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A Sound Foundation Through Early Amplification

Proceedings of the 7th International Conference 2016

Infants, auditory steady-state responses, and clinical practice

Susan A. Small, Ph.D

Abstract

In the first months of life, identification of hearing loss type and estimation of hearing threshold for frequencies important for speech understanding are diagnostic priorities to avoid long delays in medical treatment and audiological intervention. The "brainstem" or "80-Hz" auditory steadystate response (ASSR) has been under investigation for a number of years as a potential substitute or supplement to the brief-tone auditory brainstem response (ABR), which is currently the method used by most pediatric clinicians. The main advantage of the 80-Hz ASSR compared to the ABR is that the presence of a response can be determined objectively using statistical measures rather than relying on subjective judgment of response replicability. The ASSR also allows both ears and multiple frequencies to be assessed simultaneously, which potentially reduces testing time compared to the ABR—a benefit that is always welcome when infant sleep time is a clinical constraint. This paper will provide an overview of the ASSR technique for estimation of hearing thresholds in infants, summarize ASSR research findings to date, and recommend ways to incorporate this method into clinical practice. Gaps in our knowledge about the brainstem ASSR and future directions for research will also be discussed.



Introduction

The main clinical goal for the auditory steady-state response (ASSR) technique is to objectively and accurately identify the presence and type of hearing loss in young infants, and to obtain frequency- and ear-specific estimations of hearing sensitivity needed for fitting amplification devices. Similar to long-established auditory brainstem response (ABR) testing protocols (e.g., BCEHP, 2012), when air-conduction (AC) ASSR thresholds are elevated relative to established maximum levels for infants with normal hearing, the next step is to obtain bone-conduction (BC) ASSR thresholds to determine the type of loss, and the size of the conductive component when one is present. As illustrated in Figure 1, the ASSR is an auditory evoked potential (AEP) that is repetitive in nature. For rates that are sufficiently high, a "sinusoidal response" is elicited with a frequency that matches the presentation or "modulation rate". The ASSR is analyzed statistically in terms of its frequency components (i.e., it is an objective measure), in contrast to the ABR that is typically interpreted by subjective visual inspection of waveform characteristics. Amplitude maxima were discovered for ASSRs elicited to modulation rate at approximately 40 and 80 Hz in the 1980's; the 80-Hz ASSR is thought to originate primarily from the auditory brainstem, whereas the 40-Hz ASSR from the auditory brainstem and primary auditory cortex. The majority of infant research has focused on the 80-ASSR or "brainstem ASSR" because the amplitude of the 40-Hz ASSR is greatly reduced by sleep in infants compared to adults. ASSRs are also of interest because they can be elicited to either single or multiple stimuli to two ears simultaneously, which is achieved by varying the modulation rates of the carrier frequencies presented. The multiple ASSR technique potentially reduces testing time to two thirds of that required for the ABR (for review see Picton, John, Dimitrijevic & Purcell, 2003; Small & Stapells, 2107).



Figure 1: Examples of interpretation of brief-tone auditory brainstem responses for an infant at 2000 Hz. The top panel shows responses that are easy to interpret: (i) left: responses at 50 and 60 dB nHL replicate well and are clearly present, and (ii) right: waveforms are flat and no response is present. The bottom panel demonstrates waveforms that are difficult to interpret: (i) left:

waveforms at 40 dB nHL are noisy and cannot be evaluated, and (ii) right: waveforms are quiet but not flat making it difficult to determine if any of the peaks and valleys confirm the presence/absence of a wave V.

The main motivation to pursue development of a new objective method to estimate frequency- and ear-specific thresholds in young infants, such as ASSRs, is the considerable training and skill necessary to record and interpret ABR waveforms. Figure 2 provides examples of ABR waveforms that are easy (top) and difficult (bottom) to interpret. In the bottom examples, in one case, the waveforms are noisy and it is difficult to determine presence/absence of wave V; in the other, the replications are not noisy but it is difficult to determine if any of the waveform characteristics confirm the presence/absence of a wave V. There are many well-established early detection and hearing intervention (EDHI) programs around the world with experienced clinicians who are adept at using ABR testing to identify hearing loss accurately in infants; however, new clinicians, clinicians with low infant-ABR caseloads, and clinicians who are less comfortable with the complexities of recording and interpreting AC and BC AEPs (either due to lack of availability of training resources or less aptitude for working with AEPs), continue to struggle with the diagnostic ABR technique. One solution is to establish a method that requires less training and skill such as the ASSR. Another potential solution is to implement telehealth ABR services; however, regular access to an expert clinician is still required for this approach.



Figure 2: Illustration of one analysis method for multiple auditory steady-state responses. Comparison of response amplitude for a 1000-Hz carrier frequency modulated at 84.9 Hz is shown in the time domain, as a polar plot, and in the frequency domain.

Stimulus and EEG parameters

Stimuli

ASSRs can potentially be elicited by many types of stimuli to estimate hearing threshold. Early ASSR research used brief tonal stimuli, similar to those used to evoke the ABR; however, most ASSR research has focused on continuous sinusoidal amplitude-modulated (AM) stimuli. The acoustics of continuous sinusoidal AM stimuli are very frequency specific -- their spectra show energy at the carrier frequency

plus two side lobes at frequencies equal to the carrier frequency plus/minus the modulation frequency. Adding 10 to 25% frequency modulation (FM) to an AM tone (AM/FM) and exponential envelope amplitude-modulated (AM²) stimuli have also been used to elicit ASSRs. These stimuli result in somewhat larger amplitudes compared to AM tones because of their broader frequency spectra; however, the small loss in frequency specificity has generally been considered acceptable (for review see Picton et al., 2003). Newer stimuli such as narrow-band chirps have also been used to elicit ASSRs but have not been as extensively studied using both AC and BC stimuli compared to AM, AM/FM and AM² stimuli (see Chapter One for discussion of chirp stimuli). As ASSR technology has evolved and expanded, many commercial ASSR systems have become available, with many different stimuli, and in some cases new analysis methods (e.g., Kalman filtering). The first wave of clinical ASSR systems were based closely on the equipment and techniques used in much of the foundational ASSR research (e.g., the single-stimulus Viasys/GSI "Audera" was based on the Australian "ERA" system, the multiple-stimulus Neuronic "Audix", and the Natus Bio-logic Navigator Pro MASTER II based on Rotman MultiMASTER software). Today, there are additional clinical ASSR systems that use stimuli and analysis techniques that have not been studied as extensively. It is important that peer-reviewed evidence (AC and BC data) exists for that system's methodology for sufficiently large groups of infants with normal hearing and hearing loss, preferably obtained at arms-length from manufacturers and patent holders (Small & Stapells, 2017).

ASSRs have also been used to investigate BC methodological issues for infant testing such as (i) location of the bone oscillator on the skull (mastoid versus upper temporal bone versus forehead), (ii) bone oscillator coupling technique (handheld versus elastic band), and (iii) whether to leave earphones in or out for BC testing to account for an occlusion effect (Small, Hatton & Stapells, 2007; Small & Hu, 2011). Findings from these studies support that a forehead placement should be avoided, as thresholds are elevated relative to a temporal-bone placement, and that either an upper temporal bone or a mastoid placement can be used (upper temporal bone may be easier to accomplish). It has also been demonstrated that either coupling by hand or an elastic band can be used, provided clinicians or assistants are adequately trained (Small et al., 2007). ASSR findings also demonstrate that the occlusion effect is much smaller in infants such that, on average, at 500 and 1000 Hz, it is negligible in young infants (0-7 months: 2-5 dB). However, the occlusion effect appears to be large enough to affect the accuracy of BC threshold estimation in older infants (12-24 months: 8 dB). Consequently, insert earphones can be left in

the ear canal when assessing young infants with no correction required at any frequency, but should be removed for infants older than one year when estimating thresholds at 500 and 1000 Hz (Small & Hu, 2011). If 500- and 1000-Hz BC thresholds are tested with occluded ears in older infants, it is recommended that BC thresholds be adjusted using a 10-dB correction factor (Small & Stapells, 2017).

EEG recording and analysis

Clinically, ASSRs are typically recorded using a one-channel EEG set up where electrodes are placed as follows: noninverting electrode at Cz (or FCz), inverting electrode at the inion, and a ground electrode on the forehead. Two-channel EEG recordings for BC testing (an electrode on each mastoid instead of the inion only) might also have some clinical utility for isolation of the "test" cochlea and is discussed later in this chapter. Statistical analyses of either amplitude or phase measures are used to determine the presence of a response depending on the ASSR system (for review see Picton et al., 2003; Small & Stapells, 2017).

Estimation of hearing threshold

It should be emphasized that the prediction of behavioral threshold from AEP thresholds is an "estimate" of perceptual hearing sensitivity and can often be off by 10 dB, or as much as 20 dB. Brief-tone ABR thresholds (in dB nHL) and ASSR thresholds (typically in dB HL) are not directly equivalent to perceptual thresholds in dB HL. "Estimated Hearing Levels" or "eHL" correction factors take this into account as do fitting targets for amplification devices. One common method used in EDHI programs to estimate behavioral hearing level is to subtract a correction factor from the AEP threshold (BCEHP, 2012; OIHP, 2008), another is to apply a regression formula to behavioral and AEP threshold data for individuals with hearing loss. For ABR testing conducted by the BC EHP, 25 dB HL is considered the "normal behavioral threshold" across frequency, and the "normal ABR maximum level" is the stimulus level at which the majority of infants have a response present (BCEHP, 2012). An "eHL correction" is used to estimate the behavioral hearing threshold from the ABR threshold. In summary, ABR threshold (dB nHL) - eHL correction (dB) = estimated behavioral threshold (dB eHL). Table 1 summarizes current normal ABR maximum levels and eHL corrections for infants for AC and BC ABRs (BCEHP 2012; Small & Stapells, 2017). Note that the normal maximum levels at 500 Hz are 15 dB better for BC versus AC stimuli. We have wellestablished ABR normal maximum levels and eHL correction factors for 500-, 1000-, 2000- and 4000-Hz AC stimuli and for 500- and 2000-Hz BC stimuli based on research and clinical data from infants with normal hearing and hearing loss. ASSRs have not been studied as extensively as the ABR.

	500 Hz		1000 Hz		2000 Hz		4000 Hz	
	AC	BC	AC	BC	AC	BC	AC	BC
Normal ABR Max (dB HL)	40-50	30	40-45	20	40	40	40	30
Range in literature	40-52	30-40	30 to >50	10-30	30-50	30-40	28-44	10-40
BC EHP eHL correction (dB)	10-20		10-15		10-15		5-15	
Range in literature	-3 to 20		0-17		0 - <i>6</i>		-3 - 14	

Table 1: Normal ABR maximum levels and eHL correction factors for infants for air- and bone-conducted stimuli. The dashed lines indicate that the eHL correction values are not yet available (BCEHP, 2012; Small & Stapells, 2017).

Air-conduction

The time to establish normal ASSR maximum levels for infant AC ASSR was protracted by the proliferation of stimulus types and analysis techniques used for ASSR research (i.e., difficult to compare across studies). However, we currently have sufficient data to recommend normal ASSR maximum levels (in dB HL) for AC stimuli, as shown in Table 2. Based on the majority of published studies to date, and recent data from my lab (Valeriote & Small, 2015), which investigated young infants with normal hearing (500 & 2000 Hz) and mild conductive loss (500 Hz), recommended normal ASSR maximum levels are 40, 40-45, 40, and 40 dB HL at 500-, 1000-, 2000-, and 4000-Hz, respectively. AC ASSR mean threshold data also show an interesting maturational pattern, as shown in Figure 3. Infant AC ASSR mean thresholds are elevated relative to those of adults, at least for the majority of infant studies (e.g., John, Brown, Muir & Picton, 2004; Rance & Tomlin, 2006; Savio, Cardenas, Perez Abalo, Gonzales, & Valdes, 2001). It is noteworthy that this pattern is not seen for infant and adult AC brief-tone ABR mean thresholds (in dB nHL; for review see Small & Stapells, 2017).

	500 Hz		1000 Hz		2000 Hz		4000 Hz	
	AC	BC	AC	BC	AC	BC	AC	BC
8 studies (0-24 mos)								
Normal ASSR Max	40-50	30*	40-45	20*	40	40*	40	30*
(dB HL)								
Range in literature	40-52	30-40	30 to >50	10-30	30-50	30-40	28-44	10-4
BC EHP eHL, correction (dB)	10-20		10-15		10-15		5-15	
Range in literature	-3 to 20		0-17		0 - <i>б</i>		-3 - 14	

Table 2: Normal ASSR maximum levels and eHL correction factors for infants for air- and bone-conducted stimuli. The dashed lines indicate that the eHL correction values are not yet available (for review: Small & Stapells, 2017).

An additional barrier to clinical implementation of ASSRs was that earlier studies of ASSR thresholds in infants with hearing loss had not compared ASSR thresholds to "bestpractice" frequency-specific measures of thresholds (i.e., behavioral or tone-ABR thresholds). In recent years, more studies have published difference scores (AC-ASSR thresholds minus frequency-specific behavioral or tone-ABR thresholds) in infants and young children with hearing loss. Preliminary eHL corrections for AC ASSR stimuli based on these data are 10-20, 10-15, 10-15, and 5-15 dB for 500-, 1000-, 2000-, and 4000-Hz, respectively (Table 2).

Assessment of adults with conductive loss using ASSRs has received much less attention (Ishida, Cuthbert & Stapells, 2011), and more importantly, only a few studies have reported findings for either infants or children with conductive loss. As mentioned earlier, we estimated AC and BC ASSR and ABR thresholds at 500 Hz in infants with mild conductive loss and found larger air-bone-gaps for ASSR thresholds for confirmed conductive loss compared to normal-hearing infants; however, there was considerable overlap in AC ASSR thresholds for these two groups (Valeriote & Small, 2015). This variability in 500-Hz AC ASSR thresholds was also found for adults with hearing loss (D'Haenens et al., 2009; Rance et al., 2005). AC and BC multiple-ASSR and behavioral threshold data for nine infant and child cases with conductive losses (Nagishima et al., 2013) support that ASSRs have the potential to reflect similar diagnostic information as behavioral audiometry. For example, they showed that children pre- and post- treatment for middle-ear effusion demonstrated an air-bone-gap that decreased by 10-25 dB post- treatment. They also found an average BC ASSR minus behavioral difference of 11-16 dB (N=3) consistent with on average offset of 6-17 dB for infants with normal hearing (N=19-20) shown by Casey and Small (2014).

Because these ASSR studies employed a variety of stimuli and analysis methods, and not all types of hearing loss are well represented, the range of threshold-difference scores is fairly large. However, conservative AC ASSR to eHL corrections of 10 to 15 dB (i.e., less likely to over-estimate the amount of hearing loss) can be applied to young children with sensorineural hearing loss at this time. More ASSR data for infants with hearing loss of all types (ideally with the same stimuli and recording parameters for ease of comparison) are needed for further elaboration and confirmation of the ASSR technique.

Bone-conduction

Despite the need for BC ASSR threshold data for the full implementation of the ASSR as a clinical tool, few research groups have studied BC ASSRs as comprehensively as AC ASSRs. Several studies have reported bone-conduction ASSR thresholds in adults with normal hearing (Dimitrijevic et al., 2002; Jeng, Brown, Johnson & Vander Werff, 2004; Lins et al., 1996; Small & Stapells, 2008a). Figure 3 shows that adult mean BC ASSR thresholds are poorer in the low versus high frequencies (N=58 adults; Small & Stapells, 2017). Reasonably high correlations (.8-.9) have also been found between BC ASSR and behavioral thresholds at 1000, 2000, and 4000 Hz, and somewhat poorer (.7-.8) correlations at 500 Hz for adults with simulated hearing loss (Ishida, Cuthbert & Stapells, 2011). Critically, however, ASSR results from infants with normal hearing and hearing loss are still required to confirm appropriate normal levels and determine corrections for BC ASSR stimuli.



Figure 3: Mean air- (AC) and bone- (BC) conduction multiple auditory steadystate response thresholds at 500, 1000, 2000, and 4000 Hz for infants (AC: N=297; BC: N=140) and adults (AC: N=347-370*; BC: N=58) with normal hearing. Mean values for each stimulus frequency and presentation mode are shown at the top of each bar. *Taken from Tlumak, Rubinstein and Durrant (2007). These data are reviewed in detail in Small and Stapells (2017).

Currently, the majority of bone-conduction ASSR studies have investigated infants with normal hearing (Figure 3) and have shown that low-frequency BC ASSR thresholds (500 & 1000 Hz) are better (i.e., lower dB HL) in young and older infants compared to adults, supporting that low-frequency BC stimuli in infants are effectively more intense than the same stimuli in adults (by 10 dB, on average), likely due to infant skull maturation and other issues (Small & Stapells, 2008a, Mackey, Hodgetts, Scott & Small, 2016). BC ASSR thresholds for 2000-4000 Hz show little or no change with maturation (Small & Stapells, 2008a). These maturational patterns are clearly different than those for AC ASSRs and from adults, emphasizing that "normal maximum levels" and ASSR-to-behavioral correction factors for BC stimuli must be determined from infant BC ASSR data. Existing infant data are currently limited to research from my research group. Based on our findings, we recommend normal BC ASSR levels of 30, 20, 40 and 30 dB HL for infants aged 0-11 months, and 40, 20, 40, and 30 dB HL for infants aged 12-24 months at 500-, 1000-, 2000 and 4000 Hz (see Table 2; Small & Stapells, 2017).

Currently, there are only three BC ASSR studies in infants with hearing loss, and only one study that confirmed hearing status using a standard measure, such as the tone ABR. Consistent with the normative BC ASSR data, Valeriote and Small (2015) estimated BC ASSR thresholds at 500-Hz in young infants with mild conductive loss to be approximately 16-17 dB HL). Swanepoel and colleagues found similar mean BC ASSRs thresholds in children (6 months to 11 years); however, they did not confirm hearing status (Swanepoel, Ebrahim, Freidland, Swanepoel, & Potts, 2008). As discussed earlier, Nagashima et al. (2013) contributed BC ASSR data for a small sample of young children pre- and post-surgery for insertion of ventilation tubes. Additional research comparing AC and BC ASSR thresholds in infants with greater degrees of hearing loss and different types of hearing loss confirmed by behavioral (or tone-ABR) thresholds to AC and BC stimuli is still required.

Simultaneous air- and bone-conduction multiple ASSRs A recent novel study by Torres-Fortuny et al. (2016) investigated ASSRs elicited to AC and BC AM stimuli simultaneously in both ears. They presented AC stimuli at 2000 Hz (114.5 & 115 Hz in left and right ear, respectively) in combination with BC stimuli at 500 Hz (104.2 & 107.8 Hz in left and right ear, respectively) and found ASSR amplitudes were not reduced compared to ASSRs elicited to the same AC and BC stimuli presented separately using a 115-Hz modulation rate. More data are needed but these findings support the notion that combining AC and BC stimuli might have clinical utility.

Artifactual responses for high-intensity stimuli

One drawback with ASSRs compared to brief-tone ABRs is that ASSRs do not provide sensible time-domain waveforms to review when unexpected or questionable results are obtained (i.e., multiple overlapping responses that are cyclical in nature). For example, artifactual ASSRs to high-intensity AC and BC stimuli that "mimic" physiologic responses have been demonstrated for individuals who were deaf and cannot hear the stimuli (Gorga et al., 2004; Small & Stapells, 2004). Some of these artifactual ASSRs resulted from highamplitude stimulus artifact contaminating the recorded EEG due to aliasing and were subsequently minimized using optimal EEG recording parameters. However, other artifactual ASSRs have been reported in individuals with severe or profound hearing loss that are physiologic but non-auditory; these responses likely result from stimulation of the vestibular system as suggested by other studies using transient-evoked potentials (Welgampola & Colebatch, 2001). At this time, we cannot differentiate auditory and nonauditory (vestibular) responses in an ASSR recording. The responses occur in response to high-intensity stimuli, usually low-frequency, for AC stimuli (\geq 100 dB HL) and for BC stimuli (\geq 50 dB HL or higher). Occasionally, a clear early negative wave (3-4 ms post stimulus) with no wave V following is present in an ABR waveform when no response is expected due to the severity of the hearing loss. This "N3" wave has been suggested to originate from the vestibular system (Kato et al., 1998), and is likely the cause of the lowamplitude non-auditory ASSRs. Unlike the ABR technique, current ASSR methodologies do not differentiate between vestibular and auditory responses (for review see Small & Stapells, 2017).

Single- versus multiple ASSRs

ASSR research to date suggests that amplitudes are not reduced using multiple- versus the single-stimulus presentation provided the carrier frequencies within a test ear are at least an octave apart in frequency (& stimulus level \leq 60 dB SPL). Similarly, frequency specificity of AM stimuli does not appear be reduced when stimuli are presented as multiple versus single ASSRs. For adults, at intensities > 60 dB SPL, amplitudes decrease due to interactions between responses to the multiple stimuli; however, the multiple stimulus technique is still more efficient (faster) than the single-stimulus technique. Issues such as sloping audiograms, smaller amplitudes at some frequencies compared to others, and amplitude reductions due to interactions at higher stimulus intensities all decrease the efficiency of the multiple-stimulus technique such that it is, at best, only 1.5 to 3 times faster than the single-stimulus technique. It has also been shown that stimuli with broader spectra, such as AM/FM, show significantly greater interactions, even at 60 dB SPL in adults, significantly reducing the efficiency of the multiple-ASSR technique (Picton et al., 2003; Ishida & Stapells, 2012).

Although clinical systems with multiple-ASSRs are currently being marketed to clinicians, there are surprisingly few studies that have investigated the efficiency of the singleversus multiple-ASSR techniques for the infant population. Hatton and Stapells (2011, 2013) showed that normal infants demonstrate significant interactions with the multiple ASSR, even at 60 dB SPL, but their thresholds are not affected and the multiple technique remains more efficient. They recommended that the multiple ASSR be used for stimuli presented at low-to-mid intensities and that single ASSRs be considered for higher intensities when assessing infants.

Isolation of the test cochlea for bone-conduction testing

Similar to the BC ABR, two-channel EEG recordings of infant ASSRs also show significant ipsilateral/contralateral asymmetries, with responses larger and earlier in latency in the EEG channel ipsilateral to the stimulated ear (Small &Stapells, 2008b). Asymmetries are more prominent at low presentation levels (20-25 dB HL), similar to ABR findings, and consistently present for the ASSR at 500 and 4000 Hz but not at 1000 and 2000 Hz (Small & Love, 2014). In contrast, published ABR findings show consistent asymmetries at 500 and 2000 Hz (Stapells, 1989).¹ This ASSR phenomenon might be helpful clinically to determine which cochlea is responding to the BC stimulus; however, further research is needed in infants with asymmetrical or unilateral hearing loss to test this theory.

Clinical masking will be needed when the responses in the EEG channel ipsi- and contralateral to the stimulated mastoid are not unequivocally asymmetric, as is also the case for the ABR. Effective masking levels (EMLs) appropriate for infants for the ABR and ASSR are needed to isolate the test ear in these cases. We estimated EMLs for ASSRs elicited to BC stimuli at 500-4000 Hz in normal-hearing infants and adults and found maturational differences (Hansen & Small, 2011; Small, Smyth & Leon, 2013). Based on these findings, we recommend the following EMLs in dB SPL for AM/FM ASSR stimuli presented at 35 dB HL for 500, 1000, 2000, and 4000, respectively: Infant: 81, 68, 59 and 45 dB SPL; Adult: 66, 63, 59 and 55 dB SPL. Further ASSR research is needed to confirm the accuracy of using these EMLs to isolate the test ear in infants with hearing loss before applying these methods clinically. Estimation of effective masking levels for bone-conduction ABR stimuli is currently underway in my laboratory.

Conclusion

Currently, we have sufficient evidence for the use of AC ASSRs to screen for normal maximum levels for 500, 1000, 2000, and 4000 Hz in young infants. Preliminary eHL correction factors are also available for AC ASSR stimuli; however, more data in infants with a broader range of hearing loss type and degree are needed to verify the accuracy of these eHL correction factors. Normal maximum levels are also available for BC ASSR stimuli; however, the accuracy of these levels to differentiate between normal cochlear function and sensory/neural hearing loss remains to

¹ There are no published BC ABR ipsi/contra asymmetry data for 1000 and 4000 Hz.

be demonstrated. Estimated HL correction factors for BC ASSRs are not yet available. Future ASSRs studies should endeavour to fill the gaps in the infant ASSR literature to provide evidence for full clinical implementation of this technique.

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Acknowledgements:

This research was funded by a Discovery Grant from Natural Sciences and Engineering Research Council-Canada, The University of British Columbia Faculty of Medicine, and an Eric W. Hamber Professorship in Clinical Audiology.

Author

Susan A. Small, Ph.D.

Associate Professor School of Audiology and Speech Sciences The University of British Columbia Vancouver, British Columbia, Canada ssmall@audiospeech.ubc.ca

Editors

Anne Marie Tharpe, Ph.D.

Chair, Phonak Research Advisory Board Professor and Chair Department of Hearing & Speech Sciences Vanderbilt University School of Medicine Nashville, Tennessee, United States

Marlene Bagatto, Ph.D.

Research Associate and Adjunct Research Professor National Centre for Audiology Western University London, Ontario, Canada

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