Coactivation of different neurons within an isofrequency lamina of the inferior colliculus elicits enhanced auditory cortical activation

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Coactivation of different neurons within an isofrequency lamina of the inferior colliculus elicits enhanced auditory cortical activation. J Neurophysiol 108: 1199–1210, 2012. First published May 23, 2012; doi:10.1152/jn.00111.2012.—The phenomenal success of the cochlear implant (CI) is attributed to its ability to provide sufficient temporal and spectral cues for speech understanding. Unfortunately, the CI is ineffective for those without a functional auditory nerve or an implantable cochlea required for CI implementation. As an alternative, our group developed and implanted in deaf patients a new auditory midbrain implant (AMI) to stimulate the central nucleus of the inferior colliculus (ICC). Although the AMI can provide frequency cues, it appears to insufficiently transmit temporal cues for speech understanding. The three-dimensional ICC consists of two-dimensional isofrequency laminae. The single-shank AMI only stimulates one site in any given ICC lamina and does not exhibit enhanced activity (i.e., louder percepts or lower thresholds) for repeated pulses on the same site with intervals <2–5 ms, as occurs for CI pulse or acoustic click stimulation. This enhanced activation, related to short-term temporal integration, is important for tracking the rapid temporal fluctuations of a speech signal. Therefore, we investigated the effects of coactivation of different regions within an ICC lamina on primary auditory cortex activity in ketamine-anesthetized guinea pigs. Interestingly, our findings reveal an enhancement mechanism for integrating converging inputs from an ICC lamina on a fast scale (<6 ms window) that is compromised when stimulating just a single ICC location. Coactivation of two ICC regions also reduces the strong and long-term (>100 ms) suppressive effects induced by repeated stimulation of just a single location. Improving AMI performance may require at least two shanks implanted along the tonotopic gradient of the ICC that enables coactivation of multiple regions along an ICC lamina with the appropriate interstimulus delays.

Coactivation of different neurons within an isofrequency lamina of the inferior colliculus elicits enhanced auditory cortical activation of the auditory cortex; deep brain stimulation; cochlear implant; enhancement; temporal integration; neural prosthesis; auditory thalamus

Neural prostheses have achieved remarkable success in conveying information from the physical world to the brain (Zhou and Greenbaum 2009). They have been particularly successful in the auditory system with cochlear implants (CIs) because of their ability to provide sufficient temporal and spectral cues required for speech understanding (Kral and O’Donoghue 2010; Shannon et al. 1995; Zeng 2004). Central auditory prostheses, for those without a functional nerve or an implantable cochlea as required for CI implementation, have been less successful (Colletti et al. 2009; Lim et al. 2009; Schwartz et al. 2008). Surprisingly, even after 30 years and over 1,000 implanted patients, CI-based strategies are still used for these central devices because of insufficient understanding of how central neurons spatially code and functionally interact to transmit sound features to higher centers.

In 2006–2007, our clinical group implanted deaf patients with a new auditory midbrain implant (AMI) consisting of a single-shank array (20 sites) designed for stimulation along the tonotopic gradient of the central nucleus of the inferior colliculus (ICC) (Lenarz et al. 2006b; Lim et al. 2007). As shown in previous studies (Lenarz et al. 2006a; Lim and Anderson 2006; Lim et al. 2008, 2010), AMI stimulation can systematically activate frequency-specific neurons and transmit spectral cues to higher auditory centers. However, AMI stimulation appears to exhibit limited temporal coding abilities. Both acoustic and CI stimulation achieve short-term temporal integration in which presentation of a greater number of stimuli (e.g., repeated clicks or pulses) with shorter interstimulus intervals (within ~5 ms) elicits a louder sensation or lower detection threshold (Flanagan 1961; McKay and McDermott 1998; Shannon 1989; Viemeister and Wakefield 1991). More generally, short-term temporal integration can be viewed as a sliding neural window that integrates and tracks the rapid changes in the sound waveform important for speech understanding and complex auditory processing (Forrest and Green 1987; Oxenham and Moore 1994; Viemeister 1979). AMI stimulation does not achieve this temporal integration (Lim et al. 2008; McKay et al. 2011). Stimulation of a given electrode site with repeated pulses does not elicit louder sensations or lower thresholds for pulse intervals shorter than ~2–5 ms.

The ICC is a three-dimensional tonotopic structure consisting of two-dimensional isofrequency laminae (Genice and Most 1971; Malmierca et al. 1993; Oliver 2005). Numerous studies have identified different temporal firing patterns to acoustic stimuli (Rees and Langner 2005; Rees et al. 1997) and topographic maps for various temporal features (e.g., periodicity and latency) (Ehret 1997; Langner et al. 2002) along these ICC laminae. It is plausible that ICC would require coactivation of neurons located in different regions within an isofrequency lamina to transmit various temporal features. The current AMI device stimulates only one site in any given ICC lamina. The inability to achieve short-term temporal integration could be related to a neural refractory effect. In other words, repeated stimulation of a single location may artificially activate the same neurons to the first pulse and require a recovery period of a few milliseconds before further activation of those same neurons.

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As an initial step toward understanding how neurons along an ICC lamina interact and activate higher auditory centers, we investigated the effects of single- and dual-site stimulation of the ICC on primary auditory cortex (A1) activity in a guinea pig model. We discovered that repetitive stimulation of a single site within an ICC lamina, as intended for current AMI patients, elicits strong refractory and suppressive effects in A1 that could be limiting temporal coding. However, stimulation of two sites within an ICC lamina with short delays (<4–6 ms) elicits enhanced A1 activity overcoming the refractory effects and with properties consistent with short-term temporal integration. For longer delays, stimulation of two sites also exhibits less suppressive effects than observed for repeated stimulation on the same site. These findings provide new insight into how AMI electrode array designs and stimulation strategies can be improved to more effectively transmit temporal patterns to higher auditory centers.

MATERIALS AND METHODS

Basic surgical procedures and methods for neural recording and stimulation were similar to those presented in previous work (Lim and Anderson 2006, 2007c; Neuhetser et al. 2010) and performed in ketamine-anesthetized guinea pigs. The guinea pigs’ care and all experiments were carried out in accordance with the German law for animal protection and were approved by the regional government (LAVES, registration no. 05/1055). For this study, we electrically stimulated one or two regions within an ICC lamina, using single-shank arrays similar to those implanted into AMI patients (Lenarz et al. 2006b; Lim et al. 2007) (Fig. 1A). In response to ICC stimulation, the corresponding neural activity was recorded within A1 with a multisite array (Fig. 1B). The A1 recordings were obtained from sites positioned within similar best-frequency regions as the stimulated ICC sites. Acoustic-driven responses were used to guide and confirm appropriate placement of the sites within the ICC and A1. We then compared A1 activity in response to stimulation of two pulses on one AMI site versus one pulse on each of two AMI sites with varying delays between the pulses to better understand how activation of similar versus different neurons along an ICC lamina affects A1 activity.

In this paper, we only present the results for the local field potentials (LFPs) recorded on our A1 sites. We were unable to analyze the spike data because of antidiromic activity. Electrical stimulation of the ICC can antidiromically activate neurons projecting from A1. This was demonstrated in a previous study (Lim and Anderson 2007a) in which stimulation throughout the ICC antidiromically activated neurons originating predominantly from layer V of A1. Generally, antidiromic spikes could be identified and differentiated from orthodromic spikes based on cortical layer, latency jitter, spike shape, and effects to high pulse rates. Unfortunately, in this study we observed a greater extent of antidiromic activity across multiple cortical layers, making it difficult to accurately isolate the orthodromic spikes from the antidiromic activity. The stimulation sites used in this study were considerably larger than those used in Lim and Anderson (2007a) (126,000 μm² vs. 400 μm²) and may explain the larger antidiromic response. Figure 2 provides a typical example of the filtered signals (300–3,000 Hz) recorded simultaneously across four sites along a similar A1 column but in different depth locations (0 μm corresponds to layer III/IV) in response to a single electrical pulse on an AMI site. Between ~1 and 10 ms after the stimulus onset, overlapping antidiromic activity was consistently observed across trials (i.e., peaks from individual trials resembled those from the averaged curve) not only in
rectal temperature probe was used to keep the body temperature at constant levels. A warm water heating blanket controlled by a computer was used to maintain an areflexive state. Atropine sulfate (0.05 mg/kg), ketamine (40 mg/kg) and xylazine (10 mg/kg), with periodic supplements of hydromorphone (0.01 mg/kg), were used for postoperative sedation.

A majority of this antidromic activity on the main input site (at 0 m relative to the main input layer III/IV), with several large and temporally smeared peaks observed between 1 and 10 ms (arrowheads). Antidromic activity was also observed in more superficial layers, including layer III/IV at 0 μm, that could overlap with and be detected as orthodromic spikes (asterisks label negative deflections that exceeded the dashed line). Filtered signals (300–3,000 Hz) recorded simultaneously across 4 A1 sites are presented for 5 consecutive trials (gray curves) in addition to the averaged curves across those trials (black curve) to demonstrate the repeatability and precise timing of the antidromic peaks.

Fig. 2. Antidromic activity recorded across cortical layers. Electrical stimulation of an AMI site elicited both orthodromic and antidromic activity across different depth recordings in A1. The greatest antidromic response occurs in deeper layers (e.g., 400 μm relative to the main input layer III/IV), with several large and temporally smeared spikes and thus compromise the analysis. However, when two pulses are presented with varying delays, the antidromic activity can significantly overlap with the orthodromic activity. We binned the spikes into PSTHs (1-ms bins). The number of driven responses (Abeles and Goldstein 1970; Redies et al. 1989; Wallace et al. 2000), and the exposed brain was covered with agarose gel.

For placement of the two single-shank AMI arrays, we partially removed the occipital cortex to visualize the right inferior colliculus surface (Bledsoe et al. 2003; Snyder et al. 2004). To minimize damage caused by multiple insertions of the AMI array, we initially used a thinner single-shank 16-site array (5 mm long, 15 μm thick, ~50 μm wide, site area of ~400 μm²; NeuroNexus Technologies) to identify and map out the functional borders of the ICC based on acoustic-driven responses. The AMI arrays were then inserted into the ICC (Fig. 1A). A special adaptor ensured that the two arrays were separated by 1.5 mm and inserted simultaneously. Each shank is 6.2 mm long with a diameter of 0.4 mm and consists of 20 platinum ring electrodes linearly spaced at an interval of 200 μm along a silicone carrier. Each site has a thickness of 100 μm and a surface area of 126,000 μm². A stainless steel stylet is positioned through the axial center of each shank to enable insertion of the array into the brain. In humans, the stylet would be removed after array placement (Samii et al. 2007). We inserted both AMI shanks at a 45° angle to the sagittal plane into the inferior colliculus to align them along the tonotopic axis of the ICC (Lim and Anderson 2006; Malmierca et al. 1995; Snyder et al. 2004). The AMI sites had impedances of 3–20 kΩ (at 1 kHz). The remaining exposed brain was covered with agarose gel.

Stimulation and Recording Setup

All experiments were performed in an acoustically and electrically shielded chamber and controlled by a computer interfaced with TDT System 3 hardware (Tucker-Davis Technology, Alachua, FL) using custom software written in MATLAB (MathWorks, Natick, MA). For acoustic stimulation, sound was presented via a speaker coupled to the left ear through a hollow ear bar. The speaker-ear bar system was calibrated with a 0.25-in. condenser microphone (ACO Pacific, Belmont, CA) where the tip of the ear bar was inserted into a short plastic tube with the microphone inserted into the other end. The tube represented the ear canal.

To monitor the placement of the electrode arrays, we presented various levels of pure tones and broadband noise that were 50 ms in duration with 5-ms and 0.5-ms rise-fall ramp times, respectively, to elicit acoustic-driven activity in the contralateral ICC and A1. All neural signals were passed through analog DC-blocking and antialiasing filters from 1.6 Hz to 7.5 kHz. The sampling frequency used was 195 kHz for acoustic stimulation and 24 kHz for neural recording.

After placement of the electrode arrays, the AMI array was connected to an optically isolated current stimulator. The selected AMI sites were stimulated in monopolar configuration with the return through a wire in the neck muscles. The electrical stimuli consisted of biphasic pulses with varying levels and delays between sites and pulses. Neural data were recorded on all 32 A1 sites in response to stimulation of the different AMI sites. The recording ground wire was positioned under the skin ~2 cm rostral to bregma.

Placement of Electrode Arrays

Poststimulus time histograms (PSTHs) and frequency response maps were plotted online to confirm that the electrode arrays were correctly positioned along the tonotopic axis of the ICC and along the appropriate best-frequency columns in A1. Details on these analysis methods and example plots for similar types of electrode arrays are presented in previous publications (Lenarz et al. 2006a; Lim and Anderson 2006; Neuheiser et al. 2010). Briefly, we band-pass filtered the neural signals (300–3,000 Hz) and detected spikes on each site that exceeded an online determined threshold above the background activity. We binned the spikes into PSTHs (1-ms bins). The number of trials for broadband stimulation varied, whereas four trials were
presented for each pure tone and level stimulus for the frequency response maps. To create a frequency response map for each site, we calculated the driven spike rate (total minus spontaneous activity) within a set PSTH window relative to the stimulus onset (A1: 5–25 ms, ICC: 5–65 ms) and plotted that value for each frequency-level combination (Fig. 1). The best frequency was taken as the centroid frequency value at 10 dB above the level where we first observed a noticeable and consistent response. We used this best frequency measure instead of characteristic frequency (i.e., frequency corresponding to the maximum activity at threshold) because it was less susceptible to noise and more consistent with what we visually estimated from the frequency response maps.

For A1 probe placement, we first recorded surface potentials in response to pure tones using the tip site of each shank and determined the borders of A1 based on its best-frequency organization (Wallace et al. 2000). This minimized insertion damage within A1 while searching for appropriate frequency regions. Once a desired frequency region was identified, we then inserted the A1 array such that each shank was approximately aligned along a different cortical column (Fig. 1B). The A1 sites usually exhibited onset responses. To identify the site along each shank that was located in the main input layer of A1, current source density (CSD) analysis (Kral et al. 2000; Mitzdorf 1985; Muller-Preuss and Mitzdorf 1984) was performed in response to 70 dB SPL broadband noise (100 trials) with the finite difference formula:

$$CSD(z) = \sigma_z \phi(z + \Delta z) - 2 \phi(z) + \phi(z - \Delta z) \over (\Delta z)^2$$

where \(\phi\) is the averaged LFP across trials, \(z\) is the depth location of each site along an A1 array shank, \(\Delta z\) is the differentiation step size, and \(\sigma_z\) is the component of conductivity in the \(z\)-direction. \(\Delta z\) was equal to our A1 site spacing of 200 \(\mu m\), and \(\sigma_z\) was set to 1 since we were not concerned with absolute CSD values. A CSD profile is obtained by calculating the CSD(z) values over time obtained from the \(\phi\) values over time (i.e., LFP profiles). The one-dimensional CSD approximation provides a consistent representation for the current sinks and sources associated with columnar synaptic activity in the guinea pig auditory cortex and has been used successfully in previous studies (Lim and Anderson 2007a; Middlebrooks 2008). The main input layer III/IV of A1 corresponded to the site with the shortest-latency current sink (i.e., positive CSD peak). Basically, we adjusted the array position in A1 until we identified the depth with the largest LFP responses. This depth provides an initial approximation to the location of the main input layer of A1. Then by analyzing the CSD profiles for different depths slightly above and below that initial depth, we were able to localize the main input layer A1 site for each of the four shanks. We selected only the A1 site with the closest best frequency (Fig. 1B) to that of the stimulated ICC sites (Fig. 1A) for further analysis.

The AMI arrays were inserted into the ICC at a 45° angle to the sagittal plane (Fig. 1A). We confirmed that our sites were located within the ICC when we observed sustained PSTHs in response to broadband noise and frequency response maps that exhibited an orderly shift in best frequency from low to high values for superficial to deeper locations, respectively, along a shank (Lim and Anderson 2006; Snyder et al. 2004).

Electrical Stimulation Parameters

We electrically stimulated one or two AMI sites within an ICC lamina and characterized the corresponding LFP activity on the main input layer A1 site with a similar best frequency. Either two pulses on the same site (single-site stimulation, SSS) or one pulse on each of two sites (dual-site stimulation, DSS) was presented with different levels and varying interpulse intervals (IPIs) in a randomized sequence (combined with no-stimulus trials) to minimize adaptation.

Each stimulus was presented a total of 20 times with an interval of 700 ms between stimuli. The pulses were biphasic, charge-balanced, cathodic-leading, and 205 \(\mu s\) phase.

SSS. These IPIs were presented (in ms): 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, and 100. We selected AMI stimulus levels (in 2-dB steps relative to 1 \(\mu A\)) that ranged from approximately threshold activity to a reasonably large response on the selected A1 site. A large response was one in which the LFP size was comparable to that elicited by a 60 dB SPL broadband noise stimulus (−2–3 mV negative peak amplitude; see Neuheiser et al. 2010 for further details on LFP magnitude vs. stimulus level). Both pulses were always presented at the same stimulus level. After initial analysis, only a subset of levels in each set was used for the results presented in this paper (listed in Tables 1 and 2). These levels corresponded to activity that was reasonably above the noise floor but below saturation levels.

DSS. The same IPIs were used as for SSS, except for the additional case of 0 ms (simultaneous stimulation). For SSS, we always stimulated both pulses with the same level. Since stimulation of different AMI sites will elicit A1 activity with different thresholds (Lim and Anderson 2007b; Neuheiser et al. 2010), it is not clear what the “same” level is for each site with DSS (i.e., selecting some decibels or microamperes above threshold is arbitrary). As an approximation based on a more functional measure, we identified one level for each site that elicited a “reasonable” LFP response (−1 mV negative peak amplitude). We then selected one site at that reasonable level while stimulating the other site with different levels roving above and below its reasonable level (across a 10-dB range in 2-dB steps relative to 1 \(\mu A\)).

For example, in Table 2, DSS-1 P1 (site 1) was stimulated from 30 to 40 dB while P2 (site 2) was fixed at 44 dB. This ensured that we included at least one pair of “same” levels that we could more accurately determine off-line. We also compared data across the different levels to assess how activation effects varied for different volumes of stimulated neurons.

Data Analysis

If the two pulses for SSS or DSS were presented close enough in time (IPI <10 ms), only one negative LFP peak was elicited and the area was calculated for that peak (Fig. 3). A curve of LFP area as a function of IPI (up to 10 ms) was then plotted for different levels. For

Table 1. Summary of SSS data set used for analysis

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Values (in dB re 1 \(\mu A\)) are levels used for analysis for each pair of stimulation pulses (pulse P1 and P2). Seven single-site stimulation (SSS) data sets were collected. Each data set corresponds to local field potential recordings in primary auditory cortex in response to a series of different interpulse intervals (from 0 to 100 ms between 2 presented pulses) and levels of electrical stimulation within the central nucleus of the inferior colliculus (see Electrical Stimulation Parameters for further details). During the experiment, it was not possible to determine the optimal stimulation level to use for each pulse for SSS; thus a range of levels were presented and then specific levels were selected during off-line analysis. For the analysis presented in this paper, we only included levels that elicited responses that were sufficiently above threshold activity (i.e., above the noise floor) or were not saturated (i.e., response continued to increase with level).
longer IPIs, two peaks were elicited (i.e., 1 peak for each pulse). By dividing the LFP area for the second pulse by the area for an unaffected LFP to the same pulse (i.e., without any preceding pulse), we could assess whether the response was suppressed (<1) or enhanced (>1) because of the activity caused by the first pulse.

Calculation of a given LFP area consisted of three steps: 1) removal of the electrical artifact from each recorded LFP trace (Fig. 3, A and B), 2) averaging the LFP traces across 20 trials (Fig. 3C), and 3) calculation of the LFP area from the averaged curve (Fig. 3C, hatched area). For artifact removal, we eliminated a window of 1 ms from the recorded trace that started at the onset time of each stimulus pulse. Since the electrical artifact could be superimposed onto ongoing neural activity above or below the zero baseline, it was not possible to simply zero out the signal surrounding the artifact. Instead, for each of the two artifacts we connected the points at the start and end of the 1-ms artifact window with a straight line that maintained the general shape of the recorded trace. The average value during this 1-ms window was then used to calculate the DC offset of each trace. Offset correction was applied by subtracting this average value from the whole trace before averaging all 20 trials for LFP analysis. In analyzing the averaged curves, we initially calculated the negative peak amplitude of the LFP response across stimuli. However, we observed that the LFP could exhibit complex behavior for varying IPIs. For example, the peak could remain relatively constant while the width of the LFP response could increase. Simply measuring the peak would incorrectly indicate that the LFP response remained the same.

Therefore, we decided to calculate the area of the negative LFP response, which appeared to more accurately represent the extent of activation within A1 to the different stimuli. Furthermore, the LFP response corresponds to a voltage recording over time, which is also proportional to current over time based on Ohm's law (assuming neural tissue can be approximated as a linear medium). Therefore the LFP area reflects the total charge (i.e., area under a current vs. time curve), which is related to the amount of synaptic input into A1 surrounding the recording site. To calculate the area of the LFP, we used an interactive analysis program, which permitted manual identification of the onset (negative deviation from 0) of the LFP response. From this point, we created a straight horizontal line that crossed the rising portion of the LFP. We then calculated the area underneath this line, using a trapezoidal function to quantify the LFP response (Fig. 3C, hatched area).

RESULTS

The presented results are based on data obtained from six animals. We compared the A1 LFPs in response to two pulses presented on the same ICC site (i.e., SSS) with those elicited by one pulse presented on each of two ICC sites (i.e., DSS) for different levels and varying IPIs ranging between 0 and 100 ms. Four main characteristics were observed: 1) SSS elicited strong refractory effects for the activity to the second pulse for an IPI < 2 ms that was not observed for DSS. 2) Both SSS and DSS elicited enhanced A1 activity that became stronger as the IPI decreased below 6 ms; however, only DSS avoided the refractory effects observed for SSS. 3) Both SSS and DSS elicited strong suppression of the response to the second pulse for IPIs greater than ~20 ms that recovered to a larger extent for DSS compared with SSS. 4) DSS, but not SSS, could elicit full recovery and even enhanced activity to the second pulse by an IPI of 100 ms. All these findings demonstrate that DSS experiences less refractory and suppressive effects compared with SSS, and may enable more rapid and effective activation of higher auditory centers for AMI stimulation.

ICC-A1 Frequency Pairing

For this study, we collected data sets from animals in which at least one recording A1 site and one pair of stimulating ICC sites could be positioned within a similar best-frequency region. This resulted in nine trios (i.e., 1 A1 site and 2 ICC sites) from six animals in which each trio could correspond to a different best-frequency region. The best-frequency difference between each pair of ICC sites was 0.15 ± 0.12 octaves.

Table 2. Summary of DSS data set used for analysis

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Values (in dB re 1 μA) are levels used for analysis for each pair of stimulation pulses [pulse (P)1 and P2]. Twelve dual-site stimulation (DSS) data sets were collected. Each data set corresponds to local field potential recordings in primary auditory cortex in response to a series of different interpulse intervals (from 0 to 100 ms between 2 presented pulses) and levels of electrical stimulation within the central nucleus of the inferior colliculus (see Electrical Stimulation Parameters for further details). During the experiment, it was not possible to determine the optimal stimulation level to use for each pulse for DSS; thus a range of levels were presented and then specific levels were selected during off-line analysis. For the analysis presented in this paper, we only included levels that elicited responses that were sufficiently above threshold activity (i.e., above the noise floor) or were not saturated (i.e., response continued to increase with level).

Fig. 3. Calculation of local field potential (LFP) area. A: example of a single trial trace showing the negative LFP response recorded in A1 after 2 pulses presented in the central nucleus of the inferior colliculus (electrical artifacts are visible). B: the same single trace as in A after electrical artifact removal. C: the averaged LFP curve across all 20 trials used to calculate the LFP area (hatched region).
(maximum: 0.34 octaves; \( n = 9 \)). The best-frequency difference between each matched ICC and A1 site was 0.13 ± 0.10 octaves (maximum: 0.38 octaves; \( n = 18 \)). For a given trio, there are 2 ICC-A1 pairs, thus a total of 18 pairs for 9 trios. Because of time limitations, we usually collected only DSS or only SSS data from each animal. In one animal we collected both DSS and SSS data, which showed consistent trends with the individual data sets. A total of seven SSS data sets were obtained from four animals (best frequency range: 8–17 kHz). A total of 12 DSS data sets were obtained from 3 animals (best frequency range: 2–16 kHz). Note that for a given pair of ICC sites we stimulated one site first followed by the other site, and vice versa. Thus each pair of ICC sites resulted in two DSS data sets. Tables 1 and 2 provide a summary of all the data sets for SSS and DSS, respectively.

**Single-Site Stimulation**

Figure 4A presents typical averaged SSS traces for varying IPIs at one stimulus level for one ICC site (SSS-3 from Table 1). The stimulus artifact has not been removed from the traces for better visualization of the IPIs. Stimulation with two pulses elicits increasing LFPs in A1 as the IPI increases from 0.5 to \(~2\) ms, which then decrease for longer IPIs. As the IPI exceeds \(~10\) ms, the single LFP begins to separate into two LFP peaks. The second LFP peak is initially suppressed by the activity to the first pulse but eventually begins to recover with increasing IPIs. However, even for an IPI as long as 100 ms, the second LFP still has not fully recovered. This can be visually assessed by comparing the size of the suppressed second peak with the first peak in each of the bottom 10 traces of Fig. 4A. Interestingly, stimulation of two pulses with an IPI of 0.5 ms elicits an LFP (top trace) that is comparable in size to that elicited by a single pulse (first peak in bottom 10 traces). In other words, stimulation with a second pulse at a short IPI contributes no or minimal activity to the LFP already elicited by the first pulse alone.

The strong refractory effect for SSS can be better visualized by plotting the LFP area versus the different IPIs between 0.5 and 10 ms, during which only a single fused LFP exists. For IPIs greater than \(~10\) ms, there are usually two separate LFP peaks. The long term (i.e., \(>10\)-ms IPIs) effects are further discussed in *Long-Term Suppression and Enhancement*. Figure 5A displays a typical SSS data set from one animal. The LFP area for different IPIs (x-axis) and different levels (colored curves) are plotted. The y-axis corresponds to the nonnormalized (Fig. 5A) and normalized (Fig. 5B) LFP area. The nonnormalized curves show how the total LFP area increases with higher levels. Generally, the area is low at an IPI of 0.5 ms and increases as the IPI increases up to \(~2\)–3 ms. The LFP area then begins to decrease and reaches an approximate plateau between \(~5\) and 10 ms. This general trend is observed across all levels, although the curves at very low or high levels appear flatter than those for the middle levels. At very low

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**Fig. 4.** Responses to single-site stimulation (SSS) and dual-site stimulation (DSS): averaged (across 20 trials) LFP traces to SSS stimulation (A) and DSS stimulation (B) for varying interpulse interval (IPI) values. Stimulus pulse level is dB relative to 1 μA. The electrical artifacts were not removed to help with visualization of the stimulus onset for each of the 2 pulses.
levels, the LFP response is quite small relative to the background activity; thus the trend is not as clearly visible. At very high levels, we noted that the LFP activity begins to reach saturation in which the second pulse does not contribute any additional activity to that of the first pulse even outside of the refractory period (>2 ms).

To enable comparison across levels and sites in Fig. 5B, we normalized the curves in Fig. 5A by dividing the LFP area elicited by two pulses by two times the LFP area elicited by a single pulse. Thus a value of 0.5 indicates that the LFP area elicited by two pulses is equal to the LFP area elicited by a single pulse (i.e., full refractory for the second pulse). A value of 1 corresponds to a linear sum of activity. It is clear that, across all levels, there is approximately full refractory at 0.5 ms. As the IPI increases, all curves generally exhibit the same pattern in which the normalized area increases up to an IPI of ~2–3 ms and then decreases to an approximate plateau level by ~4–5 ms. The curve corresponding to 48 dB (gray dashed line) is approximately flat because of saturation, and thus was not included in the averaged curve (black dashed line) (Fig. 4B). As indicated by the averaged curve, there appears to be a neural mechanism that enhances the activity above the plateau level (~0.77 for this example) for an IPI <4 ms that then begins to decrease at ~2 ms because of a refractory effect. If there was only a refractory effect, then the activity should increase monotonically from 0.5 to the plateau level (without the hump at 2 ms) for increasing IPIs as the neurons recover from a refractory state. Interestingly, the plateau level is not equal to 1, indicating that consecutive stimulation of a similar population of ICC neurons does not simply elicit a linear sum of LFP activity in A1. It is not clear whether this is due to a subset of neurons that remain in a refractory or suppressed state for a period longer than 10 ms or related to some nonlinear way in how charge accumulates around the recording site.

The averaged normalized curves for all seven SSS data sets are plotted in Fig. 6A, in which only levels that exhibited sufficient and nonsaturating LFP activity were included in each averaged curve (levels listed in Table 1). There are some differences in the level of refractoriness at an IPI of 0.5 ms (0.43–0.57), time point for peak activity (2–4 ms), plateau level (0.55–0.81), extent of enhancement above the plateau level (4–38%), and starting point of the plateau portion (4–6 ms). In fact, the bottom curve in Fig. 6A (SSS-1) did not exhibit any noticeable enhancement effect but gradually recovered from the refractory state to the plateau level by ~4 ms. Nevertheless, they all exhibit some general trends in which a strong refractory effect occurs at an IPI of 0.5 ms that then recovers to a plateau level by ~4–6 ms, usually with an enhanced region between 2 and 4 ms. These results were consistent across all our stimulated locations, levels, and animals, indicating that the trends observed in Fig. 6A appear to reflect general properties of ICC neurons. In a future study, we will systematically stimulate different locations across an ICC lamina to assess whether the slight differences across curves observed in Fig. 6A are associated with different subregions within the ICC and specific coding properties. It is also possible that those differences correspond to varying recording locations within A1.

**Dual-Site Stimulation**

We investigated whether stimulating two sites along an ICC lamina could overcome the strong refractory effect observed for SSS. Figure 4B presents averaged traces for one DSS data set at one level pair (DSS-3 from Table 2). In contrast to SSS,
the refractory effect was not present for DSS. DSS of two sites within an ICC lamina with decreasing IPIs down to 0 ms elicited larger LFP activity. For increasing IPIs, the LFP decreased in size and eventually the fused LFP separated into two LFP peaks. Similar to SSS, the second LFP peak elicited by the second pulse (i.e., stimulation of the second site for DSS) was greatly suppressed by the first pulse that continued to recover for longer IPIs.

We then plotted the nonnormalized and normalized LFP area versus IPI for DSS (Fig. 5, C and D). Normalization was achieved by dividing the curves by the linear sum of the individual LFP areas elicited by a single pulse on each of the two stimulated sites. Thus a value of 1 indicates that stimulation of two sites with a specific IPI elicits a linearly summed response of the individually stimulated sites. Across all levels (black dashed line in Fig. 5D is averaged curve), a similar trend was observed in which the normalized area increased for shorter IPIs below ~6 ms with a flattened portion between 6 and 10 ms. For some of the lower levels, the area exceeded 1 (nonlinear summation) at the shortest IPIs, while for the highest levels of 50 and 52 dB, the area remained below 1. As was previously observed for SSS, DSS also results in a plateau level (~0.64 for this example) that is not equal to 1, indicating that consecutive stimulation of not only a similar (as for SSS) but also a different population of ICC neurons does not elicit a linear sum of LFP activity in A1. If this reduced plateau is associated with a subset of neurons that remain in a suppressed state for a period longer than 10 ms, then these neurons may be located above the ICC since similar plateau effects (timing and level) were observed for both SSS and DSS.

The averaged curves for each of the 12 DSS data sets for different ICC locations and animals are presented in Fig. 6, B and C. The levels used for each averaged curve are listed in Table 2. There are some differences across curves in the extent (0.87–1.17 at 0-ms IPI) and shape of the enhancement portion of the curve as well as the plateau level (0.64–0.82). The extent of enhancement above the plateau level varied from 20% to 59%. These differences may reflect different stimulation locations within ICC and/or recording locations within A1. Nevertheless, across curves, it is clear that a neural mechanism exists from the ICC to A1 for integrating activity projecting from multiple locations within an isofrequency lamina of the ICC and with a time window of ~6 ms. This enhancement effect was observed across locations and levels, indicating that small as well as large clusters of ICC neurons within similar ICC laminae can interact to induce greater A1 activity.

**Summary of DSS Enhancement vs. SSS Refractory Effects**

A summary of the DSS and SSS interactions for the 10-ms period presented in the previous sections is presented in Fig. 7. For clarity, we present only the mean curve and standard deviations as a function of IPI across all our SSS and DSS cases listed in Tables 1 and 2. Both SSS (gray dashed line) and DSS (black solid line) exhibit similar trends for IPIs between 2 and 10 ms in that the LFP activity increases with decreasing IPI (Fig. 7). They both exhibit a flatter region between ~6 and

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Fig. 6. Normalized area curves for SSS and DSS. A: averaged normalized area curves as presented in Fig. 5B (black dashed line) for all SSS data sets and across levels listed in Table 1. B and C: averaged normalized area curves as presented in Fig. 5D (black dashed line) for all DSS data sets and across levels listed in Table 2. We display half of the curves in B and the other half in C for better visualization of each curve.

Fig. 7. Summary of SSS vs. DSS: mean SSS (dashed gray line) and DSS (solid black line) curves across all data sets and levels listed in Tables 1 and 2. Both SSS (gray dashed line) and DSS (black solid line) exhibit similar trends for IPIs between 2 and 10ms in that the LFP activity increases with decreasing IPI (Fig. 7). They both exhibit a flatter region between ~6 and...
10 ms. The major difference between the two curves is that SSS exhibits a strong refractory effect below 2 ms in which the LFP activity converges to a normalized area of 0.5, indicating full refractory. In contrast, DSS exhibits a continuous increase in A1 activity as the IPI decreases to 0 ms.

Long-Term Suppression and Enhancement

In addition to the SSS and DSS interactions for IPIs below 10 ms, we also investigated the effects for longer IPIs up to 100 ms. As shown in Fig. 4, the LFP to the second pulse (either from the same site for SSS or from the second site for DSS) separates from the LFP to the first pulse at ~15–20 ms and continues to recover from its suppressed state for longer IPIs. To quantify this recovery effect, we computed a ratio of the LFP area for the second pulse divided by the area for an unaffected response to the same pulse (i.e., without any preceding pulse) at an IPI of 100 ms. A ratio greater than 1 indicates enhanced activity, while a ratio less than 1 indicates suppressed activity. For SSS, every analyzed case resulted in suppressed activity (n = 41; mean: 0.47, SD: 0.32, maximum: 0.96, minimum: 0). In fact, 7 of the 41 cases had complete suppression (i.e., second LFP peak was too small to be measurable, thus a value of 0). For DSS, we observed both suppressed activity (32 of 72; mean: 0.83, SD: 0.18, minimum: 0.23) and enhanced activity (40 of 72; mean: 1.15, SD: 0.21, maximum: 2.14). Complete suppression was not observed for DSS. In comparing only the suppressive cases, SSS elicited significantly stronger suppression than DSS (2-tailed Welch’s t-test, P < 1e-7).

DISCUSSION

Electrical stimulation of a single region of the ICC elicits an LFP in A1 and induces a strong refractory effect that limits proceeding activity to stimulation of the same region for a period of ~2 ms. However, coactivation of two different regions within a similar ICC lamina can elicit enhanced A1 activity that increases for shorter IPIs. We observed these refractory and enhancement effects across all our stimulated locations and animals. Although we do not have sufficient location data to identify which or if all neurons throughout the ICC exhibit these effects, our results demonstrate that at least a subpopulation of neurons within an ICC lamina, at least between 2 and 17 kHz, are designed for coactivation within a 6-ms window to elicit enhanced A1 activity.

It is possible that our identified integration mechanism is an artificial result of electrically stimulating the ICC. However, the timescale of this integration window (~4–6 ms) is quite similar to what has been identified in psychophysical studies for acoustic click (Flanagan 1961; Viemeister and Wakefield 1991) and CI pulse stimulation (McKay and McDermott 1998; Shannon 1989). In these studies, pairs or trains of stimuli were presented to subjects and the threshold decreased or loudness increased with shorter interstimulus delays below ~5 ms. Those studies have proposed a temporal integrator somewhere within the brain that is designed to track temporal fluctuations in the stimulus with an ~5-ms moving window. As shown by our results, this temporal integrator may be located within the ICC-to-A1 pathway and activated through converging inputs from different neurons across the ICC laminae.

We also observed long-term suppressive and enhancement interactions for SSS and DSS that occurred beyond 10 ms (up to our longest tested IPI of 100 ms) when the single LFP peak was separated into two peaks. Clinically relevant for the AMI, DSS achieved significantly less suppressive effects than SSS. The pattern of enhancement and suppression for DSS is consistent with the A1 LFP trends observed for two-click acoustic stimulation in cats (Eggermont and Smith 1995). Similar effects to sequential acoustic stimulation have also been observed for A1 spike activity (Brosch and Schreiner 1997; Brosch et al. 1999; Wehr and Zador 2005). In contrast, SSS elicited only suppressive effects that were much greater than typically observed for acoustic stimulation. It is possible that the use of anesthesia in our studies (ketamine) as well as for the other studies listed above (ketamine or pentobarbital) introduced greater suppressive effects than normally occurs during awake conditions (Kirby and Middlebrooks 2011; Wehr and Zador 2005), especially for the SSS condition. However, regardless of the anesthesia effects, it is clear from our results that SSS is activating the central auditory system in a different way than both DSS and acoustic stimulation, both on a short timescale (~5 ms) and on a longer timescale (~100 ms), that may be limiting overall hearing performance in current AMI patients.

An important consideration is whether the enhanced activity for shorter IPIs is due to current summation. Stimulation of two sites closely in time or simultaneously can create overlapping current fields that sum to activate a larger ICC neural population and elicit a greater A1 response. This seems unlikely considering that the 1.5-mm distance between the two sites would require current levels (roughly >200 μA; Ranck 1975) much higher than many of the lower levels in which we observed the enhancement effect in order to cause current summation (see Tables 1 and 2 for current levels). Even if there were sufficient overlapping fields, current summation would not explain the enhanced activity for IPIs up to 6 ms. Any charge accumulation on the membrane of the stimulated neurons would dissipate toward zero faster than 1 ms based on their chronaxie values (Grill et al. 2005; Miocinovic and Grill 2004; Ranck 1975). Furthermore, no apparent current summation effect was observed for SSS at 0.5 ms. For example, in Fig. 5B it can be seen that the second pulse did not increase the accumulated neural charge from the first pulse to activate additional subthreshold ICC neurons and exceed a normalized area of 0.5. This suggests that any current summation effect must occur for IPIs shorter than 0.5 ms. For DSS, this would be only the simultaneous case, assuming the levels were high enough. Therefore there must exist some neural mechanism between the ICC and A1 that is functionally integrating (up to ~6 ms) the converging inputs from two distinct ICC populations and eliciting enhanced A1 activity.

Possible Neural Mechanisms for Enhancement and Refractory Effects

The tectothalamic circuit from the ICC to the ventral division of the medial geniculate body (MGBv) and the thalamocortical circuit from the MGBv to A1 are both possible pathways contributing to the enhancement effect for DSS. The ICC is part of thelemniscal pathway that predominantly projects to the MGBv that then projects to A1 (vs. nonlemniscal regions)

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Wehr and Zador 2005). This excitatory time window of inhibitory mechanisms (Eggermont 1999; Eggermont and Smith 1995; Wehr and Wehr 2009; Wehr and Zador 2003). In other words, suprathreshold stimulation is activating a large cluster of cell bodies, axons, and presynaptic terminals in a simultaneous manner. Since we observed the enhancement effect consistently across a wide range of suprathreshold levels, a large number of output neurons can be activated while still observing enhancement in A1. Although a large number of presynaptic cells and interneurons would also have been activated, their transmission would be significantly blocked by the simultaneously activated output neurons in overlapping regions. Thus it seems more likely that the enhancement effect occurs in a neural region above the ICC.

The tectothalamic pathway from the ICC to the MGBv provides an anatomical organization that could enable enhancement to DSS. Projections from the ICC to MGBv are tonotopically organized and appear to exhibit stepwise frequency bands (Malmierca et al. 2008; McMullen et al. 2005; Schreiner and Langner 1997). Neurons within a given frequency band of the ICC generally project to a similar frequency band within the MGBv (Andersen et al. 1980; Malmierca et al. 1997; Moster 1965; Wenstrup 2005). However, ICC neurons diverge and synapse onto a larger span of neurons along the isofrequency laminae within the MGBv (Cetas et al. 2003; McMullen et al. 2005). During DSS, stimulation of two different ICC populations could sufficiently activate overlapping MGBv populations to transmit increased excitation to A1 (Broicher et al. 2010; Cruikshank et al. 2002). Longer IPIs between two stimulated ICC populations would reduce the convergent MGBv activation and lead to a smaller enhancement effect as shown in Fig. 7. Even for SSS, particularly between 2 and 6 ms, it appears that convergent MGBv activation from repeated stimulation of a similar ICC population could also lead to enhancement. However, below ~2 ms, there is decreased activity due to some refractory effect that we discuss further below.

There is some evidence to suggest that the enhancement effect may also be associated with the thalamocortical pathway. Intracellular recordings in A1 neurons have revealed a strong inhibitory component preceding the excitatory component within ~4 ms that quenches the excitatory response (Tan and Wehr 2009; Wehr and Zador 2003). In other words, excitatory synaptic activity within A1 is limited to a short time window before a strong suppression of response occurs that can last 50–100 ms (as shown in Fig. 4) and even several hundred milliseconds because of additional inhibitory and depressive mechanisms (Eggermont 1999; Eggermont and Smith 1995; Wehr and Zador 2005). This excitatory time window of ~4 ms is consistent with the excitatory window observed for DSS in which greater activity could be elicited for shorter IPIs below 4–6 ms. If two neural populations within an ICC lamina are coactivated close enough in time (approaching 0 ms), then they may be able to fully activate A1 neurons before the suppression onset and result in an approximately linear sum of synaptic activity (on average, this occurs for DSS in Fig. 7).

Unlike DSS, SSS exhibits strong refractory effects for IPIs below 2 ms. It is possible that this refractory effect is due to the inability of the same ICC neurons to be reactivated in such a short period. ICC neurons can have slow membrane time constants (e.g., ~12–33 ms; Sivaramakrishnan and Oliver 2006), limiting their ability to be activated repeatedly within a few milliseconds. However, repeated stimulation of different ICC neurons, as is the case for DSS, would be able to avoid this refractory effect. We also observed what appears to be sustained suppression in which the normalized LFP area in Fig. 6 remained below one for longer IPIs for both SSS and DSS. There are animal studies supporting the possibility that this sustained suppression may occur within the thalamus, in addition to A1 as described above. Projections from the ICC (and inferior colliculus in general) to the medial geniculate nucleus are both excitatory and inhibitory (Bartlett et al. 2000; Peruzzi et al. 1997; Winer et al. 1996). In fact, the largest tectothalamic ICC neurons are inhibitory (i.e., GABAergic, represent up to 45% (in rat; 20% in cat) of the ascending projections, and provide fast transmission to the auditory thalamus that can precede the excitatory tectothalamic input (Ito et al. 2009; Peruzzi et al. 1997; Winer et al. 1996). These strong inhibitory ICC inputs as well as other feedback inhibition circuits [e.g., from Golgi type II interneurons or thalamic reticular nucleus inputs (Winer et al. 1996)] could limit excitation of repeated tectothalamic activation, unless two discrete ICC populations are activated within a short interval to enable the enhancement mechanism (i.e., the enhancement mechanism could dominate over the suppressive mechanism for short IPIs). Considering that projections from the MGBv to the main input layers of A1 are excitatory (Broicher et al. 2010; Cruikshank et al. 2002), these suppressive effects may then be directly reflected in the A1 LFP responses.

As described in MATERIALS AND METHODS, we observed antidromic activity in A1 in response to ICC stimulation. The antidromic activity reaching the cell bodies and dendrites would not directly affect the synaptic activity recorded within the main input layers of A1 (i.e., the neurons cannot elicit activity across the synapses in the reverse direction). However, it is possible that axon collaterals projecting from those antidromically activated neurons could then synapse onto A1 neurons and alter the ongoing layer III/IV activity. This is a limitation of our experiments in interpreting the neural mechanisms underlying the enhancement and suppressive effects. However, regardless of the antidromic contributions to the SSS and DSS responses, these overall effects are induced by AMI stimulation that will affect hearing performance and need to be considered when improving electrode array designs and stimulation strategies.

Implications for an AMI

The current AMI was designed with a single shank array (20 contacts) for placement and stimulation along the tonotopic gradient of the ICC. Although a three-dimensional array to span the three-dimensional ICC was preferred, for safety reasons only a single shank array was inserted into the midbrain in each patient (Lenarz et al. 2006b; Lim et al. 2007). In light of previous AMI stimulation studies (Lenarz et al. 2006a; Lim 2007), we observed that the A1 thalamus was coactivated to an extent that was sufficient to induce a strong enhancement effect. It is possible that these results provide a basis for future improvements in AMI design and stimulation strategies.
and Anderson 2006) and what has been successfully implemented for CI patients (Wilson and Dorman 2008; Zeng 2004), it was expected that stimulation of a reasonable number of frequency regions of the ICC (Friesen et al. 2001; Lim and Anderson 2006; Lim et al. 2007) and the ability of ICC neurons to generally synchronize to the temporal envelope of the signal (Rees and Langner 2005) would enable sufficient speech understanding with the AMI using CI-based stimulation strategies (Nie et al. 2006; Shannon et al. 1995). AMI stimulation can achieve frequency-specific activation (Lenarz et al. 2006a; Lim et al. 2010). However, as shown by this study and previous human AMI results (Lim et al. 2008; McKay et al. 2011), stimulation of a single site within a given frequency lamina elicits strong refractory effects for short delays between electrical pulses as well as greater suppressive effects for longer delays than typically observed for acoustic stimulation that is likely limiting temporal coding abilities. Furthermore, there appears to be an integration mechanism for enabling enhanced A1 activity for coactivation of neurons along an ICC lamina that cannot be utilized by single-shank AMI stimulation.

On the basis of these findings, we are developing and translating a two-shank AMI array to stimulate not only within different frequency regions but also within different iso-frequency locations within the ICC. Although we would prefer to implant a multishank array to differentially activate multiple regions along an ICC lamina that are coding for different features of the stimulus, for safety reasons we are limiting the new AMI array to two shanks. However, even with two shanks, our results have shown a significant improvement in the ability to overcome strong suppressive effects and to rapidly modulate A1 activity by varying the IPI between two stimulated sites within a similar lamina. Our ongoing DSS studies are investigating IPI effects for amplitude-varying pulse trains to identify more realistic stimulation patterns that can be implemented in future AMI patients to improve hearing performance.

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS

Author contributions: R.C., M.L., A.N., V.S., and H.H.L. performed experiments; R.C. and H.H.L. analyzed data; R.C., M.L., T.L., and H.H.L. interpreted results of experiments; R.C. and H.H.L. prepared figures; R.C. and H.H.L. drafted manuscript; R.C., M.L., A.N., V.S., T.L., and H.H.L. edited and revised manuscript; R.C. and H.H.L. approved final version of manuscript; M.L., T.L., and H.H.L. conception and design of research.

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