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Cochlear Implantation in Auditory Neuropathy Spectrum Disorder

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1. Introduction

With the implementation of newborn hearing screening programs, permanent congenital hearing loss is typically diagnosed in babies within six weeks of age (JCIH, 2007). Many hearing screening programs use a two-stage transient-evoked otoacoustic emissions (TEOAEs) screen because of the ease-of-use and time- and cost-effectiveness (Hayes, 2003). Because infants are unable to provide reliable behavioural responses to sound stimuli, hearing thresholds are estimated using the auditory brainstem response (ABR), a measure of synchronous neural activity that correlates well with behavioural thresholds in infants with normal hearing and conductive and sensorineural hearing loss (Hyde et al., 1990). As a result, early intervention is targeted, resulting in spoken language development that is similar to normally hearing peers and significantly better than later identified peers, irrespective of the magnitude of loss (Yoshinaga-Itano et al., 1998).

On the other hand, Auditory Neuropathy Spectrum Disorder (ANSD) describes a unique type of permanent hearing loss that is not identified with newborn hearing screening programs that utilise otoacoustic emissions (OAEs) as a first-line screen, unless the impairment is detected through alternative risk-based screening programs (which occurs for individuals with additional and/or associated neonatal problems such as anoxia and hyperbilirubinemia; Rance et al., 2002). ANSD is characterised by significantly disordered auditory afferent neural conduction with preservation of cochlear outer hair cell function (Starr et al., 1996), based on clinical findings of normal OAEs and/or cochlear microphonic (CM) potentials with the absence or marked abnormality of the ABR. Despite poor afferent responses, individuals with ANSD have pure tone thresholds that may vary from normal to profound hearing loss in a variety of audiometric configurations (Starr et al., 2000). Therefore OAE screening would inaccurately “pass” these individuals and, while ABR screening would detect them, diagnostic ABR testing would not provide an accurate estimate of hearing thresholds.

The estimation of hearing thresholds in infancy is only one of the challenges that are faced in selecting the most appropriate intervention pathways and hearing devices for these individuals. Unlike standard sensorineural hearing losses which show impaired spectral processing, largely resulting from the loss of outer hair cells (OHCs), individuals with ANSD show distinct deficits in auditory temporal processing. Presumably, this results from the disordered or temporally jittered neural activity. This is the ability of the auditory system to detect and analyze temporal cues within an acoustic signal that occur within milliseconds (Green, 1971). Auditory temporal processing plays an important role in the development of speech perception, language and reading skills in all children and it has been speculated that this underpins most auditory processing capabilities (Benasich & Tallal, 2002; Musiek, 2003). Both fast (20-40Hz) and slow (<2-16Hz) temporal processing is needed to: (i) detect and resolve relevant phonetic sounds and the speech envelope within segregated speech; and (ii) extract speech sounds from noisy environments, where it is the perception of the sound onset that is most critical to detect speech-in-noise (Drullman et al. 1994a,b; Kaplan-Neeman et al., 2006; Shannon et al., 1995). Rapid temporal processing abilities are important for the development of phonological awareness (Nitttrouer, 1999), which is significantly correlated with language and reading ability in children (Stark & Tallal, 1979; Benasich & Tallal, 2002; Catts et al., 2002), although not exclusively related (Bretherton & Holmes, 2003). In particular, this is highlighted in many cases of dyslexia and specific language impairment (SLI) which show impaired temporal processing abilities compared with children with normal language and reading development (Farmer & Klein, 1995). However the temporal processing deficits in individuals with dyslexia and SLI appear less severe in comparison with most individuals with ANSD (see Figure 1).

2. Temporal processing & speech perception

Psychoacoustic measures in adults and children with ANSD show impairments of pitch discrimination (particularly at lower frequencies), temporal integration, gap detection, temporal modulation detection, backward and forward masking, perception of speech-in-noise and sound localization using inter-aural time differences (Rance et al., 2004; Starr et al., 1996; Zeng et al., 1999; Zeng et al., 2005). It is assumed that these deficits are caused by the disrupted temporal perception. Several studies have demonstrated that the magnitude of the disruption of temporal processing in individuals with ANSD varies considerably and it is this which determines speech perception outcomes, rather than hearing thresholds *per se* (Rance et al., 2004; Zeng et al., 1999, 2005; Kumar & Jayaram, 2005). Using amplitude modulated-broadband noise with varying modulation depths at three frequencies (10, 50 and 150 Hz), Rance and colleagues (2004) compared differences in temporal processing abilities between three populations of children; normal hearing (n=10), ANSD (n=14) and sensorineural hearing loss (n=10) and compared this with speech perception outcomes using Consonant-Nucleus-Consonant (CNC) words. The latter two groups with hearing loss showed pure tone thresholds within a mild-moderate range. While no difference existed in temporal processing abilities for individuals with normal hearing and sensorineural hearing loss, significant differences existed between these populations and children with ANSD. When the ANSD population was stratified into good ($\geq 30\%$ phoneme recognition; n=7) and poor performers ($< 30\%$ phoneme recognition; n=7), the disruption was only mild for those with good speech perception scores, and disruptions to low frequency modulations (10 Hz) only occurred in those with very poor speech discrimination. Similar outcomes have been demonstrated by Zeng et al. (2005) who examined temporal modulation detection as a

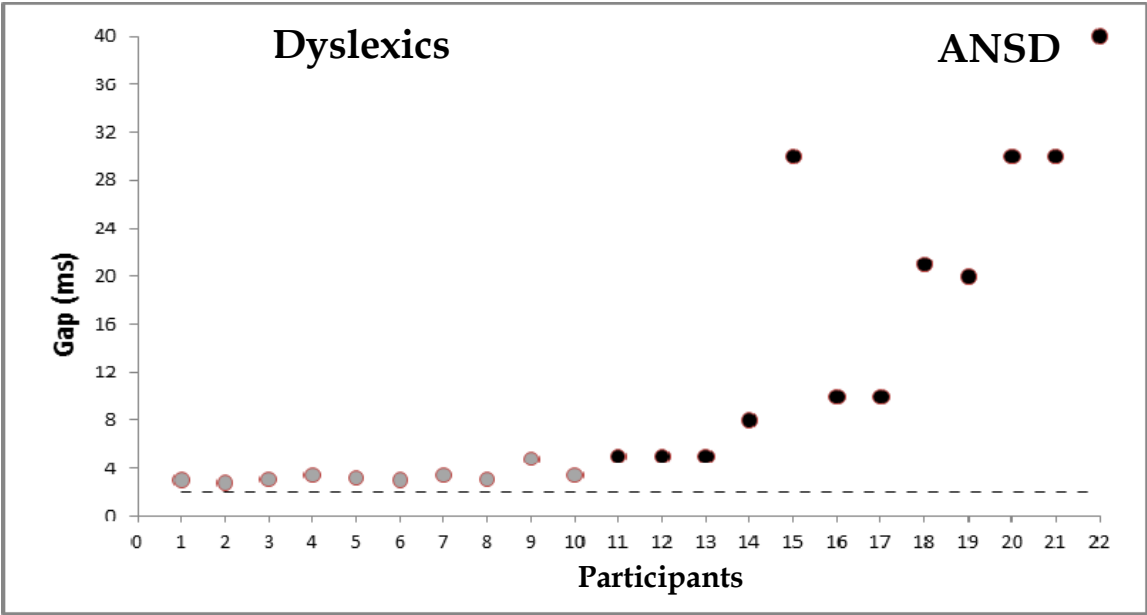


Fig. 1. Thresholds of gap detection for adults with ANSD (black circles; from Michalewski et al., 2005) and children with dyslexia (grey circles; from Van Ingelghem et al., 2001) compared to adults and children (120–144 months) without ANSD or dyslexia (dashed line).

function of modulation frequency (ranging from 2–2000 Hz) in 16 ANSD adult participants, with hearing thresholds varying from normal to severe. Additionally, Kumar and Jayaram (2005) evaluated temporal modulation detection abilities at six modulation frequencies, (4, 16, 32, 64, 128 and 200 Hz), in 14 adult ANSD participants and compared the results with 30 normally hearing participants, matched by age and gender. Results were stratified by speech perception abilities and demonstrated that ANSD participants who had speech perception scores of greater than 50% showed greater sensitivity to the temporal modulations when compared to those who had speech perception scores of less than 20%. While the results from Rance et al. (2004) indicate that those individuals with good speech perception scores show good temporal processing at low-frequency rates of modulation (10 Hz), Kumar and Jayaram’s (2005) study showed poor temporal processing at all frequencies for adults with good (>50%) and poor (>20%) speech perception scores using open-set Kannada words. Nonetheless, if averaged, temporal resolution scores for all ANSD participants seemed to be similar at 10 Hz for all three studies discussed above, of an approximate -10 dB detection threshold. In contrast to temporal modulation detection, gap detection thresholds (psychoacoustic measure of temporal resolution) are consistently impaired in individuals with ANSD. While normal-hearing listeners require 2–3 ms at supra-threshold levels (40–50 dB SPL) to detect a brief gap in noise, ANSD individuals require 20–28 ms (Starr et al., 1996; Zeng et al., 1999; Zeng et al., 2005).

In any case, for individuals with ANSD, it seems that it is the temporal processing ability that is paramount to the development of speech and language and, therefore, the success of hearing aid fitting, rather than pure tone thresholds *per se*. While objective measures of temporal processing are beginning to emerge in the literature, these are clearly needed to guide timely decisions about device fitting, particularly in view of the critical period of language development.

3. Cochlear implantation and site-of-lesion

It is clear that early detection of hearing loss minimises the longer-term consequences of auditory deprivation on speech perception, language and socio-emotional development (Geers, 2006; Moog & Geers 2010; Moog, Geers Gustus & Brenner, 2011). For individuals with severe to profound sensorineural hearing loss, cochlear implantation is commonly part of an effective intervention program, providing greater access to speech than conventional hearing aids. Earlier implantation as well as early educational placement and / or intensive habilitation facilitates more rapid and extensive language development as well as improved speech perception and production (Hayes et al., 2009; Nicholas & Geers, 2007; Svirsky et al., 2004; Tomblin, et al., 2005). Animal models of sound deprivation highlight the extent of anatomical changes that can occur within the auditory pathways and cortex with congenital hearing loss (Fallon et al., 2008). However, the effects of early implantation appear to facilitate normal synaptic and cortical development through restored sound input (Kral et al., 2001, 2002; O'Neill et al., 2010; Ryugo et al., 2005). Kral and Eggermont (2007) suggest that the sensitive period for language learning in children with pre-lingual hearing loss fitted with a cochlear implant correlates with the age of significant reduction in synaptic density in normally hearing subjects (4-5 years of age). This is consistent with electrophysiological data from Sharma and colleagues (2002a&b; 2005, 2009) who show that later implanted children (over 7 years of age) show significant and sustained delays in the latency of the P1 peak of the cortical auditory evoked potential (CAEP). On the other hand, delays in the P1 peak of earlier implanted children (under 3.5 years of age) are resolved within 6-8 months after implant surgery. It is assumed, therefore, that the comparatively better functional outcomes from earlier implantation partly result from greater synaptic development and maturity occurring within the critical period (Hammes et al., 2002; Harrison et al., 2005). While early identification and intervention are also important for children with ANSD, identifying *who* will benefit from cochlear implants and deciding *when* to implant is more challenging than for individuals with sensorineural hearing loss.

The term “auditory neuropathy” was initially used to describe this disorder, consistent with the findings from a longitudinal study of 10 individuals, 8 of which later developed concomitant peripheral neuropathies (Starr et al., 1996). In this case, it was assumed that the lesion existed at the auditory nerve resulting from demyelination of peripheral neurons. However, subsequent studies have shown that proportionally large numbers of individuals diagnosed with ANSD do not develop additional neuropathies and good functional outcomes have been reported in many cases after cochlear implantation (Mason et al., 2003; Gibson & Sanli, 2007; Shannon et al., 2001), which suggest that the lesion is pre-neural. Therefore the term has been widely contested because of the potentially negative impact this might hold for clinical decision-making, such as cochlear implantation (that is, this may be considered a deterrent for implantation). While other terms including auditory dys-synchrony (Berlin et al., 2001) were suggested as alternatives, the physiological mechanisms underpinning this disorder are unclear and are likely to be many. Certainly genetic, electrophysiological and imaging data show that multiple sites of lesion can exist (Cacace & Pinheiro, 2011; Manchaiah et al., 2010; Santarelli, 2010; Varga et al., 2003) and this is supported by the variability in objective measurements, such as electrically-evoked ABR (EABR), after cochlear implantation (McMahon et al., 2008; Shallop et al., 2001). To encompass the breadth of different lesions (whether synaptic, neural or brainstem) that could lead to the clinical classification of this disorder and the wide range of functional outcomes, an alternative term “auditory neuropathy spectrum disorder”, or ANSD, was

proposed at the International Conference of Newborn Hearing Screening (Como, 2008), although this term also has little prognostic information about functional outcomes within this population. Broadening the term may also lead to greater inclusion of identifiable lesions of the auditory nerve, such as cochlear nerve deficiency (CND; Buchman et al., 2006), or hereditary conditions of known late-onset auditory neural demyelination, such as Freidreich's Ataxia (Rance et al., 2008) and Charcot-Marie Tooth disease, which will certainly have poorer outcomes with cochlear implantation (Madden et al., 2002; Song et al 2010) than the population of ANSD without known neural lesions.

Various studies have shown that the prevalence of this disorder ranges from 0.23-24% in the at-risk neonatal population (Rance et al., 1999; Berg et al., 2005) to 5.1-15% of children with sensorineural hearing loss (Madden et al., 2002b; McFadden et al., 2002). While many cases of ANSD occur with infectious diseases, perinatal and postnatal insults and genetic disruptions (Madden et al., 2002), some have no co-morbid medical problems or familial hearing loss. Common medical insults assumed to cause ANSD include hyperbilirubinaemia (which may account for up to 48.8% of cases; Berlin et al., 2010) and/or perinatal anoxia, prematurity and low birth-weight (Berlin et al., 2010; Beutner, et al., 2007; Saluja et al., 2010). Each of these can have widespread effects on the auditory system as well as other neurodevelopment consequences, including cerebral palsy and cognitive or neurodevelopmental delay (Johnson & Bhutani, 2011; Schlapbach et al., 2011). Additionally, some infants diagnosed with ANSD within this high-risk category show full or partial recovery of ABR waveforms within 12 months of diagnosis or following medical intervention (such as exchange transfusion), which indicates that some cases of ANSD may be due to neuromaturational delay or reversible transient brainstem encephalopathy (Amin et al., 1991; Krumholz et al., 1985; Granziani et al., 1967). While ANSD can be detected early through newborn hearing screening programs or through targeted screening of the "at-risk" populations in the NICU, no uniform management plan exists because of the variability in hearing thresholds, temporal processing abilities and sites-of-lesion that cannot be measured using behavioural tests at that age. Early intervention and fitting of hearing aids, particularly high-powered aids, or cochlear implants is considered, with caution, to avoid permanently damaging normally functioning outer hair cells and neural structures, that may be immature rather than permanently disordered (Maddon et al., 2002a,b). As many individuals with ANSD show hearing thresholds within a normal to moderate range (Starr et al., 2000; Berlin et al., 2010), it is clear that neural information is being transmitted to the auditory cortex. However, the sound quality of the auditory input is variable amongst this population, with speech discrimination scores disproportionate to the pure tone audiogram (Rance et al., 2002), and often significantly poorer in noisy environments (Starr et al., 1996).

Hyperbilirubinaemia describes the high concentrations of unconjugated bilirubin that can occur in the newborn, which is a neurotoxin that can cause irreversible neurological damage, including auditory, motor and ocular movement impairments (Shapiro & Popelka, 2011). The Gunn rat pup provides a model of the effects of kernicterus in the neonate. Electrophysiological and anatomical studies have shown that severe cases of kernicterus in the Gunn rat lead to disruption of the auditory pathway from the cochlear nucleus to the higher auditory brainstem, including the inferior colliculus (Uziel et al., 1983). While both inner and outer hair cells appear to be spared by high levels of bilirubin, the spiral ganglion cells of auditory neurones can be disrupted (Shapiro, 2005), indicating a neuronal cause of ANSD. Improvements in auditory brainstem responses in infants with hyperbilirubinemia, particularly after exchange transfusions, have been noted by a number of authors (Deliac et

al., 1990; Perlman et al., 1983; Rhee et al., 1999; Roberts et al., 1982). Rhee and colleagues (1999) evaluated TEOAEs and ABR responses in 11 neonates after exchange transfusions for hyperbilirubinemia. All infants showed normal OAE responses but 3 showed absent ABR responses to clicks at stimulus levels of 90dBnHL and, within 12 months of follow-up 1 showed significant improvements in hearing thresholds, estimated using ABR.

Prematurity is identified as another major cause of ANSD. However, it is likely that it is not the prematurity *per se* that underpins the damage to the auditory system but associated conditions of low-birth weight, hypoxia from respiratory failure, hyperbilirubinemia, presence of fetal pathology (infection or retarded intrauterine growth) or perinatal pathology, or ototoxicity from antibiotics given for hyaline membrane disease (Ferber-Viart et al., 1996). Extremely low birth-weight infants are at risk of developing ANSD (Xoinis et al., 2007). A retrospective study by Xoinis and colleagues (2007) showed that the prevalence of ANSD was 5.6/1000 in the NICU (n=24) compared with 16.7/1000 infants with sensorineural hearing loss (n=71). They identified that infants with ANSD were born more prematurely (mean gestational age 28.3 ± 4.8 weeks compared with 32.9 ± 5.2 weeks of SNHL infants) and showed significantly lower birth weights (mean 1.318 ± 0.89 kg compared with 1.968 ± 1.00 kg of those with SNHL). Psarommatis and colleagues (2006) retrospectively reviewed medical records of 1150 NICU neonates and identified 25 infants with ANSD. Of these, 20 were re-examined at approximately 5 months of age and 12 showed full recovery of the ABR with 1 infant showing partial recovery (with click ABR thresholds measured to 50dBnHL). A significant difference in mean birth-weight and gestational age (GA) was found between infants who recovered (BW= 1.89 ± 0.90 kg and GA= 32.9 ± 1.1 weeks) and those who showed no recovery (BW= 3.0 ± 0.66 kg and GA= 36.4 ± 1.25 weeks), suggesting that those born more prematurely and with lower birth weight may be more at risk of delayed neuromaturational development rather than ANSD. Amatuzzi and colleagues (2001) evaluated the temporal bones of 15 non-surviving NICU infants, 12 who failed the ABR screen bilaterally and 2 who passed bilaterally. Of those who failed, 3 infants (all born prematurely) showed bilateral selective inner hair cell loss whereas both infants who passed the ABR screen showed no cochlear histopathologic abnormalities. This may suggest that pathologies related to prematurity are more likely to target inner hair cells than neural elements, making these individuals good candidates for cochlear implantation.

Two large-scale studies of individuals with ANSD both conducted in 2010 by Teagle et al. (n=140) and Berlin et al. (n=260) have provided the most comprehensive information to date about the etiologies of ANSD and outcomes of individuals fitted with hearing aids and / or cochlear implants. Berlin and colleagues reported that only 11 of 94 individuals who used hearing aids showed good speech and language development. 60% of the 258 subjects reported had pure tone thresholds characterised as being between normal to moderate-severe (within a very aidable range) and the remaining 40% had thresholds described as either moderate-profound, severe, severe-profound or profound, presumably fitting within the more typical range of CI candidacy. On the other hand, 85% of those fitted with a CI showed successful outcomes (evaluated by parent and teacher report) and 8% were too young to conclude this. Teagle and colleagues reported that of the 52 individuals with ANSD who were implanted, 50% demonstrated open-set speech perception abilities, although 30% were not tested because of their young actual or developmental age and individuals identified with CND showed 0% open-set speech perception scores. Therefore it is clear that ANSD is heterogeneous in cochlear implantation outcomes, possibly partly related to the high incidence of co-morbidity and multiple disabilities as well as differences in the site-of-lesion.

4. Role of evoked potentials in decision-making

Given the variability in the magnitude of temporal processing disruption and in the sites-of-lesion in ANSD, which is important for CI outcomes, the focus of our research has been in the development and/or evaluation of objective measures to better quantify temporal processing ability (Al-meqbel & McMahon, 2011) and identify the site-of-lesion (McMahon et al., 2008) in ANSD. Cortical auditory evoked potentials (CAEPs) have been shown to be important in the measurement of temporal processing ability because they are less reliant on rapid neural timing than the auditory brainstem responses. Rance and colleagues (2002) were the first to show that the presence of CAEPs in ANSD with a mild to moderate hearing loss correlated well with good aided speech perception outcomes. In this study, 8 of 15 children showed good aided functional outcomes, identified as >30% correctly identified phoneme scores using Phonetically-Balanced Kindergarten Words, and each of these showed present CAEP waveforms to either a pure tone (440Hz for 200ms) and/or a synthesised speech token (/daed/) presented at a comfortable level using headphones or insert earphones. The remaining 7 children who showed poor aided speech perception results also showed absent CAEP waveforms to either the pure-tone or speech stimuli. This important finding highlighted the role of evoked potentials in guiding management decisions in this population. Michalewski and colleagues (2005) used CAEPs measured with an active and passive gap-in-noise paradigm to determine temporal processing acuity in 14 adults with ANSD. They obtained CAEP responses from 11 subjects, with active responses measured in all 11 subjects but passive responses in only 7 subjects. No response was measured for 3 individuals who showed profound hearing loss. In 7 subjects who showed present passive responses to gap detection, good correlations were found between psychoacoustic and objective CAEP measures of gap detection. In 3 of 4 subjects with only active responses, a good correlation was also found. This unexpected appearance of the CAEP in response to attention may shed some light into the role of attention in the synchronisation of responses in some individuals with ANSD.

Subsequently, our retrospective study (McMahon et al., 2008) showed that the frequency-specific electrocochleographic waveforms, measured from the round-window of 14 implanted children with ANSD with severe-profound hearing loss, correlated well with the EABR measured immediately after implantation. This supports the use of frequency-specific electrocochleography (ECochG) in enabling better delineation of site-of-lesion. Electrocochleography is a useful tool in the identification of cochlear lesions because it enables more accurate recording of the summed extracellular currents from cochlear hair cells (the cochlear microphonic, CM; Figure 2A in the guinea-pig and Figure 2E in the human, and summing potential, SP; Figure 2B in the guinea-pig and Figure 2G in the human), the excitatory post-synaptic currents (known as the dendritic potential, DP) arising from the primary afferent dendrites, the terminal endings of the primary afferent neurones that synapse with the inner hair cells (Figure 2C), and the compound action potential (CAP) from the primary afferent neurones which is described by three dominant peaks, labelled N_1 , P_1 and N_2 (Figure 2D; see Sellick et al., 2003 for a review). Because there is a cascade of events that leads to the generation of an action potential (see Fuchs, 2005 for a review), the presence or absence of these potentials can indicate where a lesion is located. That is, depolarisation of inner hair cells leads to the opening of L-type calcium channels in the basolateral wall of these cells and, ultimately, the mobilisation and release of neurotransmitter from the base of these cells. This process involving the gene otoferlin that

is implicated in some types of ANSD (Roux et al., 2006). Neurotransmitter diffuses across the synaptic cleft and binds to the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) channels on the dendrite which allows an influx of positive ions, generating an excitatory post-synaptic potential (EPSP) inside

Frequency-specific electrocochleography

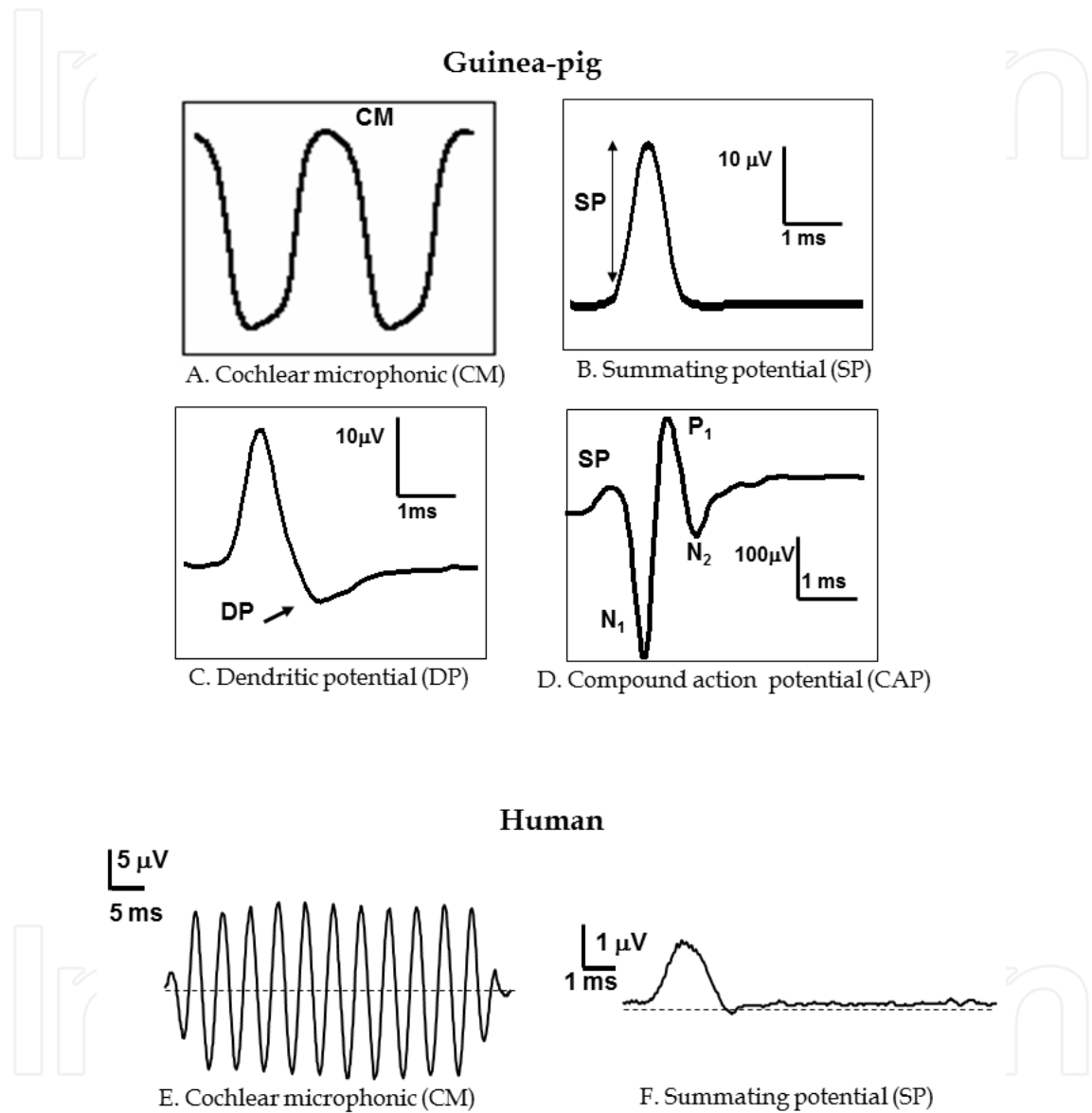


Fig. 2. Using a round-window electrode, local hair cell, dendritic and neural potentials can be measured using frequency-specific electrocochleography in the anaesthetised guinea pig (A-D) or human (E-F). A single polarity low-frequency tone-burst clearly shows the cochlear microphonic (CM) waveform (A&E). A high-frequency alternating polarity tone-burst is used to elicit the summating potential (SP; B&F), dendritic potential (DP; C) and compound action potential (CAP; D). The presence of the CAP obscures the DP, which is only observed in pathological cases such as ANSD in human. Note that the differences observed between the guinea-pig and human CM and SP are largely because of the different stimulus-frequencies and time-scales used to elicit and display the response.

the dendrite. If this voltage is large enough, it will trigger an action potential, which is often considered an all-or-none event. Selective disruption of these potentials using pharmacological block in an anaesthetised guinea-pig model demonstrates this point (Figure 2A-D). Intracochlear perfusion of the excitotoxic drug kainite which blocks the ligand-gated AMPA channels, abolishes both the CAP and the DP, whereas the SP amplitude is unchanged (Figure 2B). On the other hand, intracochlear perfusion of tetrodotoxin (TTX), a spider venom which blocks the voltage-gated Na⁺ channels, abolishes the CAP, but the SP remains and the DP can be observed in the average waveform (Figure 2C which previously was masked by the much larger CAP observed in the normal hearing guinea-pig (Figure 2D).

There are two main limitations to this technique. Firstly, the currents measured from the recording electrode are local currents (i.e. those generated within the proximity of the recording electrode) and, in our study, were measured from the cochlear round window. Therefore, to a first approximation, we assumed that any disruption identified at the round window (which has a best frequency of about 8kHz in humans) was the same throughout the cochlea. Secondly, a disruption at a particular site along the auditory pathway might be one of multiple disruptions that could occur. As previously discussed, many of the underlying causes of ANSD cause widespread disruption that may impact cochlear and brainstem structures and are not highly localised to a single site. In any case, in the study conducted by McMahon et al. (2008), we identified two types of ECoChG waveforms in 14 individuals with ANSD, each who showed normal Magnetic Resonance Imaging (MRI) recordings (with no identifiable neural abnormalities): (i) a delayed latency SP that showed little or no compound action potential, suggestive of a pre-synaptic or synaptic lesion, and (ii) a normal latency SP with a clear DP waveform that was more visible at lower sound levels (where it was assumed that the much larger SP distorted the DP waveform at higher sound levels), suggestive of a neural or post-synaptic lesion (see Figure 3). In 6 of 7 ears implanted with the pre-synaptic or synaptic ECoChG waveform, normal morphology EABR waveforms were measured from electrical stimulation of the majority of the 22 electrodes of the cochlear implant. Additionally, in 6 of 6 ears implanted with post-synaptic ECoChG waveforms, the EABR waveforms were grossly abnormal or absent for all 22 electrodes (see Figure 3).

The physiological mechanisms underlying spike failure in cases of ANSD and leading to a pre-synaptic or synaptic mechanism of disruption could be numerous. Assuming a normal distribution of EPSP amplitudes results from the quantal release of neurotransmitter (Fuchs, 2005), then a reduction in the amplitude (or number) of EPSPs would reduce the probability of spike initiation (see Figure 4A). This might occur due to disruption of transmitter-release (possibly mediated by otoferlin deficiency, Roux et al., 2006) or a scattered loss of IHCs (Amatuzzi et al., 2001). Alternatively, an increase in the trigger-level voltage could reduce the probability of EPSPs reaching this critical voltage (see Figure 4B), or, depolarisation of the dendrite itself (possibly from lateral efferent modulation; Brown, 1987) would also reduce the chance of EPSPs generating spikes (see Figure 4C).

Santarelli and colleagues (2008) also measured ECoChG waveforms in 8 children and adults with ANSD, using a forward masking paradigm of rapidly presented click stimuli to

differentiate between cochlear and neural sites-of-lesion. Given that neural potentials decay significantly with faster rates of stimulation due to neural refractoriness (Miller et al., 2001), the amount of adaption in the measured response enables differential diagnosis of the site-of-lesion. In this study, 3 patterns were identified: (i) presence of the SP without a CAP, consistent with a pre-synaptic lesion; (ii) presence of the SP and CAP, consistent with a post-synaptic lesion and (iii) significantly prolonged latency potentials (up to 12 ms), which the authors suggest may result from slowed neural conduction and/or reduced action potential generation. Since implantation in cases of cochlear nerve deficiency is known to have poorer outcomes (Buchman et al., 2006), then ECochG provides a useful tool in the differential diagnosis of ANSD.

Types of ECochG waveforms in ANSD

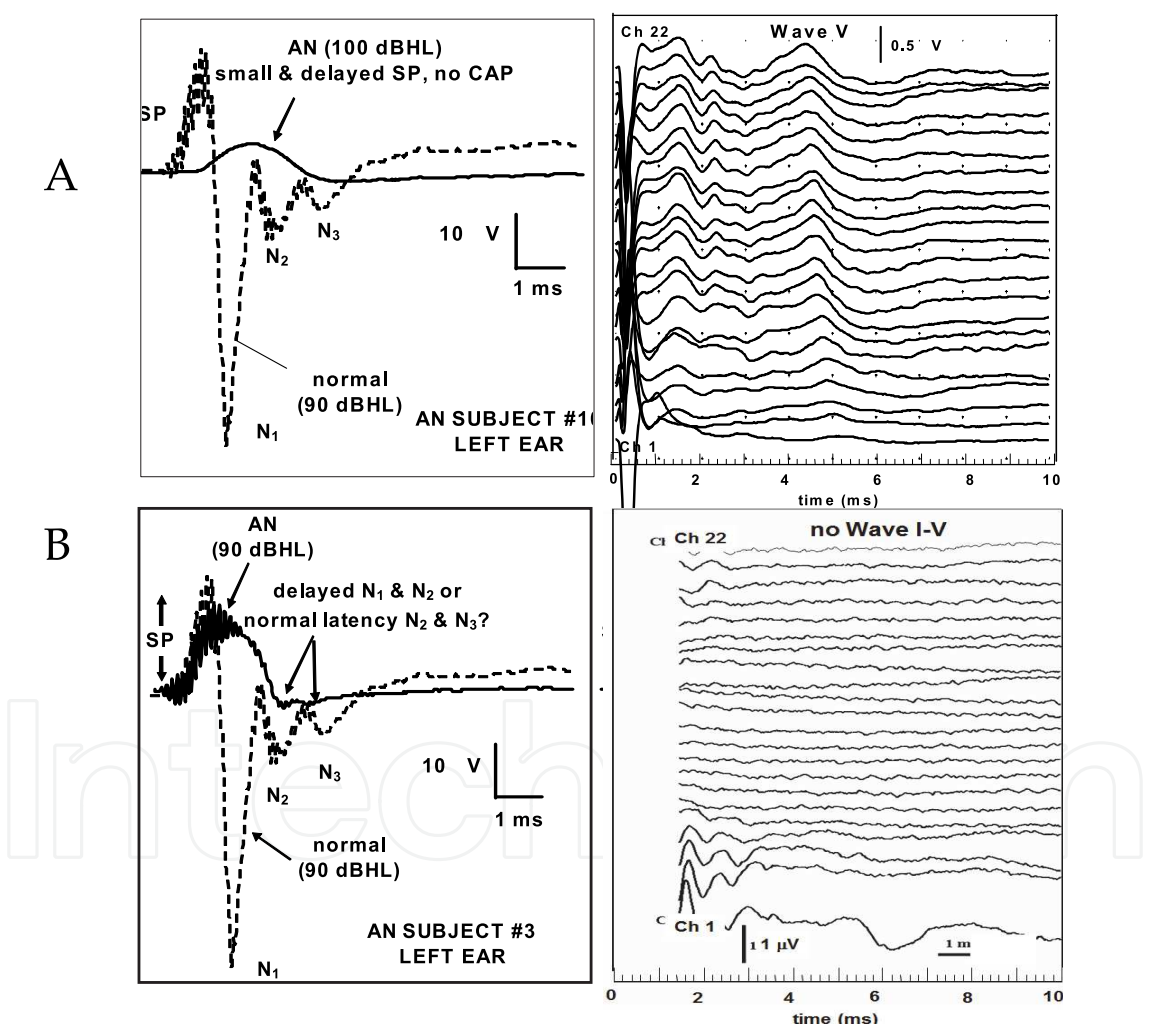


Fig. 3. Electrocochleographic recordings using an 8kHz alternating time-burst show two types of waveforms exist in the 14 ANSD individuals in this study: (A) a delayed SP with either a small or absent CAP present, consistent with normal implanted EABR waveforms suggesting a pre-synaptic lesion and (B) a normal latency SP with a DP present at lower sound levels, consistent with absent or grossly abnormal implanted EABR responses, consistent with a post-synaptic lesion.

Mechanisms of spike failure

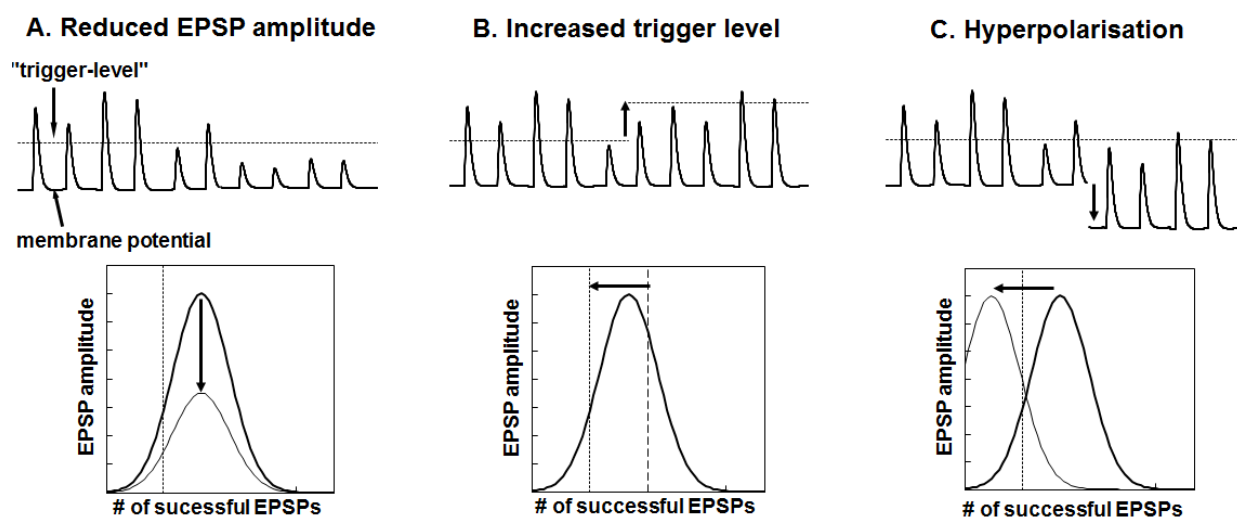


Fig. 4. Physiological mechanisms of spike failure from pre-synaptic or synaptic disruptions might include: (A) a reduction in the amplitude of the EPSPs; (B) an increase in the voltage need to reach trigger-level; or (C) hyperpolarisation of the membrane potential of the primary afferent dendrites (possibly from lateral efferent modulation).

Our next study aimed to identify whether EABR provided a good measure of functional performance in implanted individuals with ANSD and severe-profound hearing loss. In this study (Bate & McMahon, in preparation), we compared speech perception outcomes using the phoneme scores of age-appropriate word lists (either CNC words or Manchester Junior Words) presented at 65dB SPL in the free-field with a speaker located at 0 degrees azimuth with electrically-evoked CAEP (ECAEP) waveforms measured at least 1 year after implantation and EABR waveforms measured immediately after implantation. Ten individuals with ANSD diagnosed by present CM but absent ABR waveforms and with normal MRI participated in this study and each showed good speech perception (scoring >50% phonemes correct) and normal motor and cognitive development. Interestingly, only 40% of these individuals showed good EABR waveform morphology but 80% showed good ECAEP waveforms when elicited by direct electrical stimulation at a comfortably loud level from at least 2 of 3 spatially separated electrodes (representing an apical, mid- and basal position of the electrode array). This suggests that even in cases where cochlear implantation may not by-pass the lesion underpinning ANSD, it may provide the necessary amplification needed for the individual to access the speech signal. We did not perform further complex speech, language or reading testing to determine age equivalence, however, we suspect that differences between individuals with present EABR and absent EABR may exist if we evaluated the broader population base and if our testing was more extensive. Nonetheless, these results do suggest that cochlear implantation can benefit some individuals with a post-synaptic site-of-lesion. It is important to highlight that both studies we have conducted included only those individuals with normal MRI scans, indicating no structural abnormality of the auditory nerve (although it is acknowledged that even high resolution MRI cannot identify all structural abnormalities). Previous studies have shown that individuals with a known lesion on the auditory nerve (which would also be defined as a post-synaptic or neural lesion) including neural demyelination (Miyamoto et al., 1999) and auditory nerve agenesis or hypoplasia (Maxwell et al., 1999; Gray et al., 1998; Buchman et al.

2006) have significantly poorer outcomes following cochlear implantation. While some authors strongly pursue the differentiation of terminology for a true neuropathy of the auditory nerve and an endocochlear disruption that produces the same clinical results (Loundon et al., 2005), the more inclusive term of ANSD seems to be generally used within the literature. We agree that such a differentiation is important to better understand the mechanisms that underpin this disorder and to develop targeted intervention strategies.

Figure 5 shows three case studies that highlight the variability in evoked potentials and functional outcomes that occur in cases of ANSD, either with normal or abnormal MRI. Case 1 illustrates the electrophysiological test battery as being a good predictor of a good outcome after cochlear implantation in the first ear implanted (4.5 years of age), but not in the second (10 years of age). The electrophysiological test result pre-implantation measured by ECoChG and trans-tympanic EABR indicate a pre-synaptic site of lesion (as described by McMahon et al., 2008). Specifically, as shown in Figure 5A, the ECoChG results of a delayed latency SP and no evidence of a DP in both ears are consistent with a pre-synaptic lesion (McMahon et al., 2008). The preoperative test results, coupled with the evidence of normal anatomy as shown on preoperative imaging allow prediction of a good outcome. Electrophysiology post-cochlear implant insertion was measured using an intraoperative EABR which showed good responses from all channels in the left and right (data not shown) ears. No other disabilities are noted with this individual and as predicted an open set speech perception ability as measured by was achieved at 6 months post cochlear implantation. These results are consistent with those seen in other studies such as Gibson and Sanli (2007) who showed 32/39 children with good EABR results and good functional outcomes. It is possible that the poorer functional outcomes measured in the subsequently implanted ear arose from the prolonged delay in implanting the second ear (Ramsden et al., 2005; Gordon et al., 2008) although conflicting evidence exists about the impact of duration of sequential implantation on functional outcomes (Zeitler et al., 2008). In any case, in contrast to Case 1, Case 2 provides an example of a subset of individuals identified as having ANSD with additional confounding factors, including cerebral palsy, developmental delay, Autism Spectrum Disorder. While the electrophysiological test results may be similar in both cases, it is presumed that the addition of significant other factors, including cognitive or developmental impairment, may be the cause of the poorer functional outcomes. Poor morphology or the absence of wave V on an EABR post cochlear implantation has been shown to be associated with poor speech perception outcomes (Rance, 1999; Gibson & Sanli, 2007; Song et al., 2010). Case 3, shows ECoChG results with a present SP and SP and very poor morphology EABR, consistent with a post-synaptic site-of-lesion (McMahon et al., 2008). Despite this, functional assessment shows a good Manchester Words Junior phoneme score 4 years after implantation. Given the results of these studies, we present an evoked-potential protocol that might be utilised to better inform device and management decisions in individuals with ANSD (see Figure 6). It is not intended that this protocol be used alone. Intensive monitoring of auditory behaviours and receptive and expressive language development is important in providing complementary information to determine the most appropriate way to manage a child with ANSD. On the other hand, this protocol intends to support the decision-making process by providing information about the individual's temporal processing ability, needed to develop speech and language, and the location of the lesion, which might influence cochlear implantation outcomes. Roush (2008) highlights the types of speech perception and behavioural questionnaires that are useful in obtaining behaviourally relevant information in this population.

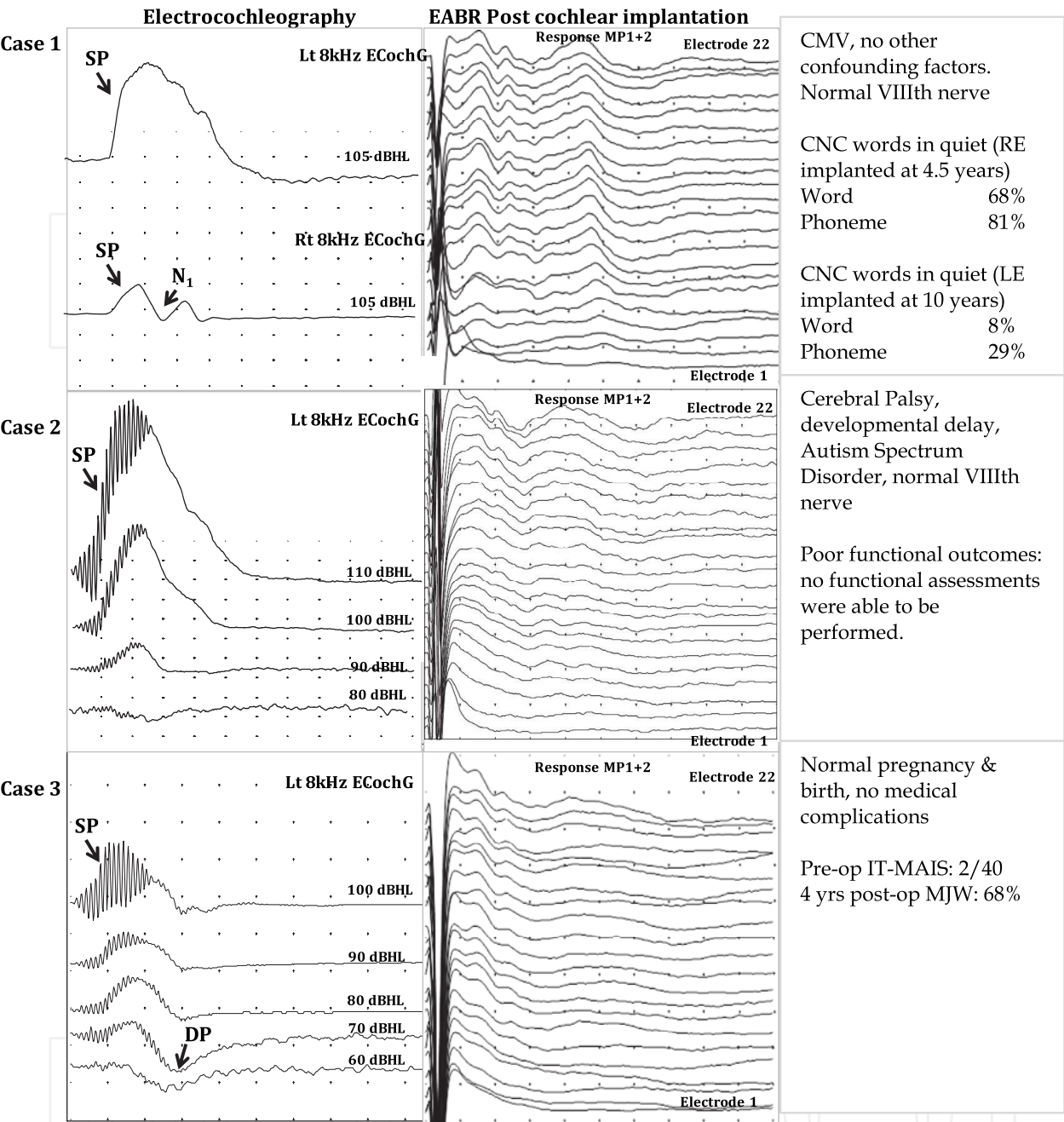


Fig. 5. Electrocochleography and EABR testing provides information useful in understanding the likely site of lesion in ANSD (McMahon et al., 2008; Gibson & Sanli, 2007). These specific cases have been used to demonstrate the variability of outcomes in this population. Case 1: a child with normal neonatal medical history who was bilaterally sequentially implanted, and electrocochleography and EABR results on both sides (EABR RE not shown) are consistent with a pre-synaptic lesion. The right ear was fitted at 4.5 years and the left at 10 years of age. Good functional outcomes were measured using CNC words in quiet with the right ear alone but poor functional outcomes were measured in the left. Case 2: a child with a significant medical history but with normal VIIIth nerve. ECoChG waveforms show a normal latency SP but no evidence of a DP, suggestive of a pre-synaptic lesion. EABR waveforms are good for basal electrodes but poorer for apical electrodes. Poor functional outcomes were reported and no functional assessments were

able to be performed. Case 3: a child born with no medical history of complications. ECoG waveforms showed the presence of the SP and DP, suggestive of a post-synaptic lesion. EABR results showed poor morphology waveforms for all channels. Despite this, good functional outcomes were measured using Manchester Junior Words.

1. To determine if sufficient hearing or timing cues exist for hearing aids to be effective measure CAEP to pure tones, speech stimuli or gaps in noise.

If CAEPs are present, then sufficient timing cues and hearing thresholds exist

If CAEPs are absent - poor timing cues and hearing thresholds

2. To determine whether the lesion is located at before or at the level of the auditory nerve measure ECoG response to an 8kHz alternating tone-burst.

Currently we are unsure of the predictive value of this so the presence of a post-synaptic - like lesion should not alone prevent implantation from taking place.

3. To determine the likely speech outcomes of implantation for children without additional disabilities, use EABR to confirm the site-of-lesion and ECAEP to determine potential functional outcomes.

The presence of the ECAEP is a better indicator of speech perception outcomes than the EABR.

Fig. 6. A possible protocol for the use of evoked potentials in directing management of ANSD. It is important to note that evoked potentials should not be used in isolation of behavioural testing and observations.

In conclusion, while the variability of ANSD presents a challenge to audiological management, a structured approach using parental questionnaires to evaluate auditory behaviours as well as objective testing may assist in guiding effective decision-making in this population in infancy.

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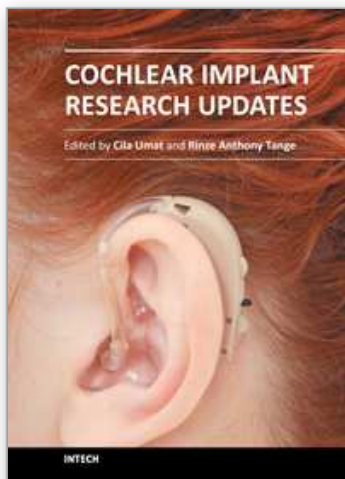
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For many years or decades, cochlear implants have been an exciting research area covering multiple disciplines which include surgery, engineering, audiology, speech language pathology, education and psychology, among others. Through these research studies, we have started to learn or have better understanding on various aspects of cochlear implant surgery and what follows after the surgery, the implant technology and other related aspects of cochlear implantation. Some are much better than the others but nevertheless, many are yet to be learnt. This book is intended to fill up some gaps in cochlear implant research studies. The compilation of the studies cover a fairly wide range of topics including surgical issues, some basic auditory research, and work to improve the speech or sound processing strategies, some ethical issues in language development and cochlear implantation in cases with auditory neuropathy spectrum disorder. The book is meant for postgraduate students, researchers and clinicians in the field to get some updates in their respective areas.

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