Published in final edited form as:

Hear Res. 2011 May ; 275(1-2): 17–29. doi:10.1016/j.heares.2010.11.007.

Mismatch Negativity and Adaptation Measures of the Late Auditory Evoked Potential in Cochlear Implant Users

Fawen Zhang^{*}, Theresa Hammer^{*}, Holly-Lolan Banks^{*}, Chelsea Benson^{*}, Jing Xiang[†], and Qian-Jie Fu^{††}

^{*} Department of Communication Sciences and Disorders, University of Cincinnati, Ohio, USA

[†] Department of Pediatrics and Neurology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

^{††} House Ear Institute, Los Angeles, CA, USA

Abstract

A better understanding of the neural correlates of large variability in cochlear implant (CI) patients' speech performance may allow us to find solutions to further improve CI benefits. The present study examined the mismatch negativity (MMN) and the adaptation of the late auditory evoked potential (LAEP) in 10 CI users. The speech syllable /da/ and 1-kHz tone burst were used to examine the LAEP adaptation. The amount of LAEP adaptation was calculated according to the averaged N1-P2 amplitude for the LAEPs evoked by the last 3 stimuli and the amplitude evoked by the first stimulus. For the MMN recordings, the standard stimulus (1-kHz tone) and the deviant stimulus (2-kHz tone) were presented in an oddball condition. Additionally, the deviants alone were presented in a control condition. The MMN was derived by subtracting the response to the deviants in the control condition from the oddball condition. Results showed that good CI performers displayed a more prominent LAEP adaptation than moderate-to-poor performers. Speech performance was significantly correlated to the amount of LAEP adaptation for the 1-kHz tone bursts. Good performers displayed large MMNs and moderate-to-poor performers had small or absent MMNs. The abnormal electrophysiological findings in moderate-to-poor performers suggest that long-term deafness may cause damage not only at the auditory cortical level, but also at the cognitive level.

Keywords

cochlear implant; neural adaptation; late auditory evoked potential; mismatch negativity; electrophysiology

1. Introduction

The human auditory system is capable of automatically detecting novel sounds within noisy and complex listening environments at the pre-attentive level. Neurophysiological studies suggest that there are two possible cortical processes underlying this pre-attentive signal

Corresponding author: Fawen Zhang, Department of Communication Sciences and Disorders, University of Cincinnati, Cincinnati, Ohio, USA, Phone: 513-558-8513, Fax: 513-558-8500, Fawen.Zhang@uc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

detection (Friston, 2002; Baldeweg, 2006; Garrido et al., 2008). The first is neural adaptation, a phenomenon in which neural responses decline over time in response to repeated stimuli. Neural adaptation may be useful for representing complex sounds by increasing the temporal precision and spectral contrast (Delgutte, 1997). Neural adaptation can be reflected by the amplitude decrement of summed neural responses such as auditory evoked potentials (AEPs), which can be recorded using non-invasive electroencephalography (EEG) techniques (von der Behrens et al., 2009). The cortically generated late auditory evoked potential (LAEP) consists of several peak components, including N1 (which occurs at a latency of ~100 ms) and P2 (which occurs at a latency of ~180 ms). The LAEP displays a reduction in response amplitude following stimulus repetition (Butler, 1968; Fruhstorfer et al., 1970; Fruhstorfer, 1971; Megela & Teyler, 1979; Prosser et al., 1981; Bourbon et al., 1987; Barry et al., 1992; Budd et al., 1998; Zhang et al., 2009a). Previous studies suggest that neural adaptation is one of the main mechanisms for this phenomenon, although neural refractory properties may also play an important role (Ritter et al., 1968; Fruhstorfer et al., 1970; Fruhstorfer, 1971; Megela & Teyler, 1979; Barry et al., 1992; Shore, 1995; Budd et al., 1998; Fitzpatrick et al., 1999).

The second cortical process may be reflected by the mismatch negativity (MMN), an event-related AEP. The MMN is typically derived by subtracting the AEP response to the standard (frequent) stimuli from the response to the deviant (infrequent) stimuli within the latency range of ~100–250 ms (Naatanen et al., 1989, 2005; Levanen et al., 1996). For MMNs, standard and deviant stimuli can differ in terms of any acoustic feature (duration, intensity, frequency, etc.). The MMN is thought to reflect the automatic (pre-attentive) detection of the differences between the neural representations of the standard stimuli in memory and the deviant stimuli in the sensory input (Giard et al., 1990; Rinne et al., 2000; Opitz et al., 2002; Doeller et al., 2003). The MMN may serve as a trigger to shift attention toward the deviant stimuli.

It has long been debated whether neural adaptation and the MMN reflect two distinct cortical processes. Some studies claim that neural adaptation at least partially, if not fully, accounts for the MMN (Jaaskelainen et al., 2004; May & Tiitinen, 2010). Jaaskelainen et al. (2004) found that the MMN arises through neural adaptation of N1 activity, rather than being generated by other auditory cortical processes, using variety of experimental approaches [e.g., 3-T functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), EEG, psychophysics]. Bottcher-Gandor and Ullsperger (1992) recorded the MMN using stimuli that were presented with different inter-stimulus intervals (ISIs): 1, 6 and 10 s. Results showed that the MMN was present even with an ISI of 10 s. They proposed that the duration of memory trace that allows for comparison between standard stimuli and deviant stimuli can last at least 10 s, similar to the recovery time from adaptation for the LAEP (Davis & Zerlin, 1966; Hari et al., 1982). These studies suggest that the MMN may result from differential adaptation effects of stimulus repetition on the N1 component of the LAEP, i.e., deviant stimuli evoke less adaptation and standard stimuli evoke more adaptation. This “stimulus-specific adaptation” (SSA), which might be a general feature of many neurons in the auditory system, has been suggested as a possible neural correlate of the MMN (Ulanovsky et al., 2003, 2004; Anderson et al., 2009). Garrido et al. (2009) proposed a general framework to unify the adaptation-based and memory-trace theories, i.e., the brain is a hierarchical system that strives to attain a compromise between bottom-up sensory inputs and top-down predictions. Prediction error is reduced during stimulus repetition by adjusting connection strengths between hierarchical levels. The physiological correlate of this reduction in prediction error is suppression of the response to the repeated stimulus. The MMN results from a failure to predict bottom-up input and consequently to suppress the prediction error (Friston, 2002; Baldeweg, 2006; Garrido et al., 2008).

On the other hand, some researchers argue against the adaptation theory of the MMN (Rosburg et al., 2004; Naatanen & Picton, 1987; Hari et al., 1992; Naatanen et al., 2004, 2007). According to these researchers, the MMN depends on a memory trace formed by preceding stimuli. Specifically, a series of standard stimuli evoke neural responses that form a neural memory trace, and the MMN will be generated if the deviant stimulus occurs while the memory trace is still available (Sussman & Winkler, 2001). Naatanen et al. (2005) reviewed prior MMN research and found evidence of different neural mechanisms that may underlie generation of the MMN and adaptation of the LAEP N1 component: 1) The MMN duration and latency do not match those of the N1. The N1 is time-locked to stimulus onset while MMN latency depends on the magnitude of stimulus difference, 2) The MMN can be elicited in the absence of any N1 response; 3) The MMN can be present when N1 adaptation cannot occur (e.g., using tones of decreasing intensity as deviant stimuli), 4) MMN is right-hemisphere predominant while N1 is contralateral hemisphere predominant, 5) the dipole sources for the MMN and N1 display different orientations, and 6) various experimental manipulations (including pharmacological manipulations) affect the MMN and the N1 in different ways.

The goal of this study was to examine neural correlates of variability in cochlear implant (CI) patients' speech performance using two different measures: the LAEP adaption and the MMN. The LAEP adaption was measured by recording the LAEP in response to a series of identical stimuli in stimulus trains while the MMN was measured by recording the event-related potential (ERP) using oddball paradigms consisting of standard and deviant stimuli. The CI is a surgically implanted electronic device that can provide useful hearing in profoundly deaf individuals. While many deaf patients benefit from implantation, there is substantial variability in patient outcomes that is not well understood (Green et al., 2007). One practical implication of this research is that, given a meaningful correlation between neural responses and behavioral speech perception performance, objective measures such as the LAEP and MMN can be used to predict performance in CI users for whom behavioral performance is unreliable or unable to be measured. Additionally, by comparing the LAEP adaptation pattern in CI users and NH listeners, we can infer the contribution of the cochlear and the retro-cochlear portion of the auditory system to cortical adaptation because the CI stimulation bypasses the cochlea. Previous studies have shown that different stages of the auditory system display adaption (Smith, 1977; Boettcher et al., 1990; Shore 1995; Babalian et al., 2003). The initial source of neural adaption is related to neurotransmitter depletion in hair cell-to nerve fiber synapses (Westerman & Smith, 1984; Zhang & Carney, 2005). Adaption at higher levels of auditory system becomes more complex (Shore, 1995; Walton et al., 1995). It is not known the role of cochlear adaptation in the formation of neural adaptation detected at the cortical level.

Previous studies have shown that the MMN is similar for good-performing CI users (in terms of speech perception) and normal hearing (NH) listeners, but absent or abnormal in poor-performing CI users (Kraus et al., 1993; Ponton et al., 2000; Roman et al., 2005). The adaptation in the LAEP for CI users was first examined by our group using 1 kHz tone bursts (Zhang et al., 2010). The results showed that the LAEP adaptation pattern in good CI performers was similar to that reported in NH listeners, and less prominent in poor CI performers.

In this study, the LAEP adaptation pattern and the MMN were examined and compared to speech performance in adult CI users. For the LAEP adaptation, both 1 kHz tone bursts and the speech syllable /da/ were used as stimuli. It was predicted that speech performance would be more strongly correlated to the adaptation for speech syllable stimulus than to the adaptation for 1 kHz tone bursts. We expected the results to provide information regarding

neural mechanisms that underlie the variability of CI speech performance, at both the auditory cortical level and at pre-attentive cognitive level.

2. Materials and methods

2.1. Subjects

Ten post-lingually deafened CI subjects (aged 34 – 72 years) participated in this study. All CI subjects were users of the Nucleus Freedom CI device, all were stimulated using monopolar stimulation, and most were fit with the ACE coding strategy. The CI subjects were recruited from the Department of Otolaryngology-Head and Neck Surgery at the University of Cincinnati. Relevant CI subject demographics are shown in Table 1. CI subjects were grouped according to clinically-measured speech performance scores using a somewhat arbitrary criterion. “Good” performers were defined as having equal to or better than 80% correct (on average) CNC word recognition in quiet, HINT sentence recognition in quiet, and HINT sentence recognition at 10 dB signal-to-noise ratio (SNR). “Moderate-to-poor” performers were defined as having less than 80% correct (on average) across the three speech measures. One consideration of using the 80% correct criterion was the same number of subjects (5) included in each group. For the MMN measures, 11 NH subjects (20–30 years) served as a control group. NH subjects’ pure tone air-conduction thresholds were < 20 dB HL at octave frequencies from 0.5 to 4 kHz. NH subjects exhibited normal type A tympanometry and normal acoustic reflex thresholds at 0.5, 1, and 2 kHz. All CI and NH subjects were free of known cognitive, psychiatric, or neurological impairment and all were right-handed. All subjects provided written consent, and the research protocol was approved by the Institutional Review Board of the University of Cincinnati.

2.2. Stimuli

LAEP adaptation stimuli—Two stimuli were used for the LAEP recordings: 1) speech syllable /da/, and 2) 1 kHz tone bursts. For both stimuli, the duration was 40 ms. The /da/ syllable, which has been used in prior studies, contained 10 ms of the consonant /d/ and 30 ms of the formant transition to the vowel /a/ (Johnson, 2008). Despite the short 40-ms duration, the stimulus preserved key acoustic phonetic information (Johnson et al., 2005). LAEPs were recorded separately for the /da/ and 1 kHz tone burst stimuli. In each condition, 30 stimulus trains, each consisting of 5 repeated stimuli, were presented. The inter-stimulus interval (ISI) was 0.7 s and the inter-train interval (ITI) was 15 s. A minimum of 5 LAEP recordings were conducted for each stimulus condition, for a total of 750 stimulus presentations in each condition (5 repeats × 30 pulse trains × 5 stimuli). The LAEP adaptation patterns for the /da/ and the 1 kHz tone bursts were compared to see whether LAEP adaptation was speech-specific.

MMN stimuli—The standard stimulus was a 1 kHz tone burst and the deviant stimulus was a 2 kHz tone burst; for both stimuli, the duration was 60 ms (10 ms rise/fall time). Two stimulus conditions were tested. The first condition (“oddball paradigm”) included the standard and deviant stimuli. This frequency pair allows for gross rather than fine-grained evaluation of acoustical sensory memory and can evoke a relatively large MMN (Näätänen & Winkler, 1999). A total of 395 standard (occurrence ratio: 84%) and 75 deviant stimuli (occurrence ratio: 16%) were presented in the oddball paradigm. Stimuli were delivered in a pseudo-random sequence with 20 standard stimuli presented at the beginning of the test and at least 3–7 standard stimuli presented between deviant stimuli. The ISI was 0.7 s. A minimum of two oddball paradigms were tested for each subject, for a total of 940 stimuli (2 repeats × 470 stimuli).

The second test condition (“deviant alone”) was a control paradigm, in which the same number of deviant stimuli (75 trials of 2-kHz tone bursts) used in the above oddball condition was presented with an ISI of 0.7 s. The MMN obtained by integrating the oddball and control conditions is thought to reflect the comparison process between the memory trace of the standard stimuli and the sensory input of the deviant stimuli (Kraus et al., 1993). This approach is better than the traditional approach in which only the oddball paradigm is presented, because the MMN derived using the traditional approach most likely reflects the neural representation of the acoustic characteristics of the standard and deviant stimuli, rather than processing of a change in sound features (Jacobsen et al., 2003). A minimum of two control paradigms were tested for each subject, for a total of 150 stimuli (2 repeats $\times$ 75 stimuli).

Stimuli were delivered in the sound field via a single loudspeaker placed at ear level, 50 cm from the test ear at 45° azimuth. Subjects were comfortably seated in a sound-treated booth. For the MMN recordings in NH listeners, stimuli were presented monaurally to the left and right ears separately. For unilateral CI users, stimuli were presented to the implanted ear. For the two bilateral CI users, each ear was tested independently, similar to NH subjects. CI subjects were instructed to use their clinical speech processors and settings for everyday speech, and once set, to not change these settings during testing. For all subjects, an earplug was used in the non-test ear to prevent any contribution to the recorded response. The subjective thresholds of NH listeners were used as the nHL values. Results showed that a 0 dB nHL tone bursts (1 kHz tone bursts in the adaptation paradigm) through the loudspeaker in the sound field had a peak equivalent SPL of 27 dB. The AEP stimuli were initially presented at 60 dB nHL. Then the sound level was adjusted so that the subject judged the loudness as a comfortable listening level, i.e., 6 on a 10-point scale in which 0 = inaudible and 10 = uncomfortably loud (Valente & Van Vliet, 1997; Hoppe et al., 2001).

2.3. Electroencephalographic (EEG) recordings

Subjects were fitted with a 40-channel Neuroscan quick-cap (NuAmps, Compumedics Neuroscan, Inc., Charlotte, NC). The cap was placed according to the International 10–20 system, with the contralateral earlobe as the reference (McNeill et al., 2007). Electro-ocular activity (EOG) was monitored so that eye movement artifacts could be identified and rejected during the offline analysis. The 1–3 electrodes located near the CI transmission coil were not used. Electrode impedances for the remaining electrodes were kept at or below 5 k Ω . EEG recordings were collected using the SCAN software (version 4.3, Compumedics Neuroscan, Inc., Charlotte, NC) with a band-pass filter setting from 0.1 to 100 Hz and an analog-to-digital converter (ADC) sampling rate of 1000 Hz. During testing, subjects were instructed to avoid excessive eye and body movements. Subjects read self-selected magazines to keep alert and were asked to ignore the acoustic stimuli. Subjects were periodically given short breaks in order to shift body position and to maximize alertness during the experiment.

2.4. Data Analysis

EEG data analysis was performed using EEGLAB 6.03, an online open source toolbox (freely available from <http://scn.ucsd.edu/eeqlab>) running under Matlab 6.3 (The Mathworks, Natick, MA). Continuous EEG data were digitally filtered using a FIR filter that preserved the phase information (band-pass filter: 0.1 to 30 Hz). Next, data epochs were extracted between –100 to 500 ms and the baseline was corrected using the pre-stimulus window. After rejecting approximately 10% of epochs that contained unique, non-stereotyped artifacts, the remaining data epochs from the repeated recordings were concatenated into single-trial data sets. Next, an average reference for each of the scalp electrodes was computed (Hagemann et al., 2001; Delorme & Makeig, 2004). EEG data

were then decomposed using independent component analysis (ICA). The ICA model decomposed the EEG dataset into mutually independent components, including those from artifactual and neutral EEG sources. For each individual data set, ICA derived approximately 40 independent components (ICs). ICs representing artifacts were identified and removed by visual inspection of IC properties including the waveform, 2-D voltage map, and the spectrum (Gilley et al., 2006; Debener et al., 2008). Details of CI artifact removal are provided in our previous papers (Zhang et al., 2009b; Zhang et al., 2010). After removing artifacts, the remaining components were then constructed to form the final EEG data set.

Analysis for the LAEP adaptation—For the LAEP adaptation paradigm, the EEG data for each condition (speech syllable /da/ or 1 kHz tone burst) were averaged across stimulus trains to obtain 5 averaged LAEPs, one for each stimulus within the train. For each averaged LAEP, the N1 and P2 were automatically identified as the maximum negative peak and maximum positive peak in a latency range of 70–160 ms and 140–300 ms, ranges similar to those used in Roman et al. (2005). Because the LAEP was largest at electrode Cz, we report the LAEP from Cz in this study.

To quantify the amount of adaptation, an adaptation index (AI) was calculated according to: $AI = 1 - (A_{3-5})/A_1$, in which A_{3-5} was the averaged N1-P2 amplitude for the LAEPs evoked by the last 3 stimuli and A_1 was the amplitude for the LAEP evoked by the first stimulus in the train. The N1-P2 amplitude was used because this measure is more stable than the amplitude for individual peaks (Prosser et al, 1981; Zhang et al., 2009a). Adaptation index values ranged from 0 to 1, with higher values indicating a greater amplitude decrement and therefore greater adaptation.

A two-way repeated-measures analysis of variance (RM ANOVA, mixed model), with subject group as the between-subject factor and stimulus type as the within-subject factor, was performed on the LAEP adaptation index values. Both bivariate correlations and linear regressions were performed to examine the correlation between the LAEP adaptation index and speech perception scores. A p-value of 0.05 was used to indicate statistical significance.

Analysis for the MMN—For the MMN, the averaged waveforms in response to the standard stimuli (STANDARD waveform) and the deviant stimuli (DEVIANT waveform) in the oddball condition were separately derived. The average waveform for the deviant stimuli (2 kHz tone) in the control condition was also derived (CONTROL waveform). Because the MMN is largest in the fronto-central area rather than any other regions of the scalp (Lang et al., 1995; Petermann et al., 2008), the responses from 9 electrodes (F3, Fz, F4, C3, Cz, C4, FC3, FCz, and FC4) in this area were averaged to form one waveform. One advantage for averaging responses from multiple electrodes was that the variability in CI data could be reduced, as the final EEG waveform would include more data trials, which would otherwise require a much longer time to collect. This approach of analyzing MMN data has been used in studies with CI users (Roman et al., 2005). Because the data were collected when stimuli were monaurally presented, there was one waveform for each type of stimuli (STANDARD, DEVIANT, and CONTROL) for each tested ear.

The CONTROL waveform was subtracted from the DEVIANT waveform to derive the difference waveform, for which the MMN was judged to be present or absent (Roman et al., 2005; Nikjeh et al., 2009). Although the difference waveform is traditionally derived by subtracting the STANDARD from the DEVIANT, Kraus et al. (1992) showed no significant difference between these two approaches, for all latency and amplitude measures. Moreover, the current approach (DEVIANT – CONTROL) more likely reflects the comparison process between the memory trace and the sensory input of the deviant stimuli. The MMN was

defined as a visually identified negativity deflecting from the baseline in the difference waveform between 100 and 350 ms after stimulus presentation (Singh et al., 2004).

The measures used to evaluate the MMN included the MMN onset latency and amplitude, offset latency and amplitude, peak latency and amplitude, and duration (offset-onset). The MMN onset was identified using the difference waveform and was defined as the point at which the DEVIANT waveform became consistently more negative than the CONTROL waveform within the latency range 50–150 ms. The MMN offset was defined as the point at which the DEVIANT and CONTROL waveforms converged within the latency range 150–350 ms. The MMN duration was the time between MMN onset and offset. The peak of the MMN was defined as the most negative point in the MMN duration.

Independent sample t-tests were performed to examine the difference in MMN measures between the NH and CI subject groups. A p-value of 0.05 was used to indicate statistical significance for all analyses.

3. Results

All EEG recordings contained stimulus artifacts, which were successfully removed using the ICA technique. Although a few of the event-related potential (ERP) waveforms appeared to have residual artifacts, most ERP waveforms showed reasonable morphologies after artifact removal. Figure 1 displays ERP waveforms obtained from multiple electrodes in one subject whose implant was on the left side. Waveforms of the response before (top plots) and after (bottom plots) stimulus artifact removal are shown. Note the difference of the y-axis scale between the top and bottom plots due to the extremely large stimulus artifact in the top plots. In the top plots, artifacts are larger for electrodes closer to the implant side. In the bottom plots, the waveforms demonstrate the typical morphology and scalp topography for the LAEP.

3.1. LAEP adaptation results

The LAEP displayed an adaptation pattern in which the response was the largest for the 1st stimulus and decreased for the rest of the stimuli in the train. Table 2 provides the means and standard deviations of N1 latency, P2 latency, and N1-P2 amplitude for /da/ stimuli and 1 kHz tone bursts. Data evoked by /da/ stimuli in one CI user were not included due to unidentifiable N1 and P2 in the waveform with a poor morphology. Generally, the N1 and P2 latencies evoked by the 1st stimulus were longer and N1-P2 amplitude was larger than those evoked by later stimuli. For /da/ stimuli, the mean N1 and P2 latencies were 113.76 ms and 215.83 ms (respectively) for the 1st stimulus and approximately 110 ms and 195 ms (respectively) for later stimuli in the train. The N1-P2 amplitude was 5.36 μ V for the 1st stimulus and approximately 2.7 μ V for later stimuli in the train. For 1 kHz, the mean N1 and P2 latencies were 120.67 ms and 228.48 ms (respectively) for the 1st stimulus and approximately 105 ms and 208 ms (respectively) for later stimuli in the train. The N1-P2 amplitude was 8.82 μ V for the 1st stimulus and approximately 4.4 μ V for later stimuli in the train.

Figure 2 shows the mean LAEPs evoked by each stimulus in the train for good and moderate-to-poor CI performers. For good CI performers (top left panel), there was strong adaptation to the second /da/ stimulus, after which the responses were quite similar across stimuli. There was little evidence of adaptation to the /da/ stimuli in moderate-to-poor CI performers (top right panel). The LAEP evoked by 1 kHz tone bursts in good CI performers (bottom left panel) also displayed a strong adaptation. The adaptation pattern and amplitude decrement in the LAEP evoked by 1 kHz tone bursts were similar to those in NH subjects in Zhang et al. (2010, see the inset). For moderate-to-poor subjects (bottom right panel), there

was some adaptation for the 1 kHz tone bursts. Good CI performers showed similar amounts of LAEP amplitude decrement for the /da/ and 1 kHz tone bursts while moderate-to-poor CI performers showed less adaptation for the /da/ stimuli than for 1 kHz tone bursts; Good CI performers showed a greater adaptation than moderate-to-poor performers; this difference was more obvious for the /da/ stimuli than for 1 kHz tone bursts. The above findings using the absolute amplitude of the LAEP are consistent with those using a normalized amplitude measure to be provided later.

Figure 3 displays the mean normalized N1-P2 amplitude as a function of stimulus order for /da/ (left panel) and 1 kHz tone bursts (right panel). The data for good CI performers and moderate-to-poor CI performers were separately plotted. The data for NH listeners evoked by 1 kHz from Zhang et al. (2009a) were plotted in the right panel as a reference. The normalized N1-P2 amplitude was calculated by dividing the response amplitude for individual stimulus by the response amplitude for the first stimulus in the train. Data were fit to an inverse first order polynomial curve, with the R^2 values indicating the goodness of fit. The equation describing the N1-P2 adaptation was $y = y_0 + a/x$, in which y was the N1-P2 amplitude variable, y_0 was the y asymptote, x was the stimulus order, and a was the curvature (similar to the slope in linear curve fitting). The parameters of the functions for different subject groups are displayed in Table 3. Note the curve for the LAEP evoked by 1 kHz is similar in good CI performers and NH listeners, indicating that the adaptation pattern was similar in these two groups. The value of y_0 is lower in good CI performers (0.19 for /da/ and 0.15 for 1 kHz) than in moderate-to-poor CI performers (0.55 for /da/ and 0.46 for 1 kHz), suggesting that the amount of adaptation is greater in good CI performers.

Figure 4 shows the mean adaptation index (AI) for good and moderate-to-poor CI subjects. The AI was calculated according to: $AI = 1 - (A_{3-5})/A_1$, with higher values indicating a greater adaptation. A mixed-model two-way RM ANOVA, with stimulus type and subject group as factors, showed a significant effect for subject group ($F_{(1,9)} = 12.73$, $p < 0.05$), but not for stimulus type ($F_{(1,9)} = 1.73$, $p > 0.05$); there were no significant interactions. Further t -tests showed that the mean adaptation index for good CI performers (0.59 for /da/, 0.6 for 1 kHz tone bursts) was significantly higher ($p < 0.05$) than for moderate-to-poor CI performers (0.26 for /da/, 0.4 for 1 kHz tone bursts).

Figure 5 illustrates CI subjects' speech performance as a function of the LAEP adaptation index; the solid lines show linear regressions fit to the data. For the two bilateral CI users, the adaptation indices from both ears were averaged. Speech performance was positively correlated to the LAEP adaptation index for the 1 kHz tone bursts ($r^2 = 0.64$, $F_{(1,9)} = 14.01$, $p < 0.01$), but not for the /da/ stimuli ($r^2 = 0.14$, $F_{(1,8)} = 1.16$, $p > 0.05$).

Figure 6 illustrates the speech perception score and AI as a function of the duration of deafness; the solid lines show linear regressions fit to all the data points except one outlier from a CI user whose duration of deafness is the longest (22 years). The outlier was plotted separately. Although the speech perception score was negatively correlated to the duration of deafness ($R^2 = 0.38$), the correlation did not reach a statistical level ($p = 0.08$). No significant correlation was found between the duration of deafness and LAEP adaptation index, although the trend of a smaller adaptation index for longer duration of deafness can be seen.

3.2. MMN results

Figure 7 shows the CONTROL, DEVIANT, and difference waveforms for all ears from all CI subjects; subjects' speech performance is shown in each panel. The asterisks in some panels indicate that an MMN was observed for these subjects. MMN was observed for 6 out of 12 ears including 5 from good performers and 1 from moderate-to-poor performers. Note

that for subject Sci15CJ (a bilateral good CI user) the MMN was observed in the right ear, but not in the left ear; however, speech performance was measured with both ears available. There was large inter-subject variability for the presence of the MMN. All NH listeners exhibited the MMN.

Figure 8 shows the grand mean ERP waveforms (DEVIANT and CONTROL) and the difference waveform for NH (top), good CI performers (middle), and moderate-to-poor CI performers (bottom). The MMN parameters (onset, offset, and peak) are shown for NH listeners and good CI performers. The 3 types of waveforms (DEVIANT, CONTROL, and difference waveforms) in good CI performers show morphologies that are similar to those in NH listeners. The DEVIANT waveform displayed negative regions compared to the CONTROL waveform. In contrast, the waveforms in moderate-to-poor performers show poor morphologies.

Figure 9 displays the difference waveforms for NH listeners, good CI performers, and moderate-to-poor CI performers. The MMN occurred at approximately 100 to 250 ms after the onset of the deviant stimulus in both CI listeners and good CI performers, with a shorter duration and smaller peak amplitude for the latter group. Moderate-to-poor CI performers did not have obvious MMN.

Table 4 lists the mean and standard deviation of various MMN features, including onset latency and amplitude, offset latency and amplitude, peak latency and amplitude, and MMN duration. Because there was no difference between ears for NH listeners in terms of MMN peak amplitude (left: $M = -1.49 \mu V$, $SD = 0.41$; right: $M = -1.19 \mu V$, $SD = 0.70$; $p > 0.05$) or peak latency (left: $M = 140.02$ ms, $SD = 24.28$; right: $M = 144.11$ ms, $SD = 22.20$; $p > 0.05$), NH data was averaged across ears. The mean peak amplitude of the MMN was $-1.13 \mu V$ in good CI users and $-1.26 \mu V$ in NH listeners. The MMN had a mean peak latency of 148.92 ms in good CI users and 138.04 ms in NH listeners. A student's *t*-test showed no significant difference between good CI performers and NH subjects in terms of MMN onset latency and amplitude, offset latency and amplitude, and peak latency and amplitude ($p > 0.05$). Although the mean MMN duration in good CI good performers (80.46 ms) was shorter than in NH subjects (105.41 ms), the difference was not significant ($p > 0.05$).

4. Discussion

One earlier study by our group first reported the adaptation pattern of the LAEP in CI users (Zhang et al., 2010). The authors reported that the LAEP adaptation evoked by 1 kHz tone bursts appeared to be more prominent in CI users with good speech perception performance than in those with poorer performance, supporting the view that neural adaptation may be one of the neural processes for detecting speech stimuli carrying temporal and spectral changes (Delgutte, 1995). The results of this study showed that the adaptation index of the LAEP evoked by 1 kHz tone bursts was significantly correlated to CI users' speech perception scores. The adaptive pattern of the LAEP in good CI users was similar to that in NH listeners. The adaptive pattern appeared to be deviant from the normal in moderate-to-poor CI users, especially when the LAEP is evoked by /da/ stimuli. The results are generally consistent with those in our prior adaptation paper (Zhang et al., 2009a). In addition, the results also showed that good CI users had an MMN similar to that in NH listeners while the moderate-to-poor CI users had a poor or absent MMN.

4.1. LAEP adaptation

Previous studies with NH listeners have reported that the LAEP response amplitude for the second stimulus within a train was approximately 50–60% less than that for the first stimulus, given a stimulus level of 80 dB SPL and an ISI ~ 1 s (Barry et al., 1992; Budd et

al., 1998; Zhang et al., 2009a). The LAEP amplitude reduction was less obvious when the ISI was longer than 8 to 10 s (Ritter et al., 1968; Zhang et al., 2009b). These studies proposed that the LAEP amplitude reduction was mainly due to neural adaptation and/or refractoriness.

The initial source of neural adaptation in the auditory system involves pre-synaptic neurotransmitter depletion in hair cell-to-nerve fiber synapses, as well as post-synaptic receptor-channel dynamics (Smith, 1977; Smith & Brachman, 1982; Westerman & Smith, 1984; Chimento & Schreiner, 1991; Shore, 1995; Litvak et al., 2003; Loquet et al., 2004http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/

-15http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/

-15http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/

-15http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/

-15http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/

-15http://64.233.167.104/search?q=cache:cF8rUT8x_uIJ:server.oersted.dtu.dk/personal/tda/.downloads/reviewed/ - 15. Central auditory neurons typically display more adaptation than do peripheral auditory neurons (Boettcher et al., 1990; Shore 1995; Babalian et al., 2003). Adaptation in groups of neurons can be reflected in the reduction of AEP amplitude during stimulus repetition (Soucek & Mason, 1992; Thornton & Slaven, 1993; Burkard et al., 1996; Budd et al., 1998). Adaptation for single neurons in the auditory cortex has been significantly correlated to that in gross cortical activities (von der Behrens et al., 2009).

Neural refractoriness may also contribute to the reduction of LAEP amplitude following stimulus repetition. Refractoriness refers to the phenomenon in which a neuron can respond to a stimulus only after a sufficient period of recovery after responding to a preceding stimulus. The refractory time for the LAEP appears much longer than that for individual neurons, which ranges from hundreds of microseconds to hundreds of milliseconds, depending on where the neurons are located in the auditory system (Parham et al., 1996; Parham et al., 1998; Fitzpatrick et al., 1999; Miller et al., 2001). The contribution of refractoriness to the LAEP adaptation pattern may reflect the recovery features of its neural generators, which consist of many neurons (Näätänen & Picton, 1987).

In CI users, the main source of neural adaptation/refractoriness would arise from the retro-cochlear portion of the auditory system, as the implanted electrodes bypass the damaged cochlea. Loquet et al. (2004) reported that single unit neural responses measured at the cochlear nucleus displayed less prominent adaptation when evoked by electric pulses than by acoustic stimuli. Our results found that the pattern and amount of LAEP adaptation in good CI performers were similar to those reported in NH listeners (see Figure 3). Together with previous studies, the present data suggests that neural adaptation/refractoriness in central processing (i.e., at the cortical level), rather than in peripheral processing (i.e., at the auditory nerve or cochlear nucleus level), is important for sound perception with a CI.

The LAEP adaptation pattern was less prominent in moderate-to-poor CI performers, compared to good CI performers, as evidenced in Figure 2–4. In figure 2, the response in good CI performers was maximal for the first stimulus and displayed a strong adaptation to the second stimulus, after which the responses were similar across stimuli. In moderate-to-poor CI performers, the adaptation pattern was less prominent, especially for the /da/ stimuli. In Figure 3, the value of y_0 (the asymptote of the normalized N1-P2 amplitude) is

lower in good CI performers (0.19 for /da/ and 0.15 for 1 kHz) than in moderate-to-poor CI performers (0.55 for /da/ and 0.46 for 1 kHz). In Figure 4, the adaptation index for good CI performers (0.59 for /da/, 0.6 for 1 kHz tone bursts) was significantly higher than for moderate-to-poor CI performers (0.26 for /da/, 0.4 for 1 kHz tone bursts). Figure 2 to 4 suggest that the amount of adaptation is greater in good CI performers than in moderate-to-poor CI performers.

One explanation for less adaptation in moderate-to-poor CI performers than in good CI performers is that neural degeneration may have altered the adaptation/refractory features of neural responses, consistent with results in previous animal models (Abbas, 1984; Zhou et al., 1995). This speculation is also consistent with the trend in Figure 6 that CI users with longer durations of deafness are likely to have poorer speech scores and display less adaptation. An alternative explanation for the poor adaptive pattern in moderate-to-poor CI users is related to the much reduced amplitude of the LAEP evoked by the first stimulus in the train and the lack of further amplitude decreases in the LAEP evoked by later stimuli. According to previous studies, the LAEP evoked by stimuli presented with a long inter-stimulus interval, i.e., the first stimulus in a train, is mainly due to the “non-specific” component generated from regions outside of the auditory cortex, while the LAEP evoked by stimuli at a fast and fixed rate is mainly generated from the auditory cortex and surrounding auditory association areas (Hari et al., 1982; Naatanen & Picton, 1987). The abnormal adaptive patterns in moderate-to-poor CI users may indicate that the “non-specific” component of the LAEP is more compromised than the component in the auditory cortex due to long-term deafness in this subgroup. Further studies will perform source analysis on the LAEP data to test our hypothesis.

The comparison in the LAEP adaptation index between 1 kHz tone and /da/ did not show a statistical difference in moderate-to-poor CI performers due to the large variance of data for /da/ stimuli (see Figure 4). It is possible that the adaptation is stimulus specific if sample size is large. The LAEP adaptation pattern in moderate-to-poor CI performers exhibited a greater deviation from that in good CI performers when evoked by the /da/ stimuli than when evoked by the 1 kHz tone bursts (see Figure 2). This suggests that speech may be processed differently from non-linguistic sounds. Moreover, the brain structure related to adaptation effect for speech stimuli may be more compromised than that for non-linguistic sounds in moderate-to-poor CI performers.

The correlation between the LAEP adaptation index for 1 kHz tone bursts and speech performance was significant and well described by a linear model (Fig. 5), while the correlation between the LAEP adaptation index for the /da/ stimuli and speech performance was not significant. This is somewhat surprising, since the /da/ stimuli would seem to be more relevant to speech perception. This lack of correlation seems to be driven by the large variability in LAEP adaptation index values for the /da/ stimuli in CI users with similarly poor speech performance. Our data agree with previous research suggesting that the normal pattern of neural adaptation may benefit speech perception (Delgutte, 1997). Moreover, our results indicate that LAEP adaptation measures are promising electrophysiological tools that can be used to objectively measure and predict outcomes of implantation.

4.2. MMN results

The mean MMN elicited by the frequency contrast (1 kHz vs. 2 kHz) was smaller for the CI group than for the NH control group. However, inter-subject variability in the MMN data was quite large. In general, the good performers tended to have a larger MMN and moderate-to-poor performers were not likely to have an MMN. There was no significant difference between good CI performers and NH subjects in terms of MMN peak amplitude and latency, onset amplitude and latency, offset amplitude and latency, or MMN duration.

The absent MMNs in moderate-to-poor performers suggest that short-term auditory memory and pre-conscious discrimination capabilities may be compromised in these CI users (to different degrees) due to long-term deafness. Similar findings were also observed in the previous behavioral studies (e.g., Pisoni & Geers, 2000; Lunner, 2003; Pisoni & Cleary, 2003). Pisoni and Geers (2000) found a significant correlation between working memory and measures of spoken language processing in deaf children with cochlear implants. Lunner (2003) also found a significant correlation between cognitive function assessed by tests of working memory and speech recognition in noise in hearing impaired adults with hearing aids. Pisoni and Cleary (2003) found that CI children's behavioral performance for tests assessing working memory was poorer than that in NH peers. Another possible reason for the poor or absent MMNs in moderate-to-poor CI users is that the encoding of stimuli needed for comparison processing is compromised (Titterton et al., 2003).

The present results agree with previous studies showing that good CI performers had similar MMNs as those of NH listeners, and that poor CI performers had small or absent MMN (e.g., Kraus et al., 1993; Ponton et al., 2000; Roman et al., 2005). Some previous studies have found significant correlations between CI speech performance and certain MMN measures such as the duration of the MMN (Singh et al., 2004; Kelly et al., 2005) and the MMN peak latency (Roman et al., 2005), while others have not (Wable et al., 2000). Also, while the MMN can roughly group CI users according to "good" or "poor" speech performance, the MMN does not well-predict individual CI users' speech performance (Groenen et al., 1996; Roman et al., 2005). Groenen et al. (1996) found that group data for three good CI performers exhibited an MMN similar to that in NH listeners, while group data for seven moderate CI performers did not. Analysis of individual data showed an absent MMN for one of the three good CI performers and for all of the moderate CI performers. Singh et al. (2004) was able to record the MMN in 80–85% of good performers and 16–20% of poor performers. Therefore, due to the large variability of the MMN across CI users, group analysis does not provide a complete picture of the data (Roman et al., 2005).

Similar to previous studies, we found limitations to the diagnostic value, predictive power and general feasibility of the MMN for CI users. First, the difference waveforms were much noisier in CI users than in NH listeners, even when responses from 9 electrodes in the fronto-central area were averaged. The noise in the difference waveform worsens after performing the waveform subtraction procedure used to derive the MMN. Second, although the MMN can coarsely group CI users according to moderate-to-poor or good speech performance, it does not well predict individual CI users' speech performance. Third, because most moderate-to-poor CI performers and even some good CI performers (Groenen et al., 1996; Kelly et al., 2005) do not exhibit MMNs, it is difficult to establish a clinically meaningful correlation between MMN measures and speech perception scores. Fourth, a large amount of time is required to measure the MMN, due to the large number of trials, and the different stimuli (deviant, standard, control). Recordings from CI subjects require an even greater number of trials due to the noisier data, relative to NH subjects. The lengthy recording procedure makes the MMN particularly difficult for pediatric CI users, who may not be willing to participate for such long periods of time. Before the MMN can be a viable clinical tool in assessing auditory memory and discrimination, these many limitations must be addressed.

4.3. LAEP adaptation vs. MMN measures

The MMN reflects short term memory trace, its measure more likely serves as an index for the performance of CI users at an auditory cognitive level. In contrast, the LAEP adaptation more likely serves as an index for the electrophysiological response of the central auditory system. Our finding of less prominent LAEP adaptation and an absent MMN in moderate-to-poor CI users suggested that long-term deafness can cause damages in the auditory

system at both auditory cortical level and cognitive level. This conclusion is consistent with the findings in other studies. Previous studies suggested that reorganization of the auditory cortex is a very common phenomenon in human subjects with hearing impairments and deafened animals (Lee et al., 2003; Sharma et al., 2007; Rajan & Irvine, 2010). Performance on cognitive tasks, which is one of the most important factors affecting post-CI speech perception scores, was shown to be poorer in CI users compared to NH peers (Pisoni & Cleary, 2003; Zeng, 2004; Wass et al., 2008).

Both LAEP adaptation measures and MMNs may be clinically useful for CI users. For instance, monitoring brain plasticity after cochlear implantation may help guide CI processors parameter settings, thereby improving speech perception. These objective measures may also help guide aural rehabilitation, e.g., identifying pre-attentive contrasts to be used in auditory training (Tremblay et al., 1998; Sharma et al., 2002). Especially for poor CI performers, intensive auditory training has been shown to significantly (and sometimes sharply) improve speech understanding (e.g., Fu et al., 2005). It is useful to know what training materials and methods are most effective; the LAEP adaptation and MMN measures may provide objective means with which to evaluate different rehabilitation approaches.

Based on the present results, we believe that the LAEP adaptation measure is preferable to the MMN for indicating CI users' speech performance, for a number of reasons. First, the LAEP adaptation measures evaluate "real" auditory responses, rather than derived responses. Second, the LAEP adaptation measure does not involve a waveform subtraction process, thereby avoiding increased noise. Third, we were able to calculate an LAEP adaptation index with high confidence in all but one subject. In contrast, we observed the MMN to be present only in (roughly) half of CI subjects, most of whom were good performers. Thus, the LAEP adaptation measure seems to be more sensitive than the MMN measure, consistent with previous studies (e.g., Hoshiyama et al., 2007). Fourth, there was a significant correlation between the LAEP adaptation index and speech performance. The lack of correlation between MMNs and speech performance was largely driven by the fact that moderate-to-poor CI performers are not likely to exhibit an MMN.

Our preference for LAEP adaptation measures over the MMN for clinical use in CI users is consistent with a recent thought regarding the utility of these objective measures in clinical settings. May & Tiitinen (2010) recently suggested that the MMN is valuable in terms of developing models of auditory information processing, and that the oddball paradigm might not be needed to study auditory processing in the cortex, as revealed by neural adaption and spatial representation. They propose using conventional, high-quality N1 measurements, which might be beneficial in the development of clinical, non-invasive objective measures. We believe the present study contributes strongly toward developing useful clinical tools to objectively measure brain responses to sound in CI users.

4.4. Limitations and future studies

There are some limitations in this study. First, the control group aged 20–30 years while the CI group aged 34–72 years. Although the current study provides the basic information of differences between abnormal and normal patterns of LAEP adaptation, age-matched control subjects should be used in future studies to rule out age effects. Second, the 80% cut-off for good vs. moderate-to-poor CI performers was somewhat arbitrary. The advantage of using this cut-off in this study is that the same number of subjects (5) was included in each group. It is more reasonable to perform statistical analysis on the speech perception scores, however, to separate subjects into different groups in future studies with a much larger sample size. Third, the comparison of LAEP adaptation data for the /da/ stimuli between CI users and NH listeners was not performed because data in NH listeners were neither available in the literature nor collected in this study. Finally, there was no significant

correlation between the adaptation index for /da/ and speech perception, largely due to the large variability in a small sample size of subjects. Further studies will increase the sample size and use different types of speech stimuli to determine the correlation between speech perception and adaptation index for speech stimuli.

Acknowledgments

The authors thank all participants in this research. The authors also thank John J. Galvin III for editorial assistance. This project is partially sponsored by National Institute of Health (NIH 1R15DC011004-01).

List of Abbreviations

AEP	Auditory Evoked Potential
AI	Adaptation Index
CI	Cochlear Implant
EEG	Electro-encephalography
EOG	Electro-oculogram
ERP	Event-Related Potential
fMRI	Functional Magnetic Resonance Imaging
ICA	Independent Component Analysis
ISI	Inter-Stimulus Interval
ITI	Inter-Train Interval
LAEP	Late Auditory Evoked Potential
MEG	Magnetoencephalography
MMN	Mismatch Negativity
NH	Normal Hearing
RM ANOV	Repeated-Measures Analysis of Variance
SNR	Signal-to-Noise Ratio
SSA	Stimulus-Specific Adaptation

References

- Abbas PJ. Long-term adaptation in hearing impaired ears. *Hear Res.* 1984; 14:29–38. [PubMed: 6746419]
- Anderson LA, Christianson GB, Linden JF. Stimulus-specific adaptation occurs in the auditory thalamus. *J Neurosci.* 2009; 29:7359–7363. [PubMed: 19494157]
- Babalian AL, Ryugo DK, Rouiller EM. Discharge properties of identified cochlear nucleus neurons and auditory nerve fibers in response to repetitive electrical stimulation of the auditory nerve. *Exp Brain Res.* 2003; 153:452–460. [PubMed: 12955378]
- Baldeweg T. Repetition effects to sounds: Evidence for predictive coding in the auditory system. *Trends Cogn Sci.* 2006; 10:93–94. [PubMed: 16460994]
- Barry RJ, Cocker KI, Anderson JW, Gordon E, Rennie C. Does the N100 evoked potential really habituate? evidence from a paradigm appropriate to a clinical setting. *Int J Psychophysiol.* 1992; 13:9–16. [PubMed: 1522037]
- Boettcher FA, Salvi RJ, Saunders SS. Recovery from short-term adaptation in single neurons in the cochlear nucleus. *Hear Res.* 1990; 48:125–144. [PubMed: 2249955]

- Bottcher-Gandor C, Ullsperger P. Mismatch negativity in event-related potentials to auditory stimuli as a function of varying interstimulus interval. *Psychophysiology*. 1992; 29:546–550. [PubMed: 1410183]
- Bourbon WT, Will KW, Gary HE Jr, Papanicolaou AC. Habituation of auditory event-related potentials: A comparison of self-initiated and automated stimulus trains. *Electroencephalogr Clin Neurophysiol*. 1987; 66:160–166. [PubMed: 2431880]
- Budd TW, Barry RJ, Gordon E, Rennie C, Michie PT. Decrement of the N1 auditory event-related potential with stimulus repetition: Habituation vs. refractoriness. *Int J Psychophysiol*. 1998; 31:51–68. [PubMed: 9934621]
- Burkard R, McGee J, Walsh EJ. Effects of stimulus rate on the feline brain-stem auditory evoked response during development. I. peak latencies. *J Acoust Soc Am*. 1996; 100:978–990. [PubMed: 8759951]
- Butler RA. Effect of changes in stimulus frequency and intensity on habituation of the human vertex potential. *J Acoust Soc Am*. 1968; 44:945–950. [PubMed: 5683660]
- Chimento TC, Schreiner CE. Adaptation and recovery from adaptation in single fiber responses of the cat auditory nerve. *J Acoust Soc Am*. 1991; 90:263–273. [PubMed: 1652600]
- Davis H, Zerlin S. Acoustic relations of the human vertex potential. *J Acoust Soc Am*. 1966; 39:109–116. [PubMed: 5904525]
- Debener S, Hine J, Bleack S, Eyles J. Source localization of auditory evoked potentials after cochlear implantation. *Psychophysiology*. 2008; 45:20–24. [PubMed: 17910729]
- Delgutte, B. Auditory Neural Processing of Speech. In: Hardcastle, WJ.; Laver, J., editors. *The Handbook of Phonetic Sciences*. Oxford: Blackwell; 1997. p. 507-538.
- Delorme A, Makeig S. EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal J Neurosci Methods*. 2004; 134:9–21.
- Doeller CF, Opitz B, Mecklinger A, Krick C, Reith W, Schroger E. Prefrontal cortex involvement in preattentive auditory deviance detection: Neuroimaging and electrophysiological evidence. *NeuroImage*. 2003; 20:1270–1282. [PubMed: 14568496]
- Fitzpatrick DC, Kuwada S, Kim DO, Parham K, Batra R. Responses of neurons to click-pairs as simulated echoes: Auditory nerve to auditory cortex. *J Acoust Soc Am*. 1999; 106:3460–3472. [PubMed: 10615686]
- Friston K. Functional integration and inference in the brain. *Prog Neurobiol*. 2002; 68:113–143. [PubMed: 12450490]
- Fruhstorfer H. Habituation and dishabituation of the human vertex response. *Electroencephalogr Clin Neurophysiol*. 1971; 30:306–312. [PubMed: 4103502]
- Fruhstorfer H, Soveri P, Jarvilehto T. Short-term habituation of the auditory evoked response in man. *Electroencephalogr Clin Neurophysiol*. 1970; 28:153–161. [PubMed: 4189933]
- Fu QJ, Nogaki G, Galvin JJ 3rd. Auditory training with spectrally shifted speech: Implications for cochlear implant patient auditory rehabilitation. *J Assoc Res Otolaryngol*. 2005; 6:180–189. [PubMed: 15952053]
- Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: A review of underlying mechanisms. *Clin Neurophysiol*. 2009; 120:453–463. [PubMed: 19181570]
- Garrido MI, Friston KJ, Kiebel SJ, Stephan KE, Baldeweg T, Kilner JM. The functional anatomy of the MMN: A DCM study of the roving paradigm. *NeuroImage*. 2008; 42:936–944. [PubMed: 18602841]
- Giard MH, Perrin F, Pernier J, Bouchet P. Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. *Psychophysiology*. 1990; 27:627–640. [PubMed: 2100348]
- Gilley PM, Sharma A, Dorman M, Finley CC, Panch AS, Martin K. Minimization of cochlear implant stimulus artifact in cortical auditory evoked potentials. *Clin Neurophysiol*. 2006; 117:1772–1782. [PubMed: 16807102]
- Green KM, Bhatt YM, Mawman DJ, O'Driscoll MP, Saeed SR, Ramsden RT, et al. Predictors of audiological outcome following cochlear implantation in adults. *Cochlear Implants Int*. 2007; 8:1–11. [PubMed: 17479968]

- Groenen P, Snik A, van den Broek P. On the clinical relevance of mismatch negativity: Results from subjects with normal hearing and cochlear implant users. *Audiol Neurotol*. 1996; 1:112–124. [PubMed: 9390795]
- Hagemann D, Naumann E, Thayer JF. The quest for the EEG reference revisited: A glance from brain asymmetry research. *Psychophysiology*. 2001; 38:847–857. [PubMed: 11577908]
- Hari R, Kaila K, Katila T, Tuomisto T, Varpula T. Interstimulus interval dependence of the auditory vertex response and its magnetic counterpart: Implications for their neural generation. *Electroencephalogr Clin Neurophysiol*. 1982; 54:561–569. [PubMed: 6181979]
- Hari R, Rif J, Tiihonen J, Sams M. Neuromagnetic mismatch fields to single and paired tones. *Electroencephalogr Clin Neurophysiol*. 1992; 82:152–154. [PubMed: 1370785]
- Hoppe U, Rosanowski F, Iro H, Eysholdt U. Loudness perception and late auditory evoked potentials in adult cochlear implant users. *Scand Audiol*. 2001; 30:119–125. [PubMed: 11409789]
- Hoshiyama M, Okamoto H, Kakigi R. Priority of repetitive adaptation to mismatch response following indiscriminable auditory stimulation: A magnetoencephalographic study. *Eur J Neurosci*. 2007; 25:854–862. [PubMed: 17328780]
- Jaaskelainen IP, Ahveninen J, Bonmassar G, Dale AM, Ilmoniemi RJ, Levanen S, et al. Human posterior auditory cortex gates novel sounds to consciousness. *Proc Natl Acad Sci U S A*. 2004; 101:6809–6814. [PubMed: 15096618]
- Jacobsen T, Schroger E, Horenkamp T, Winkler I. Mismatch negativity to pitch change: Varied stimulus proportions in controlling effects of neural refractoriness on human auditory event-related brain potentials. *Neurosci Lett*. 2003; 344:79–82. [PubMed: 12782332]
- Johnson EK. Infants use prosodically conditioned acoustic-phonetic cues to extract words from speech. *J Acoust Soc Am*. 2008; 123:EL144–8. [PubMed: 18537301]
- Johnson KL, Nicol TG, Kraus N. Brain stem response to speech: a biological marker of auditory processing. *Ear Hear*. 2005; 26:424–434. [PubMed: 16230893]
- Kelly AS, Purdy SC, Thorne PR. Electrophysiological and speech perception measures of auditory processing in experienced adult cochlear implant users. *Clin Neurophysiol*. 2005; 116:1235–1246. [PubMed: 15978485]
- Kraus N, Micco AG, Koch DB, McGee T, Carrell T, Sharma A, et al. The mismatch negativity cortical evoked potential elicited by speech in cochlear-implant users. *Hear Res*. 1993; 65:118–124. [PubMed: 8458744]
- Kraus N, McGee T, Sharma A, Carrell T, Nicol T. Mismatch negativity event-related potential elicited by speech stimuli. *Ear Hear*. 1992; 13(3):158–164. [PubMed: 1397755]
- Lang AH, Eerola O, Korpilahti P, Holopainen I, Salo S, Aaltonen O. Practical issues in the clinical application of mismatch negativity. *Ear Hear*. 1995; 16:118–130. [PubMed: 7774765]
- Lee JS, Lee DS, Oh SH, Kim CS, Kim JW, Hwang CH, et al. PET evidence of neuroplasticity in adult auditory cortex of postlingual deafness. *J Nucl Med*. 2003; 44:1435–1439. [PubMed: 12960189]
- Levanen S, Ahonen A, Hari R, McEvoy L, Sams M. Deviant auditory stimuli activate human left and right auditory cortex differently. *Cereb Cortex*. 1996; 6:288–296. [PubMed: 8670657]
- Litvak LM, Smith ZM, Delgutte B, Eddington DK. Desynchronization of electrically evoked auditory-nerve activity by high-frequency pulse trains of long duration. *J Acoust Soc Am*. 2003; 114:2066–2078. [PubMed: 14587606]
- Loquet G, Pelizzone M, Valentini G, Rouiller EM. Matching the neural adaptation in the rat ventral cochlear nucleus produced by artificial (electric) and acoustic stimulation of the cochlea. *Audiol Neurotol*. 2004; 9:144–159. [PubMed: 15084819]
- Lunner T. Cognitive function in relation to hearing aid use. *Int J Audiol*. 2003; 42(Suppl 1):S49–58. [PubMed: 12918610]
- May PJ, Tiitinen H. Mismatch negativity (MMN), the deviance-elicited auditory deflection, explained. *Psychophysiology*. 2010; 47:66–122. [PubMed: 19686538]
- McNeill C, Sharma M, Purdy SC, Agung K. Cortical auditory evoked responses from an implanted ear after 50 years of profound unilateral deafness. *Cochlear Implants Int*. 2007; 8:189–199. [PubMed: 18033739]
- Megela AL, Teyler TJ. Habituation and the human evoked potential. *J Comp Physiol Psychol*. 1979; 93:1154–1170. [PubMed: 521525]

- Miller CA, Abbas PJ, Robinson BK. Response properties of the refractory auditory nerve fiber. *J Assoc Res Otolaryngol*. 2001; 2:216–232. [PubMed: 11669395]
- Naatanen R, Paavilainen P, Reinikainen K. Do event-related potentials to infrequent decrements in duration of auditory stimuli demonstrate a memory trace in man? *Neurosci Lett*. 1989; 107:347–352. [PubMed: 2616046]
- Naatanen R, Picton T. The N1 wave of the human electric and magnetic response to sound: A review and an analysis of the component structure. *Psychophysiology*. 1987; 24:375–425. [PubMed: 3615753]
- Naatanen R, Syssoeva O, Takegata R. Automatic time perception in the human brain for intervals ranging from milliseconds to seconds. *Psychophysiology*. 2004; 41:660–663. [PubMed: 15189489]
- Naatanen R, Winkler I. The concept of auditory stimulus representation in cognitive neuroscience. *Psychol Bull*. 1999; 125:826–859. [PubMed: 10589304]
- Naatanen R, Jacobsen T, Winkler I. Memory-based or afferent processes in mismatch negativity (MMN): A review of the evidence. *Psychophysiology*. 2005; 42:25–32. [PubMed: 15720578]
- Naatanen R, Paavilainen P, Rinne T, Alho K. The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clin Neurophysiol*. 2007; 118:2544–2590. [PubMed: 17931964]
- Nikjeh DA, Lister JJ, Frisch SA. Preattentive cortical-evoked responses to pure tones, harmonic tones, and speech: Influence of music training. *Ear Hear*. 2009; 30:432–446. [PubMed: 19494778]
- Opitz B, Rinne T, Mecklinger A, von Cramon DY, Schroger E. Differential contribution of frontal and temporal cortices to auditory change detection: FMRI and ERP results. *NeuroImage*. 2002; 15:167–174. [PubMed: 11771985]
- Parham K, Zhao HB, Kim DO. Responses of auditory nerve fibers of the unanesthetized decerebrate cat to click pairs as simulated echoes. *J Neurophysiol*. 1996; 76:17–29. [PubMed: 8836205]
- Parham K, Zhao HB, Ye Y, Kim DO. Responses of anteroventral cochlear nucleus neurons of the unanesthetized decerebrate cat to click pairs as simulated echoes. *Hear Res*. 1998; 125:131–146. [PubMed: 9833967]
- Pisoni DB, Geers AE. Working memory in deaf children with cochlear implants: correlations between digit span and measures of spoken language processing. *Ann Otol Rhinol Laryngol Suppl*. 2000; 185:92–3. [PubMed: 11141023]
- Pisoni DB, Cleary M. Measures of working memory span and verbal rehearsal speed in deaf children after cochlear implantation. *Ear Hear*. 2003; 24:106S–20S. [PubMed: 12612485]
- Petermann M, Kummer P, Burger M, Lohscheller J, Eysholdt U, Döllinger M. Statistical detection and analysis of mismatch negativity derived by a multi-deviant design from normal hearing children. *Hear Res*. 2009; 247:128–36. [PubMed: 19071204]
- Ponton CW, Eggermont JJ, Don M, Waring MD, Kwong B, Cunningham J, et al. Maturation of the mismatch negativity: Effects of profound deafness and cochlear implant use. *Audiol Neurotol*. 2000; 5:167–185. [PubMed: 10859411]
- Prosser S, Arslan E, Michelini S. Habituation and rate effect in the auditory cortical potentials evoked by trains of stimuli. *Arch Otorhinolaryngol*. 1981; 233:179–187. [PubMed: 7316876]
- Rajan R, Irvine DR. Severe and extensive neonatal hearing loss in cats results in auditory cortex plasticity that differentiates into two regions. *Eur J Neurosci*. 2010; 31:1999–2013. [PubMed: 20497473]
- Rinne T, Alho K, Ilmoniemi RJ, Virtanen J, Naatanen R. Separate time behaviors of the temporal and frontal mismatch negativity sources. *NeuroImage*. 2000; 12:14–19. [PubMed: 10875898]
- Ritter W, Vaughan HG Jr, Costa LD. Orienting and habituation to auditory stimuli: A study of short term changes in average evoked responses. *Electroencephalogr Clin Neurophysiol*. 1968; 25:550–556. [PubMed: 4178749]
- Roman S, Canevet G, Marquis P, Triglia JM, Liegeois-Chauvel C. Relationship between auditory perception skills and mismatch negativity recorded in free field in cochlear-implant users. *Hear Res*. 2005; 201:10–20. [PubMed: 15721556]

- Rosburg T, Haueisen J, Kreitschmann-Andermahr I. The dipole location shift within the auditory evoked neuromagnetic field components N100m and mismatch negativity (MMNm). *Clin Neurophysiol.* 2004; 115:906–913. [PubMed: 15003772]
- Sharma A, Dorman MF, Spahr AJ. Rapid development of cortical auditory evoked potentials after early cochlear implantation. *Neuroreport.* 2002; 13:1365–1368. [PubMed: 12151804]
- Sharma A, Gilley PM, Dorman MF, Baldwin R. Deprivation-induced cortical reorganization in children with cochlear implants. *Int J Audiol.* 2007; 46:494–499. [PubMed: 17828665]
- Shore SE. Recovery of forward-masked responses in ventral cochlear nucleus neurons. *Hear Res.* 1995; 82:31–43. [PubMed: 7744711]
- Singh S, Liasis A, Rajput K, Towell A, Luxon L. Event-related potentials in pediatric cochlear implant patients. *Ear Hear.* 2004; 25:598–610. [PubMed: 15604920]
- Smith RL. Short-term adaptation in single auditory nerve fibers: Some poststimulatory effects. *J Neurophysiol.* 1977; 40:1098–1111. [PubMed: 903799]
- Smith RL, Brachman ML. Adaptation in auditory-nerve fibers: A revised model. *Biol Cybern.* 1982; 44:107–120. [PubMed: 7115787]
- Soucek S, Mason SM. Effects of adaptation on electrocochleography and auditory brain-stem responses in the elderly. *Scand Audiol.* 1992; 21:149–152. [PubMed: 1439500]
- Sussman E, Winkler I. Dynamic sensory updating in the auditory system. *Brain Res Cogn Brain Res.* 2001; 12:431–439. [PubMed: 11689303]
- Thornton AR, Slaven A. Auditory brainstem responses recorded at fast stimulation rates using maximum length sequences. *Br J Audiol.* 1993; 27:205–210. [PubMed: 8241969]
- Titterton J, Watson D, Toner JG, Henry A. What can the mismatch negativity (MMN) tell us about short-term auditory sensory memory function in cochlear implanted children? *Cochlear Implants Int.* 2003; 4(Suppl 1):70–72. [PubMed: 18792185]
- Tremblay K, Kraus N, McGee T. The time course of auditory perceptual learning: Neurophysiological changes during speech-sound training. *Neuroreport.* 1998; 9:3557–3560. [PubMed: 9858359]
- Ulanovsky N, Las L, Nelken I. Processing of low-probability sounds by cortical neurons. *Nat Neurosci.* 2003; 6:391–398. [PubMed: 12652303]
- Ulanovsky N, Las L, Farkas D, Nelken I. Multiple time scales of adaptation in auditory cortex neurons. *J Neurosci.* 2004; 24:10440–10453. [PubMed: 15548659]
- Valente M, Potts LG, Valente M. Differences and intersubject variability of loudness discomfort levels measured in sound pressure level and hearing level for TDH-50P and ER-3A earphones. *J Am Acad Audiol.* 1997; 8:59–67. [PubMed: 9046070]
- von der Behrens W, Bauerle P, Kossel M, Gaese BH. Correlating stimulus-specific adaptation of cortical neurons and local field potentials in the awake rat. *J Neurosci.* 2009; 29:13837–13849. [PubMed: 19889995]
- Wable J, van den Abbeele T, Gallego S, Frachet B. Mismatch negativity: A tool for the assessment of stimuli discrimination in cochlear implant subjects. *Clin Neurophysiol.* 2000; 111:743–751. [PubMed: 10727926]
- Walton JP, Frisina RD, Meierhans LR. Sensorineural hearing loss alters recovery from short-term adaptation in the c57bl/6 mouse. *Hear Res.* 1995; 88:19–26. [PubMed: 8575994]
- Wass M, Ibertsson T, Lyxell B, Sahlen B, Hallgren M, Larsby B, et al. Cognitive and linguistic skills in Swedish children with cochlear implants - measures of accuracy and latency as indicators of development. *Scand J Psychol.* 2008; 49:559–576. [PubMed: 18826424]
- Westerman LA, Smith RL. Rapid and short-term adaptation in auditory nerve responses. *Hear Res.* 1984; 15:249–260. [PubMed: 6501113]
- Zhang F, Eliassen J, Anderson J, Scheifele P, Brown D. The time course of the amplitude and latency in the auditory late response evoked by repeated tone bursts. *J Am Acad Audiol.* 2009a; 20:239–250. [PubMed: 19927696]
- Zhang F, Samy RN, Anderson JM, Houston L. Recovery function of the late auditory evoked potential in cochlear implant users and normal-hearing listeners. *J Am Acad Audiol.* 2009b; 20:397–408. [PubMed: 19928394]

- Zhang F, Anderson J, Samy R, Houston L. The adaptation pattern of the late auditory evoked potential elicited by repeated stimuli in cochlear implant users. *Int J Audiol*. 2010; 49:277–285. [PubMed: 20151878]
- Zhang X, Carney LH. Analysis of models for the synapse between the inner hair cell and the auditory nerve. *J Acoust Soc Am*. 2005; 118:1540–1553. [PubMed: 16240815]
- Zeng FG. Trends in cochlear implants. *Trends Amplif*. 2004; 8:1–34. [PubMed: 15247993]
- Zhou R, Abbas PJ, Assouline JG. Electrically evoked auditory brainstem response in peripherally myelin-deficient mice. *Hear Res*. 1995; 88:98–106. [PubMed: 8576009]

Figure 1.

Waveforms obtained from multiple electrodes in one CI user (S3) whose implant was on the left side. Waveforms of the response before (top plots) and after (bottom plots) stimulus artifact removal are shown. Note the difference of the y-axis scale between the top and bottom plots due to the extremely large stimulus artifact in the top plots.

Figure 2.

The mean LAEPs (across subjects) evoked by each stimulus (/da/ and 1 kHz) in the train for good CI performers (speech scores $\geq 80\%$ correct) and moderate-to-poor CI performers (speech scores $< 80\%$ correct). The different traces represent responses to the different stimuli in the train. In the plot of the LAEPs evoked by 1 kHz tone bursts in good CI performers (bottom left), traces for NH listeners (the LAEP evoked by the first stimulus and the average LAEP evoked by later stimuli in the train) available in the literature are shown at the inset (from Zhang et al., 2009a).

Figure 3.

The mean normalized N1-P2 amplitude as a function of stimulus order for /da/ and 1 kHz tone bursts. The normalized N1-P2 amplitude was calculated by dividing the response amplitude for individual stimulus by the response amplitude for the first stimulus in the train. The data were fit to an inverse first order polynomial curve with the equation: $y = y_0 + a/x$. The R^2 values and p values were indicated in the plots. The data for NH listeners were from our previous paper (Zhang et al., 2009a).

Figure 4. Mean LAEP adaptation index values for good and moderate-to-poor CI performers. The error bars show one standard deviation of the mean.

Figure 5. Individual CI subjects' speech performance as a function of LAEP adaptation index. The top panel shows data for the /da/ stimuli and the bottom panel shows data for the 1 kHz tone bursts. The solid lines represent linear regressions fit to the data. The R^2 value for each fit is shown in each panel.

Figure 6.

Individual CI subjects' speech performance and LAEP adaptation index as a function of the duration of deafness. The solid lines represent linear regressions fit to all data points except one outlier from a CI user who has the longest duration of deafness (22 years). The R^2 value for each fit is shown in each panel.

Figure 7.

The CONTROL, DEVIANT, and difference waveforms from all CI users (10 CI users and 12 ears); speech scores for each subjects are shown in each panel. The MMN was observed in 6 out of 12 ears (5 ears from 5 good performers and 1 ear from 5 moderate-to-poor performers), as indicated by the asterisks.

Figure 8.

The grand mean of ERP waveforms (solid lines) and difference waveforms (dashed lines) for NH listeners, good CI performers, and poor CI performers. The difference waveforms were derived by subtracting the CONTROL waveform from the DEVIANT waveform. The MMN parameters (on, off, and peak) are indicated in the plot for NH listeners and good CI performers.

Figure 9.

The grand mean of difference waveforms for NH listeners, good CI performers, and poor CI performers.

Table 1

CI subject demographics.

Subject	Gender	Age (years)	Ear implanted	Duration of deafness (years)	Etiology	CI experience (years)	Speech processing strategy
S1	F	63	Right	9	Unknown	2	ACE
S2	M	62	Right	8	Unknown	1	ACE
S3	F	34	Left	5	Autoimmune	2	ACE
S4	F	48	Left	7	Unknown	3	ACE
S5	F	72	Right	1	Meniere's	2.5	ACE
S6	M	72	Left	18	Unknown	1	ACE
S7	F	42	Both	10	Hereditary	Left: 1 Right: 1	ACE
S8	M	43	Left	10	Hereditary	1.5	ACE
S9	M	41	Left	22	Unknown	4.5	ACE
S10	F	58	Both	6	Hereditary	Left: 3 Right: 4.5	CIS

Table 2

The means and standard deviations (in parentheses) of LAEP measures for /da/ stimuli and 1 kHz tone bursts.

Stimulus order	/da/				1 kHz			
	N1 latency (ms)	P2 latency (ms)	N1-P2 amplitude (μV)	N1 latency (ms)	P2 latency (ms)	N1-P2 amplitude (μV)	N1-P2 amplitude (μV)	
1st	113.76 (18.94)	215.83 (45.24)	5.36 (3.03)	120.67 (17.53)	228.48 (28.05)	8.82 (3.34)	8.82 (3.34)	
2nd	104.53 (18.38)	195.25 (28.54)	3.03 (1.30)	104.62 (14.28)	213.07 (21.69)	4.53 (1.96)	4.53 (1.96)	
3rd	110.01 (14.37)	192.45 (21.41)	2.57 (1.52)	101.66 (14.34)	208.90 (22.74)	4.54 (2.47)	4.54 (2.47)	
4th	114.22 (17.32)	201.01 (25.56)	2.34 (1.12)	106.39 (18.49)	204.25 (18.34)	3.79 (1.42)	3.79 (1.42)	
5th	115.80 (22.50)	192.84 (11.92)	2.61 (1.15)	104.85 (17.52)	207.24 (16.05)	4.06 (1.82)	4.06 (1.82)	

Table 3

The parameters of the inverse first order polynomial curve for the normalized N1-P2 vs. stimulus order function.

	<i>/da/</i>		1 kHz tone	
	<i>yo</i>	<i>a</i>	<i>yo</i>	<i>a</i>
Moderate-to poor CI	0.55	0.40	0.46	0.51
Good CI	0.19	0.78	0.15	0.81
NH listeners			0.21	0.66

The best-fit equation describing the N1-P2 adaptation was $y = yo + a/x$, in which y was the N1-P2 amplitude variable, yo was the y asymptote, x was the stimulus order, and a was the curvature.

Table 4

The means and standard deviations (in parentheses) of MMN onset latency and amplitude, offset latency and amplitude, peak latency and amplitude, and duration.

	Onset latency (ms)	Onset amplitude (μV)	Offset latency (ms)	Offset amplitude (μV)	Peak latency (ms)	Peak amplitude (μV)	Duration (ms)
CI good performer (n = 5)	114.47 (26.44)	-0.34 (0.11)	194.94 (28.27)	0.07 (0.12)	148.92 (23.98)	-1.13 (0.52)	80.46 (39.09)
NH controls (n = 11)	87.76 (15.43)	-0.25 (0.22)	193.17 (32.96)	-0.07 (0.10)	138.04 (20.25)	-1.26 (0.47)	105.41 (28.22)