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Assessment of responses to cochlear implant stimulation at different levels of the auditory pathway

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Abstract

This paper reviews characteristics of both the electrically evoked compound action potential (ECAP) and analogous measures of cortically evoked responses (CAEP) to electrical stimulation in cochlear implant users. Specific comparisons are made between the two levels of processing for measures of threshold, growth of responses with increasing stimulus level, changes in stimulation electrode and, finally, in temporal response properties. The results are interpreted in a context that ECAPs primarily reflect the characteristics of the electrode-neural interface for an individual ear. CAEPs clearly are dependent on those peripheral responses but also reflect differences in central processing among individual implant users. The potential applicability of combined measures in clinical situations is discussed.

Keywords

Cochlear Implants; compound action potential; cortical evoked response; auditory change complex

1. INTRODUCTION

A number of factors can affect the ability of a cochlear implant (CI) user to identify and discriminate acoustic signals in the environment: the way the speech processor is programmed, the number of electrodes that are available, the extent to which temporal fine structure in the acoustic stimulus is transmitted. All of these factors can impact the way an acoustic signal is perceived. However, even when these device-related factors are held constant, cross-subject variability on almost all measures of post-operative performance with a CI is large (Tyler et al., 2000). Another factor that may contribute to variance in performance with a CI is the interface between the intracochlear electrodes and the neurons of the auditory nerve. Electrode insertion depth, the extent of fibrous tissue growth and the

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effective distance between the electrode contact and the stimutable neural elements will all have an impact on the way the auditory nerve responds to electrical stimuli both at threshold and suprathreshold levels and could potentially limit the amount of information transferred to the auditory nervous system (Shepherd et al., 1993; Frijns et al., 2001; Miller et al., 1993). For example, the extent to which electrical current spreads across the cochlea will influence the size of the neural population that is activated and how much overlap there is in neural populations stimulated by adjacent intracochlear electrodes (Miller et al., 1993; Shepherd et al., 1993; Liang et al. 1999; Kral et al., 1998). Results of animal studies show that the status of the auditory nerve can influence basic response properties like neural refractoriness and adaptation and as a result, have an impact on how sequences of electrical pulses presented by the CI are coded by the auditory nerve (Miller et al, 2001; Matsuoka et al, 2000). Many of these factors are also likely to be affected by neural degeneration typical in ears with sensorineural hearing loss. Cross-subject variance in the electrode neural interface and the status of the peripheral auditory nerve itself could affect sensitivity to electrical stimulation, spatial selectivity and how well the temporal fine structure in a signal is coded at the level of the auditory nerve.

Several studies have suggested that variations in performance among CI users may also be due, in part, to differences in central nervous system function (Firszt et al., 2002b; Kelly et al., 2005; Kraus et al., 1993; Micco et al., 1995). Cochlear damage can lead to degeneration of spiral ganglion cells (Leake & Hradek, 1988) and subsequently to significant changes in the central auditory pathways (Webster & Webster, 1977; Kitzes & Semple, 1985; Kral et al., 2005). Consequently, even if the response of the auditory nerve to electrical stimulation was “normal”, central processing in a long-term deafened ear may be different than in someone with a short duration of deafness or normal hearing. Several studies have shown that congenital hearing loss alters the way the central auditory system develops and that late implantation can have a significant impact on outcome with a CI (Ponton & Eggermont, 2001; Sharma et al., 2002, 2005; Kral & Sharma, 2011). As a result, the processing of a signal transmitted to the central auditory nervous system by the cochlear implant may vary significantly across individuals and the ability of those individual CI users to adapt to the novel neural patterns may also vary. Finally, psychophysical studies attempt to characterize the relationship between an acoustic signal and perception and typically rely on either detection, discrimination and/or identification paradigms.

Our early work focused on development of methods to understand how auditory signals are processed in the auditory periphery. Most of that work relied on the use of neural telemetry systems that allow us to record the electrically evoked compound action potential (ECAP) from an intracochlear electrode. ECAPs proved to be an important way we could characterize how acoustic signals were processed at the level of the auditory nerve (Abbas, Brown & Etler, 2006). Our recent work has focused on recording CAEPs. These evoked responses can be measured using surface electrodes placed on the scalp. The paradigm we typically use involves presentation of a sequence of two long duration sounds. A response is generated at the onset of the stimulus and is generally interpreted as evidence that a stimulus has been *detected*. A similar evoked potential is recorded if the listener perceives a change in the ongoing stimulus. The cortical change responses can provide a non-behavioral

measure of how well two stimuli are able to be *discriminated*. Comparison of ECAPs and CAEPs can provide some insight into the relative contributions of neural processing both at the periphery and within the central auditory pathways.

Understanding the nature and the locus of the limitations on signal processing in an individual implant user could be potentially important in developing appropriate treatment strategies. For instance, adjusting stimulation parameters at the periphery could be effective in reducing current spread and potentially reduce effects of channel interaction. Alternatively, if the limitation in electrode discrimination appears to be more central in origin, some type of training program might be a more effective intervention strategy. These issues might be particularly relevant in children where differences in the neural degeneration may be large and where, depending upon age of implantation, the processing within the central auditory pathway may be quite variable. Further, in children who are too young to perform complex listening tasks, the use of physiological measures may be particularly informative. Our goal in this paper is to summarize the results of several studies conducted in our laboratory that have addressed the similarities and differences between peripheral and central responses to cochlear implant stimulation.

2. SUMMARY OF EXPERIMENTAL METHODS

The ECAP is a measure of the response of the auditory nerve to electrical stimulation. It is typically recorded from an intra-cochlear electrode. The proximity of stimulating and recording electrodes coupled with the short latency of the ECAP makes contamination of the neural response by stimulus artifact a problem. We originally made ECAP measures in Ineraid implant users by accessing the intracochlear electrodes directly via the percutaneous plug (Brown et al., 1990). A subtraction technique was developed that takes advantage of the refractory properties of neurons to isolate and minimize the stimulus artifact. Contemporary cochlear implants do not use percutaneous connection between the speech processor and the implanted electronics. ECAPs are measured using a reverse telemetry system and an artifact subtraction technique similar to the one we originally described (Abbas et al., 1999; Frijns et al., 2002; Jeon et al., 2010; Bahmer et al., 2010). Figure 1 shows a series of such ECAPs recorded at different stimulus levels. The responses are relatively short latency, typically less than 0.5 ms. They are typically measured using a single biphasic current pulse delivered through a single electrode bypassing the speech processor of the CI. The ECAP is characterized by a negative peak (N1) followed by a positive peak (P2). The amplitude of that peak (N1-P2) grows as current level is increased. This response is thought to be a weighted sum of neural activity from the auditory nerve recorded in response to a single stimulus pulse.

ECAPs can be used to evaluate the characteristics of the peripheral electrode-neural interface. For example, they are affected by both the choice of stimulating and recording electrode and vary considerably both across individuals and across stimulating electrodes within individuals (Brown et al., 2000; Dillier et al., 2002). Shepherd et al. (1993) showed that ECAPs are sensitive to electrode placement and nerve survival in a particular location in the cochlea. The primary advantage that ECAP have over other evoked potential measures is that they can be recorded quickly from CI users of all ages and doing so does not require

application of surface recording electrodes. The measurements themselves are not dependent on attention, are not affected by muscle artifact nor are they adversely affected by sleep or sedation. All of these factors led to the use of ECAP measures in clinical practice. The primary clinical application for these measures is as a guide to programming the speech processor (Brown et al., 1995; Hughes et al., 2000). They have not proven to be useful predictors of word recognition or overall performance levels. The lack of predictive value is most likely a reflection of the fact that the ECAP represents neural responses from the auditory periphery and does not reflect contributions to neural processing at more central levels within the auditory system.

Cortical auditory evoked potentials (CAEP), recorded from surface electrodes on the scalp, can include a wide variety of different responses but here we focus on what is commonly referred to as the P1-N1-P2 response with latencies in the 50-200 ms range (Näätänen, & Picton, 1987; Hyde, 1997). These potentials are thought to reflect neural processing at cortical or pre-cortical levels and have been successfully recorded in CI users (e.g. Beynon et al., 2002; Firszt et al., 2002a,b; Kelly et al., 2005). When evoked using an electrical stimulus, the P1-N1-P2 response has a similar morphology to those recorded using acoustic stimulation. They can be recorded in passive listening paradigm but are adversely affected by sleep. Recordings reported here are made using electrodes placed on the vertex (Cz), high forehead (FPz), nape of the neck (Fz) and mastoid contralateral to the cochlear implant (Mc). An optically isolated differential amplifier is used to record the cortical responses, in most cases vertex to contralateral mastoid provides the most reliable responses. We have found that using the opposite mastoid as a reference and band-pass filtering between 1 and 30 Hz reduces stimulus artifact due to the high rate pulse train.

Figure 2 shows a series of CAEPs recorded from a CI user. In this case the speech processor of the cochlear implant was bypassed and the stimulus used to evoke the response was a train of biphasic pulses presented on a single electrode at different current levels. This response, unlike the ECAP, can be recorded using a variety of different stimuli either by bypassing the CI processor, as in Figure 2, or by routing the stimulus through the speech processor of the CI to mimic normal patterns of stimulation. In adults, the most robust features of this response are the N1 and P2 peaks that are recorded at approximately 100 and 200 ms respectively. CAEPs can be used to characterize the neural response to a wide range of ecologically valid stimuli and reflect the impact that the speech processor of the CI has on that response. It is possible to use the same acoustic stimulus to compare neural processing in NH listeners, HA and CI users. This is not possible with the ECAP. It also clearly reflects neural processing at cortical or pre-cortical levels within the auditory system while the ECAP reflects neural processing at a very peripheral level.

A disadvantage of CAEPs is that they require relatively long data collection time compared to ECAP. The response amplitudes also tend to be relatively small compared to ECAPs so more averaging is needed to measure a reliable response. Finally, the response is not fully mature until the listener is in his/her late teens or early twenties and is more affected by subject specific factors like attention and sleep state (Ponton et al., 1999; Ponton & Eggermont, 2001; Sharma et al., 2002, 2005). This, of course, could be an advantage in that the CAEP could potentially be used to monitor progress of an individual during

rehabilitation but also introduces challenges for those considering use of this response with pediatric populations.

3. RESULTS

3.1 Threshold Levels

It is possible to use either ECAP or CAEPs to measure detection thresholds. ECAP measures have the advantage of being easy and relatively fast to record in pediatric populations, however, they are very peripheral measures of neural response and the stimulus used to evoke the ECAP is typically a single biphasic current pulse presented to a single electrode. CAEPs can be evoked using more spectrally complex and longer duration stimuli such as those used for programming. Because they are measures of neural processing at higher levels within the auditory system, they also reflect the impact of temporal integration on perception and, as a result, may be more accurate measures of threshold. Studies with acoustic stimulation in hearing-impaired individuals have shown, for example, that cortical responses obtained using relatively long duration tone bursts more accurately predict audiometric thresholds than ABR or ECoG thresholds measured using short tone bursts (Stapells, 2009, Lightfoot and Kennedy, 2006; Hyde, 1997; Gorga et al., 1988; Spoor & Eggermont, 1976).

Several different research groups have described methods for using ECAP thresholds to predict MAP T-levels (Brown et al, 2000; Hughes et al. 2000; Franck & Norton, 2001 Smoorenburg et al., 2002). Typically ECAP thresholds measured using single pulse stimuli presented at rates between 30 and 80 pps are higher than perceptual thresholds used to program the speech processor measured using 300-500 ms bursts of biphasic current pulses presented at rates between 250 and 5000 pps depending on the CI and speech processing strategy selected. It seems likely that these differences are due, at least in part, to cross-subject differences in temporal integration (Brown et al., 1995). CAEPs should reflect the influence of temporal integration and can be measured using long duration pulse trains rather than single current pulses. As a result, it seems likely that CAEP based threshold estimates might be more accurate than those based on ECAP measures.

Figure 3A shows a comparison of CAEP thresholds and behavioral thresholds recorded from 13 CI users. Both the electrophysiologic and behavioral threshold estimates were obtained using the same, long duration, high rate stimulus pulse train. The correlation between the two metrics is strong. Figure 3B shows the relationship between ECAP and CAEP thresholds for a group of 14 individuals. The same intracochlear electrode was used to evoke both the peripheral and central measures. ECAP growth functions were recorded in response to a single biphasic current pulse presented at a slow rate. The CAEP growth functions were recorded using a 500-ms pulse train. Threshold was defined as the lowest level at which the response could be detected visually. While the two measures are clearly correlated, ECAP thresholds tend to be elevated relative to CAEP thresholds and the correlation between CAEP thresholds and ECAP thresholds is not as strong as the correlation between CAEP thresholds and behavioral thresholds. We have hypothesized that these differences are a reflection of the fact that the CAEP thresholds are affected by the same central integration process that affects behavioral thresholds. Since ECAP measures are peripheral and do not

show decreases in threshold with multiple pulses, they show a poorer correlation with behavioral thresholds. Note that CAEP thresholds are lower than ECAP thresholds. That is interesting particularly given the fact that ECAPs are recorded from an intracochlear electrode and tend to be much larger than CAEP responses (examples in Figs. 1 and 2). Thus even though the signal to noise ratio in ECAP recordings is advantageous, detection thresholds are still elevated, presumably due to differences in central processing. We do not interpret these results to mean that at lower levels there is no response at the periphery; clearly there must be a response peripherally to elicit a behavioral response. Rather the sensitivity at the periphery is less because of the lack of temporal integration. Finally, we note that there is significant cross-subject variability in the difference between ECAP and CAEP thresholds, suggesting that there are differences among individuals in the effects of temporal integration.

3.2 Growth of response with level

We routinely measure ECAP and CAEP growth functions. There is a great deal of variability across subjects and across electrodes for a given subject in terms of the maximum response amplitude measured as well as the slope of the amplitude growth function (Abbas et al., 1999; Kim et al., 2009). ECAP amplitude growth functions are not always linear; they often are characterized by a fairly shallow slope near threshold but steeper slope at higher current levels (Abbas et al., 1999; Caferelli-Dees et al., 2005). While slope of the ECAP growth functions in human can be variable, it is very rare that we see evidence of saturation of the response amplitudes at high stimulus levels. In contrast, saturation of the ECAP growth function is commonly observed when recordings are made from anesthetized animals (Brown and Abbas, 1990; Miller et al., 1998). It is generally assumed that the reason we do not see evidence of saturation in growth at high current levels in humans is because we keep the stimulation levels below their maximum comfort level. That is not the case for anesthetized animal preparations.

CAEP growth functions recorded from CI users are not as widely reported as ECAP growth functions. This may be because recording CAEP growth functions can be very time consuming. Figure 4 illustrates examples of ECAP and CAEP growth functions recorded from 10 CI users. ECAP growth functions (open symbols) generally have higher thresholds and larger response amplitudes. ECAP amplitude is reflected on the vertical axis on the right side of each graph. CAEP growth functions (filled symbols) have lower thresholds and smaller peak amplitudes. CAEP amplitudes can be estimated using the scale on the left vertical axis. In contrast to the ECAP data, CAEP growth functions measured using pulse trains do tend to have saturated response amplitudes at high levels. ECAP amplitudes continue to grow, even at significantly higher current levels. Since ECAP growth functions do not reach a saturated response, it is not clear by how much the dynamic range differs for the two measures, but clearly the ECAP dynamic range tends to be wider.

3.3 Discrimination: change in stimulating electrode

Cortical N1-P2 responses can also be evoked in response to a change in some aspect of an ongoing stimulus (Jerger & Jerger, 1970; Näätänen & Picton, 1987; Ostroff et al., 1998). This response has been referred to as an auditory change complex. Martin & Boothroyd

(2000) recorded responses to changes in stimulus level and/or spectral content of an acoustic stimulus. Lister et al. (2007) recorded similar responses to a brief gap in a wideband noise stimulus. This evoked potential is unique in that it has generally been considered an index of discrimination ability by the listener (Ostroff et al., 1998; Martin & Boothroyd, 2000; Tremblay et al., 2003; Lister et al., 2007).

Friesen & Tremblay (2006) used speech stimuli and recorded change responses from CI users tested while listening using their speech processors. Electrically evoked change responses were similar to those recorded using normal hearing listeners (Tremblay et al., 2003). Several other studies have used different stimuli presented either through the speech processor of the CI or directly to individual electrodes to elicit these change responses (Brown et al., 2008; Martin, 2007; Kim et al., 2009). An advantage of this technique is that it can be used to measure a response to relatively simple stimuli like changes in the current level within a constant amplitude pulse train on a single electrode or in response to a complex vowel-like stimulus that changes formant frequencies during a stimulation period. The waveform features of the change complex, including peak latencies, are essentially the same as the onset response, suggesting a common cortical origin (Brown et al., 2008). Significant correlations between cortical change responses and behavioral measures of discrimination using the same or similar stimuli have also been reported (Won et al., 2011; Hoppe et al., 2010).

Examples of responses to a change in stimulating electrode are shown in Figure 5A. In this case the stimulus was a constant amplitude pulse train (1000 pps) that was presented on electrode 10 during the 1st 300 ms of the stimulus then followed immediately by stimulation of a different electrode during the next 300 ms interval. The stimulated electrode in the 2nd 300 ms period is indicated on each trace. As expected there is a clear onset response to the stimulation on electrode 10 that is the same for each trace. When there is a large separation between the two stimulating electrodes (see Figure 5A, bottom trace), the response is relatively large. When the second electrode is closer to electrode 10, the response amplitude is smaller. If the stimulation simply continues on electrode 10 (see Figure 5A, upper trace) there is no clear change response.

In Figure 5B, amplitude of the change response measured from N1 to P2 is plotted as a function of the variable electrode in the stimulating electrode pair. Each curve represents responses recorded from a different CI user. The standard electrode was always electrode 10. In general, wider spacing between the two stimulating electrodes results in greater change response amplitudes, but there is considerable variation among individuals in both the amplitude and form of the function. In this example, N1 and P2 latencies increase and amplitudes decrease as the discrimination becomes more difficult. In order to compare sensitivity to change across individuals we have usually normalized the response amplitudes by expressing the amplitude of the change response relative to the amplitude of the onset response recorded using the same stimulus. The normalized change response amplitude presumably reflects the overlap of neural excitation to the standard and variable stimulus at a cortical level.

In general, evoked neural responses show changes in latency as well as in amplitude. Our initial assessment of latency in Brown et al. (2008) compared onset vs change response latency. At wide electrode separations, where amplitude responses are clearly different, the mean latency of N1 of the onset response and mean N1 of the change response were not significantly different ($p < 0.05$). In that paper as well as subsequent work we have chosen in most of our analyses to focus on amplitude measures.

We assume that the amplitude of the change response is dependent, at least in part, on the size of the population of neurons that respond to stimulation of the second electrode in the pair but not to the first. ECAP-based channel interaction functions are analogous measures of the response from the auditory periphery. They provide an estimate of the spread of excitation for a particular electrode. (Abbas et al., 2004; Cohen et al., 2003, 2004). We have typically recorded ECAP channel interaction functions by using a two-pulse stimulation paradigm where the first (masker) pulse is applied to one electrode and the second (probe) pulse to a different electrode. The inter-pulse interval is set to be relatively short so that any neurons responding to the masker pulse will be in a refractory state and not respond to the probe. A “channel interaction” function is then extracted by measuring the response to the probe on a fixed electrode while the masker electrode is varied. Examples of channel interaction functions from a Nucleus CI user are illustrated in Figure 6A. These functions were recorded using probes on electrodes 8, 10, 12 and 14 and current pulses presented at a level 10 clinical units below maximum comfortable level for that electrode. Because of the subtraction technique employed to minimize stimulus artifact, large amplitude responses are obtained when there is considerable overlap between the group of neurons responding to the masker and probe pulses. Small amplitude responses are recorded when there is little or no overlap between the populations of neurons responding to the two pulses. Thus, the function describing the amplitude of the ECAP response as a function of masker electrode can be interpreted as a measure of spread of excitation to the probe.

Several studies have demonstrated a relationship between behavioral measures of spectral resolution and speech perception (Henry et al., 2005; Litvak et al., 2007; Won et al., 2007; Berenstein et al., 2008). One might hypothesize that the spread of excitation at the electrode-neural interface may contribute to variations in spectral resolution and consequently speech perception. These examples illustrate our general observation that across and within individuals, we observe variations in both the overall amplitude as well as width of channel interaction functions (Cohen et al., 2003; Abbas et al., 2004; Eisen & Franck, 2005). Despite that variance, most studies have not reported finding significant correlations to performance on tests of speech perception by cochlear implant users (Hughes & Abbas, 2006; Hughes & Stille, 2008; Tang, Benitez & Zeng, 2011; van den Beek, Briare & Frijns, 2012).

The lack of correlation between ECAP measures of channel interaction and performance may be related to the fact that the ECAP is generated so peripherally. It also may be related to methodological considerations. To compare the peripheral channel interaction data to cortical responses to a change in stimulating electrode we used a procedure introduced by Hughes (2008). That procedure is illustrated in Figure 6B for the electrode pair 8 and 10. After normalizing the amplitude of these functions for each implant user, we calculate the difference between the two functions at each masker electrode. Those differences are

illustrated by the vertical lines in Figure 6B. The average of these differences across the array, defined as the channel separation index (CSI), is a number between 0 and 1. It provides an estimate of the *change* in overall activity across the array as stimulating electrode is changed from 8 to 10. The CSI for electrode pair 8-10 in this case is relatively low (0.17). Typically as the two probe electrodes are separated, there is less overlap in the channel interaction functions and consequently the CSI tends to increase. The calculated values of CSI for different electrode pairs noted in the figure legend illustrate this trend: electrodes 8-10, 0.17; 8-12, 0.21; 8-14, 0.29. We interpret this to mean that as the two electrodes in the pair are separated, there is a larger difference in the population of neurons that respond to each electrode individually.

Scheperle and Abbas (submitted, a) recently completed a study measuring channel interaction functions for 13 probe electrodes and cortical change responses to several electrode combinations with increasing electrode spacing. The goal was to use the CSI, a measure of spread of excitation at the auditory periphery, to predict the amplitude of the cortical change response to a corresponding change in stimulating electrode for different electrode combinations. Figure 7 illustrates an example from one individual where ACC amplitude is plotted as function of ECAP channel separation index for 13 different electrode combinations. This relationship tended to be well fit by a saturating exponential function, suggesting that changes at the periphery are reflected in the central responses but, particularly at larger electrode separations, the peripheral response continues to increase while the amplitude of the cortical response has saturated. Also Scheperle and Abbas (submitted, a) noted that the relationship between peripheral and central responses, such as the slope of the increasing exponential function was dependent upon individuals, suggesting that the relationship between peripheral and central responses may be different among CI users, i.e., they reflect differences in central processing.

3.4 Temporal Response

The use of the cortical change response allows us to evaluate both spatial and/or spectral changes in stimulation as well as temporal changes at the same stimulus location. Kim et al (2009) demonstrated change potentials in response to changes in current level. We have also recorded responses using short gaps introduced into a continuous constant amplitude pulse train. Figure 8A illustrates the stimulus used for these recordings. The stimulus level and pulse rate is fixed. The cortical response is recorded by triggering the averaging software at the onset of the gap. The responses that are recorded have a typical N1-P2 morphology, at least for the relatively short gap widths used in this study. Figure 8B shows the amplitude of the recorded change responses as a function of gap width for several CI users. All individuals show an increase in the response amplitude with increasing gap width but there are clear variations among individuals in amplitude of the responses as well the slope of the functions.

An analogous response at periphery is ECAP forward masking. For ECAP measures we are still limited measuring the response to a single pulse. Several investigators have characterized refractory recovery functions by using a single masker pulse and varying the interpulse interval. Recovery times are typically less than 5 ms (Brown et al, 1996;

Morsnowski et al., 2008). Refractory properties can have significant effects on the responses to trains of pulses that are typical of cochlear implant stimulation (Wilson, 1997; Wilson et al., 1997). We recently completed a study of adaptation and recovery of the ECAP using relatively long masker pulse trains (Dhuldhoya, 2013). Fig. 9A illustrates the stimulus used for these measurements. Masker pulse trains were 100 ms in duration at a rate of 1800 pps. Masker –probe interval was varied and responses to the probe stimulus were measured using a template subtraction paradigm (Hay-McCutcheon et al., 2005). Recovery functions were measured in response to stimuli at several stimulus current levels.

Figure 9B shows mean data from 14 CI users. Responses have been divided into three group according to the amplitude of the unadapted ECAP response. Our goal in analyzing the data in this way is to account, at least in part, for differences in sensitivity that are normally observed among individual CI users. Pulse trains presented at a fast rate can result in significant adaptation and can have a relatively complex time course of recovery which can take 100-200 ms. In many cases the recovery is observed to be nonmonotonic where there is a decrease in amplitude during the first few ms after pulse train offset, followed by a slower recovery which is similar in time course to that observed with CAEP gap measures (Figure 8B). We hypothesize that the pulse train is producing a conditioning effect that enhances response in some neurons while clearly adapting the response in other neurons of the population. Interestingly, while there is a great deal of variability among individuals in degree of this enhancement effect, there seem to be differences in this enhancement effect in children and adult populations (Dhuldhoya, 2013). This nonmonotonic recovery is not evident in the cortical responses to a gap in the stimulus. Nevertheless, the amplitude of CAEP vs gap duration has similar time course (Figure 9B) to more long term adaption recovery in the ECAP as illustrated in Figure 9B.

4. DISCUSSION

These data suggest that there are several parallels between peripheral responses to electrical stimulation and central cortical responses. Still it appears that there may be important information about the processing of stimuli by individual cochlear implant users that can be learned from each of these separately. For several of these measures, notably amplitude growth and changes in electrode stimulation, CAEPs are more sensitive to change at low levels or small changes while the peripheral measures are more sensitive to changes at high levels or wide separations. These effects are illustrated in Figure 4 for amplitude growth where CAEP amplitudes saturate at high stimulus levels and in Figure 7 showing the relationship between CAEP amplitude and CSI for changes in electrode stimulation.

We have attributed the differences we have observed between central and more peripheral measures of neural response, at least part, to the process of temporal integration that is clearly a central phenomenon. The fact that temporal integration may be different among individual CI users is illustrated in the variations of threshold difference between ECAP and CAEP among individuals shown in Figures 4 and 4. We would suggest that those variations are indicative of individual differences in central processing among individuals.

Comparison of both central and peripheral measures of neural response within a subject could be useful because such comparisons would allow us to determine whether perceptual challenges experienced by CI users reflect limitations at the auditory periphery or at more central levels within the auditory system. Such information may drive decisions regarding rehabilitation. For instance, subjects with similar thresholds for ECAP and CAEP (e.g. Z16 in Figure 4) may have relatively poor temporal integration and are likely limited by peripheral sensitivity. Steep functions relating ACC amplitude with peripheral channel separation index (Figure 7) may be indicative a central system that is particularly sensitive to changes in peripheral input. Furthermore, the combination of peripheral and central measures can better predict performance. Scheperle and Abbas (submitted, b) were able to use the CSI in combination with CAEPs to predict performance on psychophysical tasks as well as speech perception. The combination of electrophysiological measures could also be helpful in programming and fitting an implant in young children and/or other difficult to test populations.

Behavioral measures are usually the most convenient to assess appropriateness of programming options and/or progress with rehabilitation strategies in adults. Physiological measures can be particularly important in children and difficult to test populations. Separation of peripheral and central differences among individuals can be useful in dictating the design of treatment options, evaluating progress and subsequently choosing alternative treatment options if needed. For instance, peripheral measures such as the ECAP may be most useful for simple tasks such as mapping appropriate levels for the implant processor. CAEPs have been shown to be sensitive to interventions such as speech sound training (Tremblay et al, 1998, 2001, 2002) and consequently might be more useful for assessing progress in rehabilitation.

Finally, as noted above, a key advantage of CAEPs, whether onset or change response, is that they can be elicited with a variety of stimulus types, either by direct stimulation of a particularly electrode or by acoustic stimulation through the implant processor. We have successfully used a variety of complex acoustic stimuli – speech, music, ripple noise to elicit the change potential in cochlear implant users. Using such stimuli for CAEPs can be more like “everyday” listening situations and therefore may correlate more closely with perceptual measures such as speech perception and allow for more direct comparisons of physiological responses evoked from cochlear implant users to similar responses evoked from normal and hearing impaired populations.

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HIGHLIGHTS

- Summarize differences between peripheral and central response measures to electrical stimulation.
- Observe variations in both peripheral and central responses among individual cochlear implant users.
- Interpret these variations as evidence of differences between both peripheral stimulation as well as central processing.
- Combined measures may be particularly informative in clinical situations.

Figure 1.

Plots of electrically evoked compound action potentials (ECAP) recorded from a Nucleus cochlear implant user. Stimulation is on electrode 18, recording from electrode 19. Level of the probe stimulus is indicated by each waveform.

Figure 2.

Recordings of an electrically evoked cortical response (CAEP) to stimulation of electrode 11 in an Advanced Bionics cochlear implant user. Pulse rate of the stimulus was 2017 pps and duration of the pulse train 500 ms. Recordings shown reflect measures obtained using surface electrodes at the vertex(+) relative to contralateral mastoid (–) with forehead ground. Level of the pulse-train stimulus is indicated each waveform. The vertical line indicates stimulus onset and offset. Responses are generally characterized by an initial positive peak (P1), usually small in adults. This is followed by a negative peak at approximately 100 ms after stimulus onset (N1) and a second positive peak (P2). Response amplitude is typically calculated as the difference between N1 and P2.

Figure 3.

A. Behavioral threshold is plotted as a function of CAEP threshold for the same stimulus. Both perceptual threshold and CAEP thresholds were measured using a 500-ms pulse train with rate of 2017 pps, and pulse-width 21 us/phase presented on a single electrode. Data are plotted for 13 individuals including both Advanced Bionics and Nucleus implant users and a total of 14 ears. A calculated linear regression line is superimposed on the scatter plot.

B. ECAP threshold in response to a single pulse is plotted as a function of CAEP threshold in response to a pulse train. Stimulus for the CAEP was as described in part A. ECAPs were recorded in response to a single biphasic current pulse presented at a 30-80 pps, with pulse width 25 us/phase. Data are plotted for 14 individuals, most of the same subjects as in part A, and a total of 16 ears. A calculated regression line is superimposed on the scatter plot.

Figure 4.

Amplitude of response as a function of stimulus level is plotted for both ECAP and CAEP measures in individual CI users. CAEP amplitude is plotted with filled symbols; ECAP is plotted with open symbols. The stimulus for CAEP was a 1000 pps pulse train; the stimulus for ECAP was a single probe pulse, using the normal masker/probe subtraction paradigm (Brown et al., 1990). Each graph represents data from an individual ear. In general, threshold is higher for ECAP and, in contrast to CAEP, and saturation is not evident.

Figure 5.

A. Examples of recordings of the auditory change response where the stimulus is a change in the stimulation electrode. For each trace the initial 300 ms was a pulse train on electrode 10. At 300 ms after stimulus onset (change is indicated by the vertical line), the stimulation is changed to a different electrode. The stimulated electrode for the second segment is indicated by each trace.

B. Amplitude of the CAEP change response is plotted as a function of the variable electrode where the initial (fixed) electrode was electrode 10. Responses from 12 individuals using the Nucleus implant plotted.

Figure 6.

A. Examples of channel interaction functions calculated from ECAP responses recorded from a Nucleus implant user. For each probe electrode, masker electrode is varied, keeping masker level at 10 clinical units below C-level. By subtracting the responses with and without the masker pulse present, the amplitude of response represents a measure of the overlap in stimulation between masker and probe electrodes. Therefore when masker and probe are on the same electrode, the responses tend to be maximum. As masker is separated from the probe, the responses tend to decrease suggesting less overlap.

B. This plot illustrates the calculation of channel separation index (CSI, Hughes, 2008) based on the channel interaction functions for probe electrodes 8 and 10 in part A. Each vertical line represents the difference between the functions at each masker electrode. The average of the absolute value of these differences constitutes the CSI. In general, the CSI increases as the separation between electrodes is increased. For instance, for the data shown in part A, CSI for 8-10 is 0.17, for 8-12 is 0.21 and for 8-14 is 0.29.

Figure 7.

An example of ACC amplitude plotted as a function of channel separation index for an individual CI user where each point represents a different separation between stimulating electrodes. This individual is typical of findings in other subjects in that ACC amplitude tends to saturate for electrode pairs showing relatively wide CSI, although the form of the function differs across individuals (See Scheperle & Abbas, submitted, a).

Figure 8.

A. Schematic of stimulus used to elicit cortical response to temporal gap. Width of temporal gap is varied.

B. CAEP amplitude in response to a gap in a pulse train as a function of gap width. Data are plotted for 8 individual CI users. Increasing gap tends increase amplitude of response but both amplitude and sensitivity differs across individuals.

Figure 9.

A. Schematic of stimulus used to elicit ECAP response in a forward masking paradigm. Time interval between masker pulse train offset and probe pulse is varied.

B. Amplitude of the ECAP normalized to the amplitude of the ECAP in response to a single pulse is plotted as a function masker-probe interval. Data are plotted from 14 Nucleus cochlear implant users. Recovery functions are averaged across subjects for levels that have relatively low amplitude unadapted responses (<31 μV), medium (31-150 μV) and high amplitude responses (>150 μV). Recovery tends to

be nonmonotonic, particularly at high stimulus levels, but recovery after the initial 10 ms shows a time course similar to CAEP gap recovery functions in Figure 9B.