An in vivo investigation of inferior colliculus single neuron responses to cochlear nucleus pulse train stimulation

Stefan J. Mauger,1,2,3 Mohit N. Shivdasani,1,2,3 Graeme D. Rathbone,2,3 and Antonio G. Paolini1,2

1School of Psychological Science, La Trobe University, Melbourne, Victoria, Australia; 2Bionics Institute, East Melbourne, Victoria, Australia; and 3Department of Electronic Engineering, La Trobe University, Melbourne, Victoria, Australia

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An in vivo investigation of inferior colliculus single neuron responses to cochlear nucleus pulse train stimulation. J Neurophysiol 108: 2999–3008, 2012. First published September 12, 2012; doi:10.1152/jn.01087.2011.—The auditory brain stem implant (ABI) is being used clinically to restore hearing to patients unable to benefit from a cochlear implant (CI). Speech perception outcomes for ABI users are typically poor compared with most CI users. The ABI is implanted either on the surface of or penetrating through the cochlear nucleus in the auditory brain stem and uses stimulation strategies developed for auditory nerve stimulation with a CI. Although the stimulus rate may affect speech perception outcomes with current stimulation strategies, no studies have systematically investigated the effect of stimulus rate electrophysiologically or clinically. We therefore investigated rate response properties and temporal response properties of single inferior colliculus (IC) neurons from penetrating ABI stimulation using stimulus rates ranging from 100 to 1,600 pulses/s in the rat. We found that the stimulus rate affected the proportion of response types, thresholds, and dynamic ranges of IC activation. The stimulus rate was also found to affect the temporal properties of IC responses, with higher rates providing more temporally similar responses to acoustic stimulation. Suppression of neural firing and inhibition in IC neurons was also found, with response properties varying with the stimulus rate. This study demonstrated that changes in the ABI stimulus rate results in significant differences in IC neuron response properties. Due to electrophysiological differences, the stimulus rate may also change perceptual properties. We suggest that clinical evaluation of the ABI stimulus rate should be performed.

Due to electrode size and placement of the ABI, stimulation of the CN usually results in broad fields of neural activation. This may cause the activation of multiple neuron populations and probably the activation of multiple parallel ascending pathways.

In CI recipients, the stimulus rate providing best speech perception outcomes and general rate preference is typically user specific, ranging between 250 and 1,800 pulses/s (pps) (Arora et al. 2011; Vandi et al. 2000). A clinical study of three auditory midbrain implant recipients found that a stimulus rate of 250 pps was most suitable, with lower rates resulting in unwanted rate-pitch effects and higher rates resulting in rapid loudness adaptation (Lim et al. 2008, 2009). The historical, and still the predominant, stimulus rate used in ABIs is ~250 Hz (Colletti et al. 2009b; McCreery 2008; Otto et al. 2002; Schwartz et al. 2008). Clinical studies using higher stimulus rates have suggested that this may result in improved speech perception (Behr et al. 2007; Colletti 2006; Colletti et al. 2005, 2009b) or improved activation of specific neuron types (McCreery 2008). A systematic investigation of the effect of ABI stimulation rate has not been performed electrophysiologically or perceptually. Such results may lead to improved speech performance outcomes for ABI users.

The aim of this study was to investigate neural firing rate and temporal response properties of single inferior colliculus (IC) neurons from penetrating ABI (PABI) stimulation at a range of clinically relevant stimulus rates. Electrical stimulation of the CN with different stimulus rates may elicit a range of complex firing rate and temporal responses in the IC, due to multiple cell types and parallel pathways of processing between the CN and IC. A further aim of this study was to investigate if inhibitory neural pathways between these structures are activated through ABI stimulation.

MATERIALS AND METHODS

Surgery and electrode implantation. Experiments were performed on male hooded Wistar rats (n = 15) weighing between 265 and 410 g (Flinders University, Adelaide, SA, Australia) and anesthetized with urethane [intraperitoneally, 20% (wt/vol) in distilled H2O, Sigma-Aldrich, Castle Hill, NSW, Australia]. Recordings were performed in a sound-attenuating Faraday room on a gas antivibration table (Technical Manufacturing, Peabody, MA). Animals were mounted in a stereotaxic frame with ear bars (David Kopf Instruments, Tujunga, CA), and their temperature was maintained at 37°C. A section of the cerebellum was aspirated to aid in electrode placement in the left CN. A multichannel electrode array (Neuronexus Technologies, Ann Arbor, MI) was implanted using a microcontroller into the ventral CN (VCN) at an ~30° caudorostral angle. The VCN electrodes consisted...
of four shanks spaced 200 μm apart with eight 413-μm² iridium-oxide electrode sites spaced 200 μm apart on each shank. Electrode activation was performed before implantation (Anderson et al. 1989), lowering electrode impedences to ~90 kΩ at 1 kHz.

After VCN probe placement, tones ranging from 10 to 60 dB sound pressure level (SPL) (10-60 SPL steps) and from 1 to 60 kHz (1/4 octave steps below 4 kHz and 1/7 octave steps above 4 kHz) were presented (20 repetitions) to determine the response area and characteristic frequency (CF; the frequency that produced the highest response rate at the lowest acoustic intensity) of each electrode site. All tones were 50 ms in duration with 5-ms rise and fall times and a 500 ms intertrial interval.

Single neurons in the contralateral central nucleus of the IC (CIC) were recorded from using quartz glass microelectrodes filled with 1 M potassium acetate solution. Electrodes were advanced through the CIC at an ~15° rostrocaudal angle. When a single CIC neuron was isolated, an approximate best frequency (BF; the frequency that produced the highest response rate at a given acoustic intensity) was found at 60-DB SPL by manually varying the tone frequency. An automatic protocol was then initiated that presented acoustic tones at 60-30 dB SPL over a three-octave bandwidth, with five repetitions per 1/7th octave frequency increment, with the neuron's approximate BF in the center of this range. Recordings in the CIC were verified through a gradual increase in BF in a dorsoventral direction (Merzenich and Reid 1974) and no habituation of response to acoustic stimulation (Spitzer and Semple 1993). All surgical procedures and protocols were approved and carried out in accordance with the La Trobe University Animal Ethics Committee (Protocol no. 03/13) and the St. Vincent’s Hospital Animal Ethics Committee (Protocol no. 35/06).

**CN electrical stimulation and CIC recordings.** After IC responses to acoustic stimulation were determined, electrical stimuli were presented to electrode sites in the VCN that had similar CFs to the BF of the CIC neuron. Pulse trains of varying stimulus rates were presented for the first 50 ms of each 500-ms repetition. Pulse train stimulus rates of 100, 200, 400, 800, and 1,600 pps were used. Five repetitions of the same stimulus parameters were presented at 12–15 current levels ranging from 0 to 40 μA. Single pulse stimuli were additionally presented for neurons where intracellular recordings were achieved. In these cases, a single pulse at the start of each 500-ms repetition was presented at the same current levels used for pulse train stimulation.

All electrical pulses were cathodic-leading biphasic pulses of 120 μs/phase with a 40-μs interphase gap. For CIC neurons that responded with short time-locked latencies indicative of antidromic activation, a collision test was performed (Bishop et al. 1962; Darian-Smith et al. 1963). Antidromic behavior was confirmed by presenting an acoustic click stimulus, resulting in a CIC spike, which caused the abolition of a subsequent spike produced from delayed CN stimulation (Mauger et al. 2010). Common ground stimulation was used with one stimulation site and the surrounding electrode sites as returns. This type of stimulation was selected as it has been shown to provide more place-specific activation than monopolar stimulation (Cicione et al. 2012).

**Artifact removal.** Artifacts in IC extracellular recordings were ~10 times the amplitude of action potentials. Signal-processing techniques were used to suppress artifacts while maintaining spikes in recordings. Response traces were imported to Matlab (The Mathworks, Natika, MA) and processed with custom-made programs. Five responses to the same parameter set were high-pass filtered to remove direct current components and normalized so that each repetition had the same root mean square power during the stimulus period. The median of the five traces was then subtracted from each trace individually, enabling action potentials to be located (Litvak et al. 2001). For intracellular recordings, signal processing was used to maintain low-frequency intracellular recording content such as excitatory postsynaptic potentials and particularly inhibitory postsynaptic potentials (IPSPs). For pulse rates of 400 pps and above, a low-pass Butterworth filter was used to suppress high-frequency artifacts. The remaining artifact was removed using a moving average filter with a temporal length of the stimulus period. For pulse rates of 100 and 200 pps, a technique was used where samples just before and just after stimulation were interpolated between to remove artifacts (O’Keeffe et al. 2001).

**Data analysis.** A second custom Matlab program was then used, which located action potentials for both acoustically and electrically evoked CIC responses. All response traces were visually checked as some spikes were not found through the automatic method. This ensured that all spikes were included in the analysis, particularly in traces with the same stimulus parameters that exhibited very little variability in spike latency from each other. In the small number of such cases, the accuracy of visually locating spikes was not different from the automatic method.

Thresholds at each stimulus rate were determined as the lowest current level that produced a firing rate, in the first 70-ms poststimulus onset, higher than the mean ± 2SD of the spontaneous firing rate (calculated from 90 to 300 ms in the poststimulus onset). Where the spontaneous firing rate was <1 spike/repetition, threshold was determined as the current level that produced at least 1 spike/repetition in the first 70 ms of the stimulus.

**Rate-level functions.** Rate-level functions of CIC neurons from VCN electrical stimulation at each stimulus rate were categorized into four groups (Fig. 1A), as previously defined by acoustic stimulation experiments (Aitkin and Schuck 1985). Rate-level functions exhibiting an increasing firing rate with increasing current level were classified as monotonically increasing. Rate-level functions where the firing rate increased with current level but then remained constant or decreased slightly, but not below 50% of the maximum firing rate, were classified as plateau. Rate-level functions where the firing rate increased but then decreased below 50% of the maximum firing rate were classified as nonmonotonic. A fourth group of rate-level functions that did not fit into any of the first three categories were classified as complex. For monotonic responses, saturation was calculated as the maximum current level used. For plateau responses, a sigmoid curve was fitted to the rate-level function, and the current level at 90% of the asymptote of the sigmoid was used as the neuron's saturation. For both nonmonotonic and complex neural responses, the current level that produced the maximum firing rate was taken as the CIC neuron's saturation. Thresholds and saturation current levels were used to calculate dynamic ranges.

**RESULTS.** Data from 33 CIC neurons were collected, of which 24 were extracellular recordings and 9 were intracellular recordings. Extracellularly recorded neurons were included in the database where BF was found and where VCN stimulation using at least one stimulus rate was performed at all current levels. Of these neurons, 14 neurons (58%) responded to at least one stimulus rate, 4 neurons showed suppression in neural firing, 2 neurons showed antidromic behavior, and 4 neurons showed no response to electrical stimulation. Detailed analysis on the effect of pulse rate on neural responses was performed on the 14 responsive CIC neurons. Analysis of CIC neurons whose spontaneous action potentials were suppressed by electrical stimulation was also performed. Of the nine intracellularly recorded neurons, five neurons were recorded in response to single pulse stimulation and four neurons were recorded in response to both single pulse and pulse train stimulation of the VCN.

**CIC rate-level functions.** Analysis of rate-level functions found that 8% of the neurons exhibited a monotonic response to 100 pps, whereas for stimulus rates >400 pps, ~35% of responses were monotonic. Plateau responses were the most...
common when a stimulus rate of 1,600 pps was used. The highest proportion of nonmonotonic responses was seen with 200 pps followed by 400 pps, whereas 800 pps showed almost 50% complex responses. A decreasing trend in nonresponses was found with increased stimulus rate (Fig. 1B). It should also be noted that electrical stimulation did not activate four of the recorded neurons at any stimulus rate.

Thresholds and dynamic ranges. Thresholds in the CIC from electrical stimulation ranged between 2 and 40 μA. Some variance was seen between neurons, with many neurons having thresholds decreasing to 2 μA at higher stimulus rates (Fig. 2A). For statistical analysis, neurons that did not reach threshold by the maximum current level (40 μA) were given the maximum as their threshold. One-way repeated-measures ANOVA on thresholds showed a significant main effect of stimulus rate \((F_{4,38} = 6.00, P < 0.001)\). Newman-Keuls post hoc comparisons found significant decreases in thresholds from 100 pps compared with all other stimulus rates \((P < 0.05)\), 400 pps \((P < 0.01)\), 800 pps \((P < 0.01)\), and 1,600 pps \((P < 0.05)\).

Dynamic ranges in the CIC from electrical stimulation ranged from 0 to 26 dB (Fig. 2B). Much variance in the dynamic range across stimulus rates was seen. In the analysis of dynamic range, repeated-measures ANOVA found no significant main effect of stimulus rate \((F_{4,38} = 1.77, P = 0.162)\). This could be, in part, due to missing data points from neurons not reaching threshold.

Neural firing rate. CIC neuron firing rates of <5 spikes/repetition in response to VCN electrical stimulation were common (Fig. 2C); however, firing rates of up to 19 spikes/repetition were found for some neurons. In the analysis of firing rate, repeated-measures ANOVA showed a significant main effect of stimulus rate \((F_{4,38} = 5.265, P < 0.001)\). Newman-Keuls post hoc comparisons did not show significant differences between stimulus rates.

Vector strength and interspike interval. A measure of the degree of phase locking (vector strength) to individual electrical stimuli was calculated for each CIC neuron. A similar method previously used for phase locking to acoustic stimuli was implemented (Goldberg and Brown 1969; Greenwood and Durand 1955; Johnson 1980), where the time point of each spike \((i)\) was considered defining a vector of unit length with phase angle \(\theta_i\), as follows (Eq. 1):

\[
\theta_i = \frac{2\pi \times \text{Spike time}_i}{\text{Stimulus period}}
\]  

The \(n\) vectors, characterizing spike trains at the saturation current for each neuron at each stimulus rate, were used to calculate vector strength, as follows (Eq. 2):

![Fig. 1. A: examples of rate responses to a range of current levels. Solid black lines show rate-level functions, dashed lines show 50% of the maximum firing rate, and shaded lines show the spontaneous firing rate. Spikes/Rep, spikes per repetition. B: percentage of neurons at a range of stimulus rates grouped by response type. The stimulus rate is shown in increasing order, with the bars for each group representing (from left to right) 100 pulses/s (pps; \(n = 14\)), 200 pps (\(n = 13\)), 400 pps (\(n = 12\)), 800 pps (\(n = 11\)), and 1,600 pps (\(n = 6\)).](http://jn.physiology.org/)

![Fig. 2. A: absolute thresholds of central nucleus of the inferior colliculus (CIC) neurons at a range of stimulus rates. Each line represents data from a single neuron. A significant decrease in threshold was seen across stimulus rates (*\(P < 0.05\); **\(P < 0.01\)). B: dynamic range (in dB) of neurons plotted against stimulus rate. C: individual lines showing the maximum firing rate at any current level plotted against stimulus rate. D: vector strength plotted against stimulus rate for each IC neuron.](http://jn.physiology.org/)
Vector strength = \sqrt{\left(\sum \sin \theta_i\right)^2 + \left(\sum \cos \theta_i\right)^2} \tag{2}

For stimulus rates of 100 and 200 pps, vector strengths as high as 0.98 were seen, whereas for stimulus rates of >400 pps, a maximum vector strength of 0.6 was seen (Fig. 2D). The effect of rate on mean vector strength across all neurons was analyzed with repeated-measures ANOVA and was found to be not significant (F_{4,15} = 0.639, P = 0.643).

**Temporal response comparison.** To investigate the stimulus rate that produced a neural response with temporal characteristics most similar to those produced by acoustic stimulation, peristimulus time histograms (PSTHs) were constructed using 10-ms bins (Fig. 3, A and C). Each PSTH was normalized so the sum of all bins was 1. Normalized PSTHs were averaged across all neurons for both acoustic stimulation (Fig. 3B) and electrical stimulation (Fig. 3D). In response to acoustic stimulation, CIC neurons typically responded with a peak in neural firing between 10 and 20 ms after the stimulus onset, with a decreasing response after this period. In response to electrical stimulation using stimulus rates of 100 and 200 pps, neurons tended to show more consistent firing rates over the duration of the stimulus. At stimulus rates of 800 and 1,600 pps, responses peaked between 10 and 20 ms and gradually decreased thereafter (Fig. 3D), similar to acoustic stimulation. Differences between PSTHs elicited by acoustic and electrical stimulation are shown in Fig. 3E, with mean differences shown in Fig. 3F. A rate of 800 pps produced the lowest average difference in firing rates between acoustic and electrical stimulation (Fig. 3F).

To further compare temporal responses, correlation coefficients between acoustic and electrical PSTHs were calculated for all stimulus rates (Fig. 3G). Stimulus rates of 100 and 200 pps were poorly correlated to acoustic stimulation, whereas stimulation rates of 400 pps and above gave correlation coefficients as high as 0.9 (Fig. 3H). One-way ANOVA found a significant change in the correlation coefficient across stimulus rates (F_{4,25} = 3.07, P < 0.05).

**Suppression of spontaneous firing.** Of the total 24 neurons recorded extracellularly, 4 neurons (17%) showed suppression in neural firing to electrical stimulation. An example of the typical suppression pattern is shown as a raster plot in Fig. 4A for a single neuron at stimulus rates of 100, 400, and 1,600 pps. Suppression of spontaneous activity increased in duration in a monotonic fashion with an increase in current level for all four neurons. Stimulus rates of 100 pps produced long-lasting suppression, up to 50 ms after stimulus cessation. Higher stimulus rates were found to produce shorter suppression periods. Excitation was also seen at low current levels (8–15 µA) using 400 and 1,600 pps (Fig. 4B). This excitation was not seen at higher current levels. Neural firing post-suppression tended to recommence at similar times for traces at the same current level. Spontaneous activity had a period of ~50 ms.

**Intracellular responses.** Intracellular recordings of nine CIC neurons to VCN electrical stimulation were analyzed to see the effects of excitation and inhibition. Responses of four neurons were recorded to both single pulse and pulse train VCN stimulation. Responses of two intracellularly recorded neurons to acoustic and electrical stimulation at a range of stimulus rates are shown in Figs. 5 and 6. Acoustic responses showed early onset inhibition (Fig. 5A) or no inhibition (Fig. 6A), characterized by the presence of IPSPs. At low stimulus rates, inhibition from each stimulus pulse was found, which resulted in strong inhibition for the duration of the electrical stimulation (Figs. 5B and 6B). At higher stimulus rates, inhibitory responses became more complex, with the length of inhibition shorter than the stimulus duration (Figs. 5B and 6B). Action potentials, after the cessation of the stimulus at low rates and directly after the cessation of inhibition at higher rates, were also found (Fig. 6B). Both inhibition depth (Figs. 5C and 6C) and inhibition duration (Figs. 5D and 6D) were measured across current level for each stimulus rate. Inhibition depth was found to increase relatively linearly with current level for each stimulus rate. Higher stimulus rates had comparatively lower inhibition levels across current levels. Inhibition duration for 100 and 200 pps lasted the whole stimulation duration for current levels above threshold. A more gradual increase in inhibition duration was found for 400 and 800 pps (Figs. 5D and 6D). In the case of 800 pps, the duration of the inhibition seemed to plateau at ~22 ms for moderate to high current levels.

Intracellular responses to single pulse stimulation at a number of VCN electrode sites with similar CFs to the BF of the CIC neuron were analyzed (Fig. 7). Strong inhibition after electrical stimulation was seen from stimulation of all electrode sites (Fig. 7A). Inhibition depth was found to increase with current levels, but at different rates for different stimulating electrodes (Fig. 7B). Electrodes located closer to the octopus cell region (ventrocaudal) showed stronger inhibition in CIC neuron 9-1, but little difference was seen for CIC neuron 13-3 (Fig. 7C).

**DISCUSSION**

**Excitatory responses.** Unlike CIC responses from auditory nerve stimulation, where rate-level functions are predominantly monotonic (and plateau) and less commonly nonmonotonic (Semple and Kitzes 1985; Shepherd et al. 1999), a fourth response type was observed in this study. These complex rate-level responses have also been reported in a previous VCN electrical stimulation study (Shivdasani et al. 2008). High stimulation rates produced a higher proportion of monotonic and plateau responses and the least number of nonresponses. However, an increase of complex response patterns was also found at higher rates. Lower average thresholds and higher firing rates were expected from higher stimulus rates due to increased total current, but could also be as a result of increased excitability or decreased inhibition from higher stimulus rates.

The temporal arrangement of spikes is thought to contain information from many acoustic features, including amplitude, frequency, and source location (Furukawa and Middlebrooks 2002; Heil 2004; Moore 2003). We therefore compared temporal spike arrangement in the CIC in response to VCN electrical stimulation. Higher electrical stimulus rates produced responses with lower vector strength (increased stochasticity), which in a stimulation strategy is thought to desynchronize the fiber population and may improve temporal resolution and dynamic range (Rubinstein et al. 1999). A comparison of PSTHs in response to acoustic and electrical stimulation showed that high stimulus rates better represented acoustic
temporal firing patterns in CIC neurons from stimulation of central VCN regions. It is possible that higher stimulus rates may also provide benefit to ABI users compared with the present clinical stimulus rate of 250 pps. A number of studies have suggested that higher stimulus rates may lead to improved speech perception (Behr et al. 2007; Colletti 2006; Colletti et al. 2005). More recently, a consortium of data has shown that using stimulus rates above 1,200 pps can result in significant improvements.

Fig. 3. A: individual lines showing the proportion of spikes falling in the first 70 ms after the start of acoustic stimulation for each CIC neuron. B: mean acoustic peristimulus time histogram (PSTH) for all neurons showing a moderate onset response followed by a decrease in activation toward the end of stimulation. C: individual lines showing the proportion of spikes falling after the start of electrical stimulation for each neuron at a range of current levels for different stimulus rates. D: mean electrical PSTHs for all stimulus rates. E: differences between acoustic and electrical PSTHs (acoustic minus electrical) for each neuron. F: mean differences between acoustic and electrical PSTHs for all stimulus rates. G: correlation coefficients between each neuron’s acoustic and electrical PSTH at each stimulus rate. H: average correlation coefficients for each stimulus rate. All PSTHs were computed using 10-ms bin width.
speech improvement results compared with rates below 1,200 pps ($P < 0.027$) in ABI patients (Shannon 2012). But as stimulus rate also affected clinical thresholds, and pulse widths were not consistent across stimulus rate, the effect of rate alone could not be definitively stated.

**Inhibitory responses.** Although VCN neuron populations providing inhibitory input to the CIC are well described, there has been very little discussion on the effects of activating these pathways through VCN electrical stimulation. Extracellular recordings showing suppression of neural firing and intracellular recordings showing IPSPs in this study have been able to
demonstrate electrical activation of ascending inhibitory pathways. This could be through the activation of octopus cells, which respond to signal onsets (Hemmert et al. 2005), providing fast inhibition to the CIC through the ventral nucleus of the lateral lemniscus (Nayagam et al. 2005). Another possibility could be through GABAergic intrinsic connections within the CIC itself (Adams and Mugnaini 1984; Faingold et al. 1991). Similar long-lasting suppression of spontaneous firing, such as seen in our extracellular recordings at low stimulus rates, has also been described in response to acoustic stimulation, although the origin of such inhibition is unknown (Carney and Yin 1989). A previous VCN electrical stimulation study showed that two VCN electrodes “when stimulated individually” were able to elicit CIC responses; however, when they were stimulated together, it was possible to abolish the CIC response (Shivdasani et al. 2010), suggesting complex interactions between excitation and inhibition. Although the inhibitory pathway is important and well described for acoustic stimulation, the effects of inhibition from ABI stimulation are unclear. A systematic study to investigate the effect of increased or decreased activation of the inhibitory pathway from ABI stimulation would help in determining its contribution and importance.

The suppression seen in extracellular recordings and the presence of IPSPs in our intracellular recordings were highly dependent on the stimulus rate used. Low electrical stimulation rates were found to provide more suppression of firing, whereas higher rates provided shorter durations of suppression. Similarly, for low stimulus rates, inhibition was seen to last longer than the stimulation duration and had increased depth, whereas at higher stimulus rates, both the depth and duration of inhibition decreased. The location of the stimulation was also found to affect inhibition depth. An increase in inhibition from the stimulation of more ventral and caudal VCN electrodes was observed, possibly due to their proximity to the octopus cell region. It is possible that the reduction of inhibition at higher stimulus rates, particularly at 800 pps, might be attributed to the bandpass characteristics of octopus cells, which have been shown to have an upper band limit of ~650 Hz (Godfrey et al. 1975; Hemmert et al. 2005).

Clinical translation. Similarities between mammalian auditory systems have enabled the extensive use of rats and cats in auditory research (Adams 1986; Moore 1987; Moore and Osen 1979); however, some differences would influence the implications of our results for humans. The human VCN contains relatively fewer octopus neurons than the rat VCN. If the inhibition seen in our recordings is through the octopus cell pathway, then the effect of activating these pathways through CN stimulation may be decreased in humans. Another significant difference is the much larger granule cell domain in humans that contains GABAergic small cells. The projections of such neurons are predominantly to the fusiform cells in the dorsal CN (Mugnaini et al. 1980), which, in turn, project to the CIC (Berrebi and Mugnaini 1991). Our study was conducted with the auditory nerve intact. ABI recipients typically do not have a functioning auditory nerve, and, therefore, it is accepted that responses may differ due to plastic changes. In many NF-2

Fig. 6. A: intracellular responses of CIC neuron 13-3 (five traces overlaid) to acoustic stimulation at the neuron’s best frequency showing excitation. B: mean responses to electrical stimulation of neuron 13-3 at 40 μA (solid trace) and 20 μA (shaded trace). C: plot of the depth of inhibition across current level. Each symbol type represents a different stimulus rate. Linear trend lines through each stimulus rate are also shown. A drop in inhibition depth can be seen for 400 and 800 pps compared with lower rates. D: plot of the duration of inhibition across current level. Symbols representing the same stimulus rates as in C. A decrease in inhibition duration can be seen for 400 pps compared with lower rates and for 800 pps compared with 400 pps.
cases, the auditory nerve would at least be partially functioning before tumor removal, resulting in a short deafness period and possibly minimal long-term deafness changes in neural reorganization. It may be important to investigate how plasticity due to auditory nerve removal affects responses to VCN electrical stimulation. The use of anesthesia may also influence our experimental findings and needs to be considered when our results are compared with those of awake function.

**Implications for ABIs.** Current ABIs use vocoder stimulation strategies developed for CIs that aim to vary the level of activation of frequency-specific neural populations through current level. This study has shown that the stimulus rate has a range of effects on CIC neural response properties. A clinical ABI study on stimulus rate should be carried out to determine if significant psychoacoustic changes or changes in speech perception outcomes are also found at higher rates.

One study has suggested that specific cell types, such as T-stellate neurons, which are thought to carry frequency information to the CIC, may be important to activate by ABIs (McCreery 2008). Although neuron groups in the VCN are unable to be stimulated separately, being intermingled with or in close proximity to other neuron groups, it may be possible to target specific neural populations by varying the stimulus rate. Such targeted stimulation is supported by the different depolarization patterns between cell types, such as T-stellate and octopus neurons (Ferragamo and Oertel 2002). Selection of a stimulus rate that activates a desired neuron type over other neuron types in proximity may be possible, either continuously or dynamically.

Electrode location in this study was also suggested to affect the level of inhibition. The clinical PABI was designed to target cell populations in the central VCN similar to the regions activated in this study. Unfortunately, there has been no significant improvement in speech perception results from PABI recipients compared with ABI users (Otto et al. 2008). The PABI, with its surface and penetrating electrodes, would be well suited to assessing perception from both electrode location and stimulus rate.

**Conclusions.** This study systematically investigated rate response properties, temporal response properties, and inhibition in the IC from CN electrical stimulation. Higher stimulus rates produced lower thresholds and more similar temporal responses to acoustic stimulation compared with lower stimulus rates. Strong inhibition was found from electrical stimulation, with the stimulus rate found to affect the depth and duration of inhibition. These complex inhibitory and excitatory results may have implications for the development of future ABI stimulation strategies. Additional electrophysiological testing is required to further explore the effect of electrode placement on inhibition. Due to many differences in IC response properties seen across the stimulus rate, clinical testing with ABI and PABI recipients with a range of stimulus rates, particularly high rates, may lead to improved outcomes.

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**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the author(s).

**AUTHOR CONTRIBUTIONS**

Author contributions: S.J.M., M.N.S., G.D.R., and A.G.P. conception and design of research; S.J.M., M.N.S., and A.G.P. performed experiments; S.J.M.

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