JASA ARTICLE

Optimizing non-invasive functional markers for cochlear deafferentation based on electrocochleography and auditory brainstem responses[a)]

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ABSTRACT:

Accumulating evidence suggests that cochlear deafferentation may contribute to suprathreshold deficits observed with or without elevated hearing thresholds, and can lead to accelerated age-related hearing loss. Currently there are no clinical diagnostic tools to detect human cochlear deafferentation *in vivo*. Preclinical studies using a combination of electrophysiological and post-mortem histological methods clearly demonstrate cochlear deafferentation including myelination loss, mitochondrial damages in spiral ganglion neurons (SGNs), and synaptic loss between inner hair cells and SGNs. Since clinical diagnosis of human cochlear deafferentation cannot include post-mortem histological quantification, various attempts based on functional measurements have been made to detect cochlear deafferentation. So far, those efforts have led to inconclusive results. Two major obstacles to the development of *in vivo* clinical diagnostics include a lack of standardized methods to validate new approaches and characterize the normative range of repeated measurements. In this overview, we examine strategies from previous studies to detect cochlear deafferentation from electrocochleography and auditory brainstem responses. We then summarize possible approaches to improve these non-invasive functional methods for detecting cochlear deafferentation with a focus on cochlear synaptopathy. We identify conceptual approaches that should be tested to associate unique electrophysiological features with cochlear deafferentation. © *2022 Acoustical Society of America*. https://doi.org/10.1121/10.0010317

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I. INTRODUCTION

Noise overexposure and aging can cause permanent changes in the cochlea and central auditory system. These changes include synaptic loss between inner hair cells (IHCs) and spiral ganglion neurons (SGNs) in the cochlea, and atrophy of the SGNs' endbulbs of Held in the brainstem, that often occur prior to sensorineural hearing loss (Stamataki *et al.*, 2006; Sergeyenko *et al.*, 2013; Furman *et al.*, 2013; Fernandez *et al.*, 2015; Fernandez *et al.*, 2020; Muniak *et al.*, 2018). Initial findings have suggested that this synaptic loss between IHCs and SGNs starts specifically with SGNs that have a low spontaneous-rate (SR) and higher thresholds (e.g., Kujawa and Liberman, 2006, 2009; Furman *et al.*, 2013). However, recent data have demonstrated cochlear synaptic loss of both low- and high-SR SGNs (Suthakar and Liberman, 2021). The specific loss of cochlear synapses has now been termed cochlear synaptopathy (Sergeyenko *et al.*, 2013; Bramhall, 2021). Although cochlear synaptopathy can be identified by longitudinal measurements of the auditory brainstem response (ABR) and validated by post-mortem histological quantification in animal models (Kujawa and Liberman, 2015), its confirmation in humans remains challenging (Fulbright *et al.*, 2017; Grinn *et al.*, 2017; Prendergast *et al.*, 2019). In addition to cochlear synaptopathy, noise and aging also contribute to deficits in glia cells and the myelin sheath encompassing afferent auditory nerve (AN) fibers (Xing *et al.*, 2012; Panganiban *et al.*, 2018). Disruptions in myelin are thought to interfere with the generation and propagation of action potentials, thus contributing to deficits in AN function. In addition, even before the loss of cochlear synapses, ototoxic drugs such as cisplatin can cause mitochondrial loss in SGNs (Chen *et al.*, 2021). Therefore, a sensitive and reliable functional diagnostic tool for detecting cochlear deafferentation and dysfunction *in vivo* is needed.

II. LACK OF RELIABLE CLINICAL DETECTION METHODS FOR COCHLEAR DEAFFERENTATION

Hearing loss is a pervasive public health concern, resulting in significant decreases in quality of life for a large segment of the population. Currently, the audiogram is still the primary clinical tool for assessing hearing loss (e.g., Bao *et al.*, 2020). Unfortunately, AN deficits, including synaptic loss and demyelination of SGN fibers, can occur without measurable changes in audiometric thresholds and are

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thought to contribute to hidden hearing loss (HHL) (Schaette and McAlpine, 2011). Such AN deficits in patients with normal audiometric thresholds could be the cause of the difficulties these patients often have with speech perception in noise, hyperacusis, and tinnitus (e.g., Sanchez *et al.*, 2005; Pryce *et al.*, 2010; Sheldrake *et al.*, 2015). Moreover, AN deficits are likely exaggerated in patients with hearing loss, yet the potential impact of AN pathology on auditory function remains largely unknown (e.g., Krumm and Cranford, 1994). A number of non-invasive physiological measures have been developed to detect AN dysfunction/loss in the laboratory: (1) ABR or electrocochleography (ECochG) (recent review, Bramhall, 2021); (2) auditory steady-state responses and the subcortical steady-state responses such as envelope following response (Attias *et al.*, 2014; Bharadwaj *et al.*, 2015; Shaheen *et al.*, 2015; Coffey *et al.*, 2019; Wang *et al.*, 2019); and (3) the middle-ear muscle acoustic reflex (Valero *et al.*, 2018; Guest *et al.*, 2019; Mepani *et al.*, 2020). However, inconsistencies across methods and studies highlight the difficulty in detecting cochlear deafferentation in humans.

An ABR/ECochG based detection approach may be ideal for detecting auditory dysfunction because (1) they employ equipment already used in clinical settings, and (2) decreased ABR wave-I amplitude is associated with cochlear synaptopathy in animal studies (Kujawa and Liberman, 2015; Kobel *et al.*, 2017). ABR and ECochG measures are potentials evoked by brief auditory stimuli (typically broadband clicks, or narrowband tone bursts), extracted from the subcortical auditory pathway. High neuronal activity within the pathway generates prominent waveform peaks within the electrophysiologic tracing that can be quantified for diagnostic and screening purposes. In humans, there are five prominent wave peaks that are labeled waves I, II, III, IV, and V, with the earlier waves (I, II, III) generated by the AN and inferior portion of the pons, and later waves (IV, V) generated by higher levels of the brainstem (Fig. 1; Henry, 1979). Five similar waves can be observed in animal models (Waves 1–5). ECochG measures are generated mainly by the peripheral auditory areas, presenting two prominent waves: the summating potential (SP) which is a direct current generated by IHC receptor potentials, and the compound action potential (CAP-N1) which is generated by action potentials at the distal AN (equivalent to wave I of the ABR) (for review, Gibson, 2017). ABR and ECochG measures are similar between humans and rodent species with slight discrepancies in waveform morphology and latencies (Henry, 1979; Burkard and Sims, 2001). Clinically, however, ABR/EcochG evaluations generally involve simplified analyses of response latencies and peak amplitude, or ratios between different wave peaks (i.e., latency difference between waves I and V). These techniques limit their clinical utility and often require other tests including magnetic resonance imaging to aid their diagnostic relevance. In animal studies, a significant decrease in ABR wave-1 amplitude has been shown to be associated with cochlear synaptopathy (for review, Kujawa and Liberman, 2015). Similarly, a shift of latency is associated with early damage of mitochondria in SGNs (Chen *et al.*, 2021). Attempts to translate this decrease in amplitude of the ABR wave to human cochlear synaptopathy have produced inconsistent results (for recent review, Bharadwaj *et al.*, 2019; Bramhall, 2021). While some studies have found an association between reduced ABR wave I amplitudes and possible cochlear synaptopathy or AN dysfunction during aging (Burkard and Sims, 2001; Johannesen *et al.*, 2019; Harris *et al.*, 2021) or noise exposure (Bramhall *et al.*, 2017; Bramhall *et al.*, 2018; Grose *et al.*, 2017; Ridley *et al.*, 2018; Skoe and Tufts, 2018), others have reported a lack of significant correlation (Fulbright *et al.*, 2017; Grinn *et al.*, 2017; Spankovich *et al.*, 2017; Guest *et al.*, 2019; Prendergast *et al.*, 2019). One potential reason is that human ABRs are often recorded using surface electrodes instead of the subcutaneous electrodes used in animals which are positioned much closer to the AN. The far field responses of surface electrodes diminish the signal strength and make the recording more susceptible to noise and electrical interference, causing variability in peak amplitude measures (Plack *et al.*, 2016; Kujawa and Liberman, 2019). This issue can be improved by using ECochG, (e.g., Liberman *et al.*, 2016; Grant *et al.*, 2020), where the electrode is placed closer to the tympanic membrane, through the use of TIPtrodes, or tympanic membrane electrodes. However, the use of these electrodes in conventional recording montages for humans is still considered far-field measurements, and while their repeatability is usually higher than that of human ABR recordings, there is still a concern regarding wave amplitude variability. Aside from recording interference, individual characteristics such as head size, gender, and genetic heterogeneity, as well as inconsistent electrode placement and

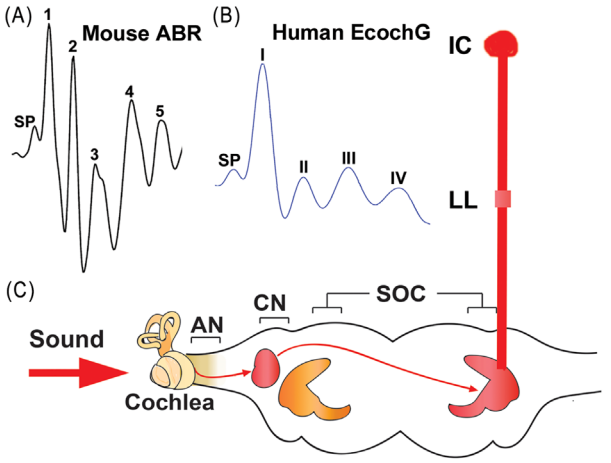

FIG. 1. (Color online) ABR/ECochG waves and their origin. (A) One averaged trace of mouse ABR waves to a click at 90 dB normalized hearing level (nHL). (B) One averaged trace of human ECochG waves to a click at 90 dB nHL. (C) A diagram of the auditory pathway underlying the origin of ABR/ECochG waves. Wave 1 or I mainly comes from the AN; wave 2 or II comes from the cochlear nucleus (CN); wave 3 or III comes from the contralateral superior olivary nucleus (SOC); wave 4 or IV mainly comes from the contralateral lateral lemniscus (LL); and the wave 5 or V comes from the contralateral inferior colliculus (IC).

myogenic interference can all account for some of this variability (e.g., Stamper and Johnson, 2015a,b).

III. POSSIBLE IMPROVEMENTS TO ABR/ECOCHG METHODS

To address these obstacles, here, we review the relevant literature and propose several possible approaches to optimizing ABR/ECochG assessments. Cochlear synaptic loss and AN deficits can be readily quantified in rodent models. One general strategy should be to improve objective measures, including ABR/ECochG in well-established rodent models, which can be validated by direct pathologic quantification, and then apply them to human diagnosis. A main rationale for this general approach is that there are similar auditory pathways from the cochlea to the auditory cortex shared by both rodents and humans, although recent studies have suggested certain differences even among different animal models (e.g., Furman *et al.*, 2013; Suthakar and Liberman, 2021). In addition, non-invasive functional markers can be cross-validated if they come from different functional assays. Last, improvements in ABR/ECochG testing can be explored in three major areas: new stimulation paradigms, improved data quantification, and innovative data analysis. The goal here is to increase sensitivity and specificity and address variability issues that limit the clinical diagnostic utility of these measures (Table I). These improvements can be achieved through the modification of both the hardware and software used in current ABR/ECochG testing equipment and applying new analysis strategies.

A. Stimulation paradigm

Using a gerbil model of cochlear deafferentation, Earl and Chertoff (2010) found that the amplitude of CAP-N1, evoked with high-level tone burst stimuli, was highly correlated with AN survival. However, high-intensity sound stimulation triggers SGN firing across a large area of the cochlea. Signal-in-noise action potentials (SiNAPs) can be obtained by varying the bandwidth of a high-pass masking noise to systemically limit the cochlear activation area while using high-level broadband stimuli, such as a click or broadband chirp, to evoke CAP-N1 (Earl and Chertoff, 2012).

TABLE I. Potential improvements of ABR/ECochG methods to identify cochlear deafferentation. OHC, outer hair cell.

Area	Name	Examples	Advantages	Future directions
Stimulation Paradigm	SiNAPs	Earl and Chertoff (2010, 2012)	(a) Sensitive to spiral ganglion afferents independent of outer hair cell pathology; (b) Larger ECochG wave I due to chirp stimuli compared to tone burst stimuli	Validation with human studies
	Forward Masking	Walton *et al.* (1999); Lewis *et al.* (2015) Mehraei *et al.* (2016); Mehraei *et al.* (2017); McClaskey *et al.* (2020)	(a) Supported by both animal and human studies (b) Specific to a loss of low-SR fibers	Further testing for individual human diagnosis
	Paired Click Stimulation	Abbas and Brown (1991) Relkin *et al.* (1995); Lang *et al.* (2002); Ohashi *et al.* (2014); Lee *et al.* (2021)	(a) Sensitive to the temporal processing function of ribbon synapses (b) Confirmed by animal studies	Validation with human studies
Quantification	Automation	Bradley and Wilson (2005); Kamerer *et al.* (2020); Krumbholz *et al.* (2020)	(a) Reduced variability (b) Improved efficiency	Validation across clinical populations and universal adoption
	SP-AP measurements	Liberman *et al.* (2016); Grant *et al.* (2020)	(a) Reduced variability (b) Independent of baseline noise	SP amplitude itself as a potential marker
	Calibration Pulse	Munson *et al.* (1986); Nishimura *et al.* (1993); Brigell *et al.* (1998)	(a) Established for clinical electrophysiology of vision (b) Used for evoked nerve potentials and intracellular recording	ABR/ECochG studies
Analysis	Wave 1 amplitude	Kujawa and Liberman (2009); Furman *et al.* (2013); Fernandez *et al.* (2015)	(a) Consistently able to detect cochlear synaptopathy in rodent models	It is not sensitive enough for human diagnosis, and multi-metric method should be developed
	Multi-metric approach	Harris *et al.*, (2018); Harris *et al.* (2021); Guest *et al.* (2019); McClaskey *et al.* (2020)	(a) A new approach to increase the specificity for identifying cochlear nerve pathology	Validation by other methods
	Computational Simulation	Verhulst *et al.* (2015); Verhulst *et al.* (2018); Fontenot *et al.* (2017)	(a) Possible to differentiate OHC deficits from cochlear synaptopathy	Proof-of-Concept from animal studies

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The advantage of this method is that it can provide a location-specific estimate of cochlear deafferentation. Further human studies are needed to evaluate this technique for possible clinical use.

Since low-SR fibers may be more sensitive to aging and noise exposure than high-SR fibers and may have a slow recovery rate after damage (Suthakar and Liberman, 2021), several experimental paradigms have been tested to exploit known differences in function across fiber types. Low-SR fibers have higher thresholds, larger dynamic ranges, saturate at higher sound levels, and recover more slowly from prior stimulation than high-SR fibers (Liberman 1978; Relkin *et al.*, 1995; Taberner and Liberman, 2005). Taking advantage of differences in the rate of recovery, several studies have used a forward masking recovery function to characterize a loss of low-SR fiber function. The approach has been used successfully in animals and humans and has demonstrated that latency changes in ABR human wave V or mouse wave 4, and the recovery of wave I response amplitude are sensitive to the heterogeneity of AN fibers, and may be sensitive to loss of low-SR fibers (Zeng *et al.*, 1991; Zeng and Turner, 1992; Boettcher *et al.*, 1995; Walton *et al.*, 1999; Lewis *et al.*, 2015; Mehraei *et al.*, 2016; Mehraei *et al.*, 2017, McClaskey *et al.*, 2020). Limitations of the forward masking paradigm include the time needed to collect responses at varying times between masker and probe, and the difficulty in assessing responses at shorter recovery intervals. Therefore, it is currently unclear if this functional marker is sensitive enough to detect cochlear deafferentation in individual patients. Additional structure-function studies are needed to determine the extent to which differences in forward-masked recovery functions are associated with synapse loss, myelin changes, changes in endocochlear potential, or a loss of AN fibers.

Paired-click sound stimuli are often used to measure temporal resolution in both animals (e.g., Abbas and Brown, 1991; Parham *et al.*, 1996) and humans (e.g., Ohashi *et al.*, 2014). Because the functional recovery of SGN fibers is sensitive to the inter-click interval (Relkin *et al.*, 1995; Lang *et al.*, 2002), it has been shown to be sensitive to human cochlear synaptic damage (Ohashi *et al.*, 2014). Recent animal data show that the ABR recovery threshold in the paired-click paradigm is correlated with cochlear synaptic quantification (Lee *et al.*, 2021). Thus, this paired-click paradigm could be a useful tool in diagnosing human cochlear deafferentation.

B. Data quantification

To address the variability issue of ABR/ECochG data, we found three possible areas of improvement. First, automated quantification of ABR/ECochG wave amplitudes and latencies has been developed (e.g., Bradley and Wilson, 2005; Kamerer *et al.*, 2020; Krumbholz *et al.*, 2020), but not widely adopted. ABR/ECochG metrics are still largely estimated from the peaks picked by expert technicians, a time-consuming process and subject to human error that can introduce variability into the data. Clinical studies are needed to compare the different auto-quantification approaches that have been developed and validate them for clinical use. Importantly, many of these automated techniques have not yet been tested on clinical populations, where waveform morphology may be less clear (noisy data), thus impacting peak detection. A second method utilizes the SP to wave I ratio. The ratio of SP/wave I amplitudes has been used as a means of minimizing the variability in ABR amplitudes for detecting AN deficits in individuals without elevated hearing thresholds (e.g., Liberman *et al.*, 2016). However, a subsequent study found that the strongest correlation between speech scores and ECochG measures was with the SP amplitude itself: the higher the SP amplitude, the lower the speech identification score (Grant *et al.*, 2020). Thus, it may not be ideal to use SP measures as a reference for reducing the variability of ABR amplitudes in detecting cochlear deafferentation because other sources, such as presynaptic potentials from hair cells and post-synaptic potentials from ANs also contribute to the SP (Pappa *et al.*, 2019). In individuals with hearing loss, the SP is predicted to be reduced and may be difficult to identify, thus limiting the potential clinical utility of this approach. A third approach involves the use of a calibration pulse. This calibration approach is used in measures of other sensory systems to reduce unexplained variability. For example, a calibration pulse is used in measuring clinical visual evoked potentials (Brigell *et al.*, 1998), spinal cord evoked potentials, and intracellular recordings (e.g., Munson *et al.*, 1986; Nishimura *et al.*, 1993). However, a similar calibration method is not currently available on ABR/ECochG equipment. A close collaboration between academic research and commercial development to implement such a calibration pulse across acquisition systems may provide a potential solution to strengthening data comparisons longitudinally and across different samples in clinical studies.

C. Data analysis

In addition to improving reliability, researchers have begun to look across multiple features of the neural response or to identify patterns of change that may reflect the underlying pathology such as cochlear synaptopathy and demyelination of the AN. ABR/ECochG assessments traditionally focus on individual measures of peak amplitude and latency, with larger response amplitudes and earlier peak latencies, generally associated with a "healthier" AN. However, several factors may impact these individual measures making it impossible to identify the underlying pathology. One technique to increase detection sensitivity is to use a multimetric approach, where changes are examined across metrics. This approach is aided by the inclusion of traditional measures of amplitude and latency as well as estimates of wave half-width and neural synchrony (Harris *et al.*, 2018; Harris *et al.*, 2021; McClaskey *et al.*, 2020). Neural synchrony can be estimated from the ABR/CAP by calculating the inter-trial coherence (ITC), or the phase locking value

(PLV), which reflects the consistency of the response phase at a given time and frequency across individual response trials (Delorme and Makeig, 2004). Half-width is calculated as the time in milliseconds between the onset and the peak of a response wave, typically wave I. Recently, four curvature quantification methods were compared by simulated ABR waves, and the cubic spline method using five data points was identified to produce the most accurate quantification. The cubic method was then used to quantify ABR waves from an established mouse model with cochlear synaptopathy. The data clearly demonstrated that curvature measurement is more sensitive and consistent in identifying cochlear synaptic loss in mice compared to the amplitude and latency measurements (Bao *et al.*, 2022). By examining multiple metrics derived from the ABR/CAP across different stimulus intensity levels within an individual, researchers can infer and separate the effects of a loss/disengagement of AN fibers from factors that impact neural synchrony (Harris *et al.*, 2018; McClaskey *et al.*, 2020; Harris *et al.*, 2021). In addition, machine learning has been developed as an effective statistical analysis technique for identifying multiple features associated with complex phenomena and has been successfully applied in auditory research (e.g., Bramhall *et al.*, 2018; McKearney and MacKinnon, 2019). Such machine learning approaches could be useful in developing programs to automatically identify key features of the ABR/ECochG waveform to compute metrics for cochlear deafferentation within clinical settings. Finally, computer simulation data along with ABR recordings could potentially differentiate OHC deficits from cochlear synaptopathy (Verhulst *et al.*, 2015; Verhulst *et al.*, 2018). Similarly, computer simulation data using cochlear microphonics and AN neurophonics along with ECochG recording is able to isolate hair cell and neural activity in response to low-frequency tones (Fontenot *et al.*, 2017). Since many patients are likely to have both hair cell and synapse damage within their cochleae, these methods could be useful, if validated within clinical studies.

IV. SUMMARY

Based on a review of the current literature, we have identified two major technical difficulties in detecting cochlear deafferentation using ABR/ECochG methods. Due to a lack of quantitative validation for human diagnosis of cochlear differentiation, we suggest a general strategy to develop new objective detection methods in well-established rodent models in which AN loss/dysfunction can be directly validated by histological quantification. We review several emerging techniques that may improve detection sensitivity and specificity through the use of novel stimulation paradigms, data quantification and analysis. While other functional detection methods show promise, this review focused on ABR/ECochG methods as they are objective and already in clinical use.

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