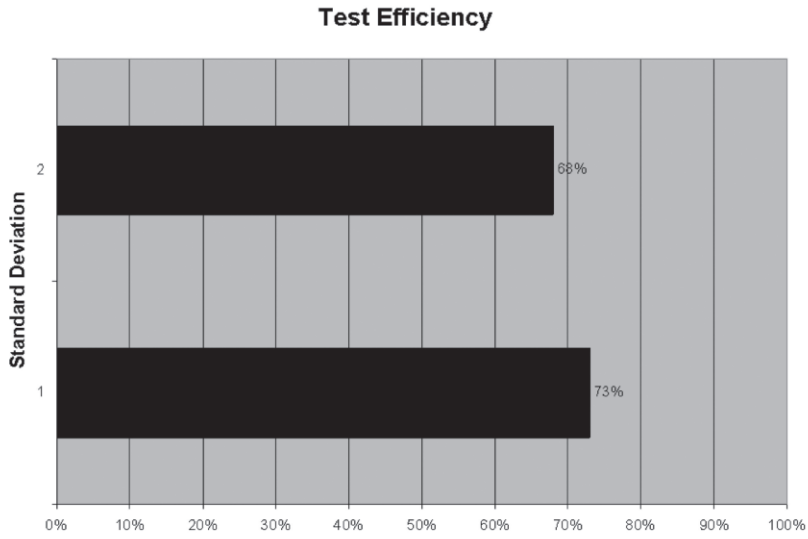

Figure 5. Overall test efficiency using one (bottom) and two (top) standard deviations.

as the likelihood that a disorder will be present in comparison to the likelihood that it will be absent. According to Hanley and McNeil (1984), a ROC area measure falling between 0.7 and 0.9 is associated with a good test. Anything greater should be considered an excellent test and anything less should be considered a poor test. The area under the ROC curve (Figure 6) was 0.77 for the $IRATE_{2000}$ which is considered good. However, the area under the ROC curve for the $IRATE_{500}$ was poor at only 0.50. These results suggest that the $IRATE_{2000}$ may provide a means for detecting dysfunction of the CANS.

DISCUSSION

Physiological Manifestation of Neural Involvement

Results from the present investigation clearly demonstrate a discrepancy between behavioral tests results and estimated ASSR thresholds in the case of CANS compromise. This phenomenon, however, is not unique to the present investigation. Rance and colleagues (1999, 2005) demonstrated the effects of retrocochlear lesions on the ASSR. This particular study investigated a group of children identified with presumed auditory neuropathy based on a repeatable cochlear microphonic but absent auditory brainstem responses (ABRs). These subjects were evaluated both by behavioral and ASSR measures and compared to a control group. Of note are the similarities between the work of Rance and colleagues and the present investigation with respect to both the poor correlations, in general, but also to the poorer correlations at higher intensities for the neurological group. Like the study by Rance and colleagues (1999), the present investigation noted what visually, although not statistically evaluated, appeared to be poorer correlations at high intensities.

The poor correlations for neurological subjects found in both studies may be attributed to the lack of neural substrate contributing to the responses at higher intensity levels. Although the aforementioned and present studies utilized different recording parameters with respect to both the carrier and mod-

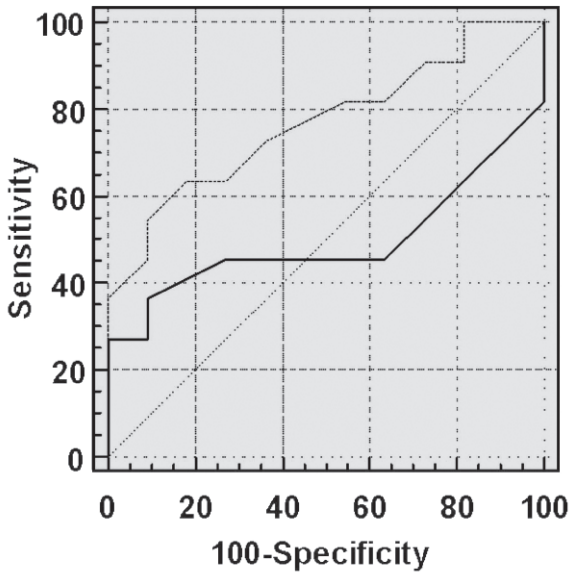

Figure 6. ROC curves for the IRATE index at both 500 (solid line) and 2000 Hz (dotted line).

ulation frequencies, the results demonstrated clear similarities. The difference in correlations between the experimental groups is most likely rooted in the electrophysiological responses. They are elevated (poorer) in neurological patients in comparison to the actual behavioral thresholds noted in these subjects. If the electrophysiological responses are elevated, then the estimated responses would in turn be elevated. The poor correlations demonstrated by the neurological group were perhaps a result of their need for greater neural substrate, than what was available, in order to elicit a response. Theoretically, where an individual with strong neural integrity may require only a small percentage of neural substrate to elicit a phase locked response, the compromised system may require a significantly larger percentage or area of neural substrate to elicit a similar response. This is only accomplished by increasing the level of the stimulus. For example, in a normal individual, many nerve fibers fire in response to auditory stimuli, even at very low intensity levels (such as at or near threshold). However, in instances where there is compromise of the CANS, a larger neural area must be recruited in order to elicit the same response that is seen in an individual with a normal auditory system. This is accomplished by presenting the stimuli at a higher intensity level, which in turn initiates the recruitment of a greater area of neural substrate, thus artificially elevating the thresholds. In order for a phase-locked response to occur, the intensity must be elevated to an intensity level that recruits enough neural fibers to provide a measurable response. This would thus yield the large discrepancies observed between behavioral and estimated ASSR thresholds, resulting in the weak correlations.

The poor correlations noted in both studies may also be attributed to the poor phase coherence in subjects with lesions of the CANS. Phase coherence is a statistical measure of phase variance in the analysis of steady state responses (Picton et al., 2001). The presence or absence of an ASSR response is dictated by the phase coherence value. Those phase coherences at or near 1 suggest a strong ASSR response, whereas those near 0 indicate poor phase coherence. For example, if a subject demonstrated a phase coherence value of 0.89, this would suggest good phase locking and, therefore, a high probability of a response being observed. A phase coherence value of 0.1, however, suggests weak phase locking and decreases the likelihood of a response being seen. Phase coherence is required in order to demonstrate an ASSR to a modulated stimulus. If low phase coherence is present, then no response is elicited. As a result of the neurological compromise and coincident interruption in neural processing, the experimental group may demonstrate poor phase coherence even at levels above their behavioral thresholds.

Poor phase coherence in individuals with speech perception deficits [a form of an auditory processing disorder (APD)] has been demonstrated in the literature. Ali and Jerger (1992) investigated two groups of elderly subjects, one of which demonstrated speech understanding which was consistent with their degree of hearing sensitivity and a second that demonstrated speech understanding which was considerably poorer than would be expected given a similar level of hearing sensitivity. The authors illustrated that for steady-state evoked responses, phase coherence although observed for both groups, was significantly poorer in the group with disproportionate speech understanding scores. Poor speech understanding scores may be directly linked to an underlying APD, such as the lack of synchronicity or a temporal processing deficit (Mendelson and Ricketts, 2001; Downie et al., 2002). Although the subjects in the neurological group of the present investigation did not undergo a full auditory processing test battery, many of them expressed difficulty with speech comprehension based upon their reported histories. This may be directly linked to poor phase coherence which could result in poor correlations between behavioral and electrophysiological thresholds. Although speech perception was not evaluated in the present investigation, temporal processing was assessed. Speech perception could not be evaluated due to the fact that some of the neurological subjects were collected in England and were not native speakers of American English, or English was there second language. This would suggest that there is perhaps an underlying temporal processing deficit (as a result of poor phase locking) which is likely contributing to the results of the present investigation.

It is likely that the poor correlations between behavioral thresholds and estimat-

ed ASSR thresholds seen in the neurological group are a result of weak underlying phase locking of the neurons involved. This may be associated with abnormal temporal processing. If this is indeed the case, a temporal processing deficit would result in the lack of synchronicity and in turn an inability to phase lock. This would thus result in poor correlations as seen in the present investigation. The calculation of the differential between the behavioral and ASSR estimated thresholds is similar to those described by Marangos and colleagues (1999). The investigators in that study concluded that an ABR threshold discrepancy greater than 30 dB may provide an additional indicator of retrocochlear pathology.

Recall, the present study demonstrated that there was an average of 6.1 dB differential at 500 Hz and an 11.8 dB differential at 2000 Hz in the normal group when the behavioral thresholds were compared to estimated ASSR thresholds. The neurological group presented with a mean discrepancy of 8.9 dB at 500 Hz and nearly a 24 dB discrepancy at 2000 Hz. This discrepancy at 2000 Hz is twice that noted for the control group, and as a result, it is a statistically significant difference! The present study clearly demonstrated that for subjects with neurological insult, there was a discrepancy between the behavioral and electrophysiologically estimated thresholds, particularly at high frequencies. Statistical analysis demonstrated a significant difference at 2000 Hz not only between groups, but also within groups when comparing frequencies. On the average, the IRATE value was significantly smaller at 500 Hz than at 2000 Hz. This finding is not unique to the current investigation, as similar findings have been reported previously in the literature (Cone-Wesson et al., 2002 a). The poorer ASSR threshold correlations in the higher frequencies for the general population are likely a contributing factor to the significant results at 2000 Hz in the present study.

Elevated threshold estimation is not unique to the ASSR and may be more pronounced for EPs generated from the auditory cortex. Soliman and colleagues (1993) investigated a large group of patients with epileptic seizures using behavioral audiometry, as well as the MLR and ASSR. MLR recordings for 40.7% of their population showed thresholds that were elevated over pure-tone thresholds. The elevated thresholds were attributed to a disturbance in the neurotransmission of impulses at both the brainstem and cortical levels. Ineffective neurotransmission in individuals with neurological impairment may play a vital role in the inability of the ASSR to accurately and reliably predict behavioral thresholds. .

One must also consider that processing of the ASSR stimuli is not instantaneous, but that the processing of the signal must course through the entire auditory system. It has been suggested that phase locking deteriorates as it ascends the central auditory pathway (Kidd and Weiss, 1990), creating a loss of synaptic transmission known as synaptic "jitter" (Blackburn and Sachs, 1989). Phase locking has also been found to deteriorate as the frequency increases. This is particularly evident at or above 2-3 kHz. The combination of synaptic jitter and the decrement of phase locking for mid to high frequency tones may contribute to the present findings of a statistically significant $IRATE_{2000}$ between the two groups. If, in a healthy neurological system, there is some degree of synaptic degradation, then it follows that an impaired neurological system will undergo an even greater degree of degradation by the time the signal reaches the auditory cortex.

Demyelination may also contribute to the results seen in this study. It has been established that axonal degeneration and demyelination occurs after central nervous system injury (Milanov, 1995). This provides an interesting link to auditory neuropathy. It has been suggested that auditory neuropathy results from demyelination or possible axonal loss of the auditory nerve (Starr, Picton and Kim, 2001). This would affect the ability of the auditory system to fire synchronously and at high rates. As indicated by Starr and colleagues (2003), this would have a direct impact on the auditory system's ability to precisely encode temporal cues, and would likely result in impaired speech comprehension and poor gap detection abilities. Starr and colleagues (1991) also indicated that this lack of synchronous firing would also result in the inability to obtain an ABR. If some degree of demyelination or axonal loss of the neural substrate is occurring within the central system as a result of a lesion, it is likely that this condition may be influencing the ability of the neurologically compromised subject to demonstrate an accurate and reliable ASSR. It should be noted that this may

not only be true for auditory neuropathy, but also for other disorders of the central nervous system.

As stated above, there are several theories and data which may explain the discrepancies observed in the present investigation. Further research using both human and animal models has the potential to assist in investigating the causes of such discrepant results. However, it is a result of the differential observed between behavioral and estimated ASSR results that the ASSR may actually prove to be a powerful tool in the diagnosis and detection of lesions of the CANS.

A Diagnostic Index

The present study demonstrates that in the cases of compromise to the CANS, ASSR demonstrates weaknesses in its ability to accurately and reliably determine hearing sensitivity. In particular, the ASSR demonstrate poor correlations between behavioral and estimated ASSR thresholds. However, in light of this negative finding, the authors propose the possible use of ASSR in the assessment and diagnosis of individuals with auditory processing disorders. An auditory processing disorder (APD), as defined in the *Journal of the American Academy of Audiology*, is as follows:

> An APD may be broadly defined as a deficit in the processing of information that is specific to the auditory modality. The problem may be exacerbated in unfavorable acoustic environments. It may be associated with difficulties in listening, speech understanding, language development and learning. In its pure form, however, it is conceptualized as a deficit in the processing of auditory input. [Jerger and Musiek, 2000, pp 467-468]

The assessment of individuals with APD through behavioral methods has existed for more than 30 years. The use of evoked potentials for this purpose is now being implemented into clinical test batteries. The question may be raised as to why neurological patients have been used historically in the development of central auditory tests. Perhaps the key phrase used in the working definition above as it relates to the present study is the "deficit in the processing of auditory input." Subjects with lesions of the CANS are essentially the only population that can be used in a clinical investigation. It is known that subjects with known lesions of the CANS will often present with auditory processing difficulties because key structures responsible for proper central auditory function have been compromised. Therefore, by definition, they may be labeled as presenting with an APD in some form.

Additionally, subjects with known lesions are advantageous to study because today's technology allows for the implementation of advanced imaging techniques. Researchers are therefore better able to profile APD as it relates to very specific sites of lesion and structures involved, making these individuals ideal subjects to study. Not all individuals who present with APD have discrete lesions of the CANS as identified by imaging techniques. In fact, a majority of the patients seen clinically are those who present with central auditory compromise without such evident damage. These are often children and adults with longstanding difficulties processing auditory information in spite of the fact that they have "normal" auditory structures, at least as far as can be determined by modern imaging techniques.

So why investigate subjects with lesions to make a diagnosis of APD for individuals without lesions? Quite simply, the only manner in which a central auditory test can be truly assessed is to first test a group of subjects with known lesions of the CANS. This serves two purposes. The first is that it provides us with a better understanding of how lesions of the CANS affect actual test results (Lusted, 1978). Second, it allows clinicians and researchers to obtain sensitivity, specificity and efficiency data, which help to determine the clinical utility of a test. The rationale of the present study was not only to determine the effects of neurological lesions on the ASSR, but also to probe its ability to be used in a clinical APD test battery. Although some degree of discrepancy would be expected, it is perhaps the degree size of the discrepancy which should be considered clinically significant.

Sensitivity and Specificity

Although the weakness of the ASSR to accurately and reliably predict auditory thresholds in the presence of neurological insult of the CANS is evident based upon the previous findings, it was still hoped that perhaps this tool would still have value in its ability to accurately identify cases of possible CANS involvement. The present study yielded sensitivity and specificity measures, of

64% and 81% for 1 standard deviation and 45% and 91% for 2 standard deviations. Although the sensitivity values are only fair for both cut-off criteria, the specificity measures for the test using the $IRATE_{2000}$ are quite good. The ASSR, recorded using a frequency modulation of 46 Hz, is believed to be generated by mechanisms similar to the MLR (Cone-Wesson et al., 2002a). Therefore, associations will be made between the sensitivity and specificity of the traditional MLR in comparison to the ASSR at a 46 Hz frequency modulation rate.

ROC curves demonstrated the trade-off between sensitivity and specificity for various criteria of the $IRATE_{2000}$ index. The ROC curves indicated that the best sensitivity and specificity measures were obtained using a criterion of 17.5 dB as the cut-off between normal and abnormal performance. Using this value yielded a sensitivity of 64% and a specificity of 82%, which were similar to the results noted above when a one standard deviation cut-off criteria was applied. The area under the ROC curve was 0.769 which is considered good. There is generally an inverse relationship between the sensitivity and specificity of any diagnostic test. More precisely, as sensitivity is increased, specificity is generally decreased and vice versa (Turner, Robinette and Bauch, 1991). Therefore, in order to increase the sensitivity of this index, the specificity would also be compromised.

The sensitivity of the traditional MLR for the detection of lesions of the CANS has not been extensively investigated. Kraus and colleagues (1982) studied a group of subjects with lesions of the CANS and found the sensitivity of the MLR to be about 50%. The highest sensitivity reported in the literature thus far was 73.3% for subjects with multiple sclerosis (Celebisoy et al., 1996). Musiek and colleagues (1999) investigated several measures of the MLR to determine which yielded the best sensitivity and specificity measures for the detection of lesions of the CANS, similar to the sensitivity in the present investigation. They found that using a contralateral amplitude differential measurement of greater than 20% between the two ears provided the best combination of sensitivity and specificity measures. These findings support the consideration of the amplitude of the ASSR at supra-threshold response as an alternative index.

The most recent investigation of sensitivity and specificity for EPs compared traditional ABR, MLR and slow cortical responses in subjects with multiple sclerosis (Japaridze, Shakarishvili and Kevanishvili, 2002). The MLR demonstrated a sensitivity of 42.5%, similar to the results for the ASSR obtained in the present study. Additionally, when the MLR was used in conjunction with the ABR, sensitivity increased to 80%. By obtaining the ASSR at both low (46 Hz) and high (> 80 Hz) frequency modulations, it would be reasonable to expect that the overall sensitivity in the detection of lesions of the CANS would also increase. The authors acknowledge the fact that few studies have looked at the lower modulation rates and the present findings should not be over-generalized.

Although the sensitivity of the present study was not as strong as had been anticipated, this measure may have improved with a larger sample size. Additionally, the ASSR may prove to be more sensitive for brainstem lesions than for sub-cortical or cortical lesions. However, the size of the current population (four subjects with brainstem lesions and seven with lesions of the sub-cortex and cortex) did not allow for differential testing in the present study. As additional confirmed CANS lesions are added to the sample, it is expected that this investigation will obtain a more accurate indication of the sensitivity and specificity of the ASSR in the detection of lesions of the CANS.

Implications

The results of the present study have significant implications with respect to the use of ASSR in the screening and diagnosis of hearing loss for both pediatric and adult populations. Perhaps the most significant concern is the use of ASSR with infants, particularly those at risk for neurological insult. Additionally, as the ASSR popularity expands, so will its use in adult and difficult-to-test populations who are also at risk for neurological compromise.

In 1994, it was documented that neurological disease or insult accounts for 20% of all hospital admissions (Playford, Crawford and Monro, 1994). Of those, strokes accounted for 26% of the diagnoses, followed by degenerative diseases at 10%. In 2002 alone, 4.8 million adults in the United States had experienced a stroke at some point in their lifespan

(National Center for Health Statistics, 2005); that translated into a prevalence rate of 2.4%. Depending on where the site of lesion is located, many of these individuals may exhibit auditory deficits.

Perinatal stroke has also become increasingly recognized. The current estimates of perinatal stroke are 1 in 4000 births (Lynch and Nelson, 2001). This rate may also be artificially low as it is acknowledged that perinatal stroke is often not diagnosed. A majority of these perinatal strokes involve the middle cerebral artery, which is the primary blood supply to the auditory cortex. With such a high incidence rate, there is an increased possibility of the misdiagnosis of a hearing loss and/or the overestimation of the degree of hearing loss in newborns and young children if the hearing status is determined by current ASSR procedures.

Many other pathologies, such as hyperbilirubinemia, perinatal asphyxia, cytomegalovirus and meningitis, also place children at risk for neurological impairment. The Academy of Pediatrics reported that approximately 60% of infants born in the United States develop clinical jaundice. Neonatal hyperbilirubinemia is a pathology which may lead to central nervous system toxicity and often results in hearing loss related to brainstem dysfunction. When it reaches toxic levels, hyperbilirubinemia is known as "kernicterus." Kernicterus has been associated with severe neurological impairments and is believed to be responsible for pathologies such as brainstem compromise (Moller, 2000).

The prevalence of neurological impairments in the pediatric population is currently not reported. Clinicians, however, have a responsibility to their patients to be keenly aware of their neurological status. Additionally, they should understand the effects of lesions on the CANS for both behavioral and electrophysiological test results. The results of the present study, as well as those from investigators such as Rance and colleagues (1999), indicate that clinical audiologists should be concerned about the accuracy of the estimated ASSR thresholds in individuals with neurological compromise of the CANS. Additionally, and perhaps more importantly, elevated ASSR thresholds may indicate neurological compromise, in particular in infants with neurological history.

Specifically, the ASSR may overestimate the degree of hearing impairment for a given individual in the presence of an abnormal CANS. For example, a child with a perinatal stroke due to a traumatic birth history may receive an electrophysiological evaluation to determine hearing sensitivity due to a failed newborn hearing screening. If the ASSR is used as the sole screening procedure, this infant could be diagnosed with a hearing impairment that may not be present, or if it is present, it is not as severe as the estimated ASSR thresholds indicate. This type of neurologic compromise may result not only from a stroke, but also from conditions affecting the neurological system. These may include trauma, seizures and hydrocephalus, as well as hyperbilirubinemia.

As it is currently administered, the ASSR may not accurately and reliably estimate hearing sensitivity in an adult neurological population. This leads one to question its ability to do so in the pediatric population. It is anticipated that the procedure may have limited application for use with those infants and children with neurological compromise. Although this study demonstrated some possible negative implications with respect to the use of the ASSR in the assessment of hearing sensitivity in adults with possible compromise of the CANS, it may show promise as an objective central auditory test if additional modifications to the current protocols can be made. It may provide an alternative means for detecting and diagnosing disorders of the CANS, such as auditory processing disorders, temporal processing deficits and speech perception impairments.

Summary

The present investigation may be the first to study the effects of lesions of the CANS on the ASSR. The current investigation has demonstrated some possible negative implications with respect to its ability to accurately and reliably determine ASSR thresholds in cases of CANS involvement. However, in spite of this potential limitation, the ASSR may still prove to be a highly useful diagnostic tool in the detection of abnormal CANS functioning in both pediatric and adult populations. Currently, diagnostic measures such as the ABR and MLR are used in both threshold estimation and the diagnosis of CANS involvement. The ASSR has the potential to also be clinically implemented in a similar

manner.

The ASSR is an attractive tool in the diagnosis of possible CANS compromise because it possessed some diagnostic elements which are lacking in more mainstream EPs. These include frequency specificity, modulated stimulus and some relative flexibility with respect to the stimulus. Additionally, the ASSR may provide a means for electrophysiological correlates to psychoacoustic measures such as temporal modulation transfer functions. There are likely many ways in which the ASSR could be implemented in the diagnostic arena which have yet to be explored.

The ASSR is currently in its infancy, particularly with respect to its use on populations with retrocochlear pathologies and disorders not related to peripheral hearing impairment. As a result, there are many avenues which have yet to be investigated that deserve attention in the future. Further research on the ASSR will hopefully yield promising results with respect to its use in the detection of CANS compromise. In addition, it may prove to be a useful tool in determining efficacy of subsequent remediation.

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