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Rate of Neural Recovery in Implanted Children with Auditory Neuropathy Spectrum Disorder

Susan L. Fulmer, MD1, Christina L. Runge, PhD1, Jamie W. Jensen, AuD1, and David R. Friedland, MD, PhD1

Abstract

Objectives. The study objectives were to compare the rate of neural recovery and speech perception performance in children with auditory neuropathy spectrum disorder (ANSD) and children with sensorineural hearing loss (SNHL) from other etiologies.

Study Design. Cohort study.

Setting. Academic hospital and cochlear implant center.

Subjects and Methods. Ten children with ANSD were matched based on type of implant and age at implantation with peers diagnosed with SNHL. Electrically evoked compound action potential (ECAP) recovery functions were obtained to measure neural refractory behaviors in response to stimulation from the cochlear implant. Speech perception performance was measured using speech recognition thresholds (SRTs) for monosyllable and spondee word stimuli. These outcome measures were compared between groups.

Results. There was no difference in average recovery function exponent in children with ANSD compared to children with SNHL. Similarly, there were no differences in average SRTs in quiet and in noise in children with ANSD compared to children with SNHL. Relationships between SRT and recovery rate were not present within groups or for all subjects for SRT in quiet, but a significant relationship was found for all subjects for SRT in noise (P = .04).

Conclusions. Dyssynchronous neural activity in ANSD may affect temporal encoding of electrical stimulation from a cochlear implant. As a group, children with ANSD did not demonstrate slower neural recovery compared to those with SNHL, but there was slower neural recovery observed for some subjects. The utility of ECAP recovery functions on optimizing the stimulation rate for individual patients with ANSD requires further investigation.

Keywords

otology/neurotology, cochlear implants, pediatric otolaryngology

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Auditory neuropathy spectrum disorder (ANSD) is a type of hearing loss that is characterized by disruption of the synchronous neural responses of the auditory pathway with present outer hair cell function. Clinical diagnosis of ANSD specifies present otoacoustic emissions and/or cochlear microphonic responses and absent or impaired auditory brainstem responses.1

There is considerable variability in the causes and sites of lesion in ANSD, which likely contribute to the wide range of audiologic findings in these patients.1,2 There are several potential sites of lesion, including presynaptic (ie, inner hair cell) and postsynaptic (ie, dendritic or axonal) anomalies that result in impairments in temporal synchrony.1,3-8

Psychophysically, patients with ANSD present with varying severities of temporal impairment that affect speech perception, particularly in the presence of background noise.9-11

Currently, the site of lesion are rarely able to be localized in a given case of ANSD, which introduces challenges in the optimization of treatment approaches such as amplification and cochlear implantation. Amplification is useful in some patients with ANSD, but many require cochlear implantation.12-14 Although cochlear implants are effective in many children with ANSD, optimizing programming parameters is still under investigation.

Because ANSD is characterized by temporal impairment, there is question as to whether assessing temporal response behaviors from the auditory nerve may assist in optimizing cochlear implant programming parameters for children with ANSD.
ANSD, such as stimulation rate. For example, a study by Peterson and colleagues suggested that speech perception may improve with a slowed stimulation rate in children with ANSD. Objective measures such as the electrically evoked compound action potential (ECAP) are often used to set programming parameters in young children, particularly the upper level of loudness. The ECAP is the response from a population of electrically stimulated auditory nerve fibers and can be recorded in a clinical setting using the cochlear implant device.

The purpose of this study was to objectively measure the neural rate of recovery or ECAP recovery in children with ANSD and to compare it to children with sensorineural hearing loss (SNHL) from other etiologies. It was hypothesized that neural recovery will be slower for children with ANSD than for those with SNHL. In addition, the relationship between neural recovery and speech perception abilities in quiet and noise was examined. This objective measure may eventually be used to optimize cochlear implant settings and/or to help with predicting success with a cochlear implant in children with ANSD.

**Subjects and Methods**

**Subjects**

Subjects were recruited from the population of implanted children followed by the Koss Cochlear Implant Program at the Medical College of Wisconsin. Ten implanted children with ANSD participated in the study, and 10 implanted children with SNHL were matched to each subject with ANSD based on type of implant, age at implantation, and age at testing. The ANSD group ranged in age from 3 to 17 years, and the SNHL group ranged in age from 3 to 18 years. There were no significant differences in the average age at implantation or the average age at testing between the 2 groups (P = .52 and P = .31, respectively). Subjects’ demographic data are included in Table 1 (ANSD) and Table 2 (SNHL), and the subjects with SNHL were numbered to correspond to the ANSD subjects’ numbers.

**ECAP Recovery Functions**

Two consecutive pulsatile stimuli, a masker and a probe, were presented to assess the rate of recovery of the auditory nerve. The masker pulse was presented first, with the probe pulse following the masker separated by increasing lengths of time, or interpulse intervals (IPIs). The recovery function was derived by comparing the amplitude of the response to the probe stimulus for IPIs from 0.4 to 8.0 milliseconds.

ECAP recovery functions were obtained for each implanted ear using the applicable software for each of the 3 cochlear implant systems: Cochlear Corporation Custom Sound EP 3.0, Advanced Bionics Bionic Ear Data Collection System (BEDCS), and MED-EL Corporation Maestro Auditory Nerve Response Telemetry (ART). All stimuli were presented from the computer through a programming interface and headpiece to stimulate the internal device.

Stimulation level for recording recovery functions was determined by measuring the maximal comfort level (MCL) for each subject. To measure MCL, the stimulation level was gradually increased until the child reported that it was too loud or showed other signs of emerging discomfort (eg, squinting). The stimulus intensity was then reduced to the maximum value that was comfortable. The masker was set at the MCL, and the probe was presented at 80% of the MCL. A mid-range electrode was stimulated, and a response was recorded from an electrode 2 positions apical from the stimulus electrode. The stimulated electrode varied slightly in some cases when electrodes were deactivated or did not generate an ECAP.

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The recovery function was plotted and fit to an exponential rise to a maximum (nonlinear) regression curve using the following equation:
**Otolaryngology–Head and Neck Surgery** 144(2)

**Table 2. Demographic Information for Control Subjects Diagnosed with SNHL**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Implant Type</th>
<th>Ear Implanted</th>
<th>Age at Implantation, y</th>
<th>Age at Testing, y</th>
<th>Preoperative Hearing Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>AB 90K</td>
<td>B</td>
<td>1.7 (R) and 4.9 (L)</td>
<td>7.7</td>
<td>Severe-profound</td>
</tr>
<tr>
<td>S2</td>
<td>Med-El Pulsar</td>
<td>B</td>
<td>1.1 (R)</td>
<td>3.8</td>
<td>Profound</td>
</tr>
<tr>
<td>S3</td>
<td>Med-El Sonata</td>
<td>B</td>
<td>4.8 (R)</td>
<td>5.5</td>
<td>Profound</td>
</tr>
<tr>
<td>S4</td>
<td>AB 90K</td>
<td>R</td>
<td>2.7</td>
<td>8.2</td>
<td>Severe-profound</td>
</tr>
<tr>
<td>S5</td>
<td>AB CII</td>
<td>R</td>
<td>4.2</td>
<td>10.3</td>
<td>Severe-profound</td>
</tr>
<tr>
<td>S6</td>
<td>Nucleus Freedom</td>
<td>L</td>
<td>10.5</td>
<td>11.1</td>
<td>Severe-profound</td>
</tr>
<tr>
<td>S7</td>
<td>AB CII</td>
<td>R</td>
<td>2.6</td>
<td>10.5</td>
<td>Profound</td>
</tr>
<tr>
<td>S8</td>
<td>AB 90K (R), CII (L)</td>
<td>B</td>
<td>2.2 (L) and 6.0 (R)</td>
<td>8.7</td>
<td>Severe</td>
</tr>
<tr>
<td>S9</td>
<td>Med-El Pulsar</td>
<td>R</td>
<td>3.9</td>
<td>6.9</td>
<td>Severe</td>
</tr>
<tr>
<td>S10</td>
<td>Nucleus Freedom</td>
<td>R</td>
<td>14.8</td>
<td>18.8</td>
<td>Profound</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.9 (4.4)</td>
<td>9.2 (4.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For bilaterally implanted subjects, the ear included in analysis was matched as closely as possible to the age at implantation of the corresponding subject with auditory neuropathy spectrum disorder (boldface type). B, bilateral; L, left ear; R, right ear; SNHL, sensorineural hearing loss.

**ECAP**

The value of the exponent $b$ is the recovery function constant and was used to quantify recovery from refractoriness for this study. A larger recovery function constant value indicates a steeper slope of the curve.

**Speech Perception Testing**

Each subject also underwent speech perception testing during the same session and using his or her daily-use condition (ie, with both cochlear implants if a bilateral user). The Children’s Realistic Index for Speech Perception Junior (CRISP Jr.) test was used in an adaptive paradigm to assess speech perception performance. The CRISP Jr. consists of 16 monosyllable and spondee words likely to be in the vocabulary of an average 2.5- to 3-year-old child. The CRISP Jr. is a closed-set, 4-alternative forced-choice task that measures the speech recognition threshold (SRT), defined as 79.4% correct on the psychometric function, in both quiet and noise. Each adaptive trial began with the word presented at a level of 60 dB SPL, and the level was varied using a modified adaptive 3-down/1-up algorithm following the first incorrect response. In the noise condition, the competing stimuli were 2-talker babble sentences presented at a constant overall level of 45 dB SPL. The testing was terminated following 3 reversals, and SRT was calculated using an average of the last 2 reversals.

This study was approved by the Children’s Hospital of Wisconsin Institutional Review Board and was performed in accordance with the principles expressed in the Declaration of Helsinki.

**Results**

The recovery function constants are shown for both groups in Figure 1. The recovery function constants were highly variable in both groups, and although the mean recovery constant value was smaller for the ANSD group, there was no significant difference between groups (ANSD mean 0.72 ± 0.32 milliseconds; SNHL mean 0.97 ± 0.34 milliseconds; t test $P = .11$).

SRT in quiet showed great individual variability, particularly for the ANSD group (Figure 2). Although the mean SRT was higher for the ANSD group, there was no statistically significant difference between the 2 groups (ANSD mean 48.5 ± 9.4 dB; SNHL mean 41.6 ± 6.4 dB; t test $P = .07$). In noise, SRTs for both groups were higher than in quiet because of the increased difficulty of the task, and variability was smaller (Figure 3). Similar to the SRTs in quiet, the ANSD group showed higher SRTs, but there was no significant difference between groups (ANSD mean 64.6 ± 5.5 dB; SNHL mean 61.9 ± 5.8 dB; t test $P = .29$).

To examine whether speech perception performance was related to neural recovery, regression analyses were performed for SRTs plotted as a function of the recovery time constants. The SRT in quiet (Figure 4) showed no relationship to...
recovery time constant for either group alone or when the data
from both groups were combined (ANSD $r = 0.10$, $P = .78$;
SNHL $r = 0.03$, $P = .94$; all subjects $r = 0.21$, $P = .38$). There
was no relationship between SRT in noise and recovery time
constant for either group alone (ANSD $r = 0.58$, $P = .08$;
SNHL $r = 0.25$, $P = .49$), but a significant relationship was
found for all subjects together ($r = 0.45$, $P = .04$; Figure 5).

Discussion

The purpose of this study was to compare the rate of neural
recovery in implanted children with ANSD to those with
SNHL of other etiologies. It was hypothesized that because of
the potential for temporal impairment in ANSD, the neural
derty would be compromised in this
population. Although the neural recovery constants were, on
average, lower than the SNHL group, there was no significant
difference between groups. The lack of difference may indi-
cate true similarities between these populations with different
etiologies, as both ANSD and SNHL can include presynaptic
and postsynaptic sites of lesion. It is also possible that ECAP
recovery functions are not purely assessing rate of recovery.
In a recent study by Botros and Psarros, the ECAP recovery
was found to be dependent on the size of the neural popula-
tion rather than temporal responsiveness, with a larger neural
population resulting in slower ECAP recovery. Greater tem-
poral responsiveness based on psychophysical testing was

Figure 3. Speech recognition thresholds (SRT) in noise for
auditory neuropathy spectrum disorder (ANSD) and sensorineural
hearing loss (SNHL) subjects. Individual data are plotted along with
the mean ± 1 SD. SRT tended to be higher for the subjects with
ANSD; however, the difference was not statistically significant.

Figure 4. Speech recognition threshold (SRT) in quiet as a function
of recovery function time constant. There was no relationship
found between these measures for either group or for all subjects
together. ANSD, auditory neuropathy spectrum disorder; SNHL,
sensorineural hearing loss.

Figure 5. Speech recognition threshold (SRT) in noise as a function
of recovery function time constant. There was no relationship
found between these measures for either group alone, but a significant
relationship was found for all subjects together. ANSD, auditory
neuropathy spectrum disorder; SNHL, sensorineural hearing loss.
also associated with slower ECAP recovery. The results from the Botros and Psarros study were the opposite of what was expected based on previous physiologic investigations. Individuals with ANSD have temporal processing abnormalities, and thus one may expect that individuals with ANSD or those with slower temporal responsiveness would have slower ECAP recovery than those with SNHL. In the current study, there was no difference in the ECAP recovery between a group of children with ANSD and a group of children with SNHL due to other etiologies. This study is limited by its small sample size, but it is likely that the relationship is not this straightforward. There is significant variability in the sites of lesion in patients with ANSD. The ECAP recovery measures the peripheral aspect of the auditory pathway and would not be an indicator of temporal processing impairments central to the auditory nerve.

There is also evidence that faster rates of recovery correlate with improvement in word recognition scores; thus, the recovery function may be a useful parameter for programming cochlear implants for individuals. Since neural recovery is not typically of concern in cochlear implant patients without neuropathy, ECAP recovery functions are not commonly employed in clinical practice. As cochlear implant technology improves, however, coding strategy stimulation rates tend to increase. This introduces a potential need for objective tools to assess the auditory nerve’s ability to encode rapidly occurring stimuli, particularly in the presence of neuropathy. The relationship between the recovery function and speech recognition scores has, however, been inconsistent. Although some investigations have found a significant relationship between neural recovery rates and word recognition scores, others have not found an association. In the present study, there was a significant effect of lower SRT in noise with faster ECAP recovery for all subjects. Patients diagnosed with ANSD have more difficulty with speech perception abilities in implanted children who are too young to test behaviorally. This study’s small sample size limits a more definitive conclusion and requires further examination.

The usefulness of the ECAP recovery function in optimizing the implant stimulation rate in children with ANSD is unclear. Although slowing stimulation rate in some patients with ANSD may improve speech perception, the relationship between the rate of recovery and stimulation rate preference remains undefined. In adult subjects with SNHL, Kiefer and colleagues found a correlation between recovery function time constants and word recognition scores, but this relationship was seen across all stimulation rates. In addition, the recovery time constant did not correlate with a preferred stimulation rate or sound-coding strategy. Shpak and colleagues, however, found a significant association between auditory nerve recovery time and stimulation rate preference, with longer neural recovery associated with preference for slower stimulation rates.

Conclusions
In ANSD, it is possible that dyssynchronous neural activity may affect the temporal encoding of an electrical signal from a cochlear implant. Objective measures of neural refractory behaviors may assist in programming young children with ANSD if there are deficits in temporal neural function. As a group, children with ANSD did not demonstrate slower neural recovery compared to those with SNHL, but there was slower neural recovery observed in some subjects. Further studies are necessary to investigate the utility of ECAP recovery functions on optimizing the stimulation rate on speech perception for individual patients with ANSD.

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Author Contributions
Susan L. Fulmer, data acquisition, data analysis, drafting manuscript, final approval of version to be published; Christina L. Runge, concept and design, data acquisition, data analysis, drafting manuscript, final approval of version to be published; Jamie W. Jensen, data acquisition, data analysis, drafting manuscript, final approval of version to be published; David R. Friedland, concept and design, data analysis, drafting manuscript, final approval of version to be published.

Disclosures
Competing interests: Christina Runge is on the Med El Corp Audiology Advisory Board and the Advanced Bionics Corp Audiology Advisory Board. David Friedland is on the Med El Corp Surgeon’s Advisory Board.

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