

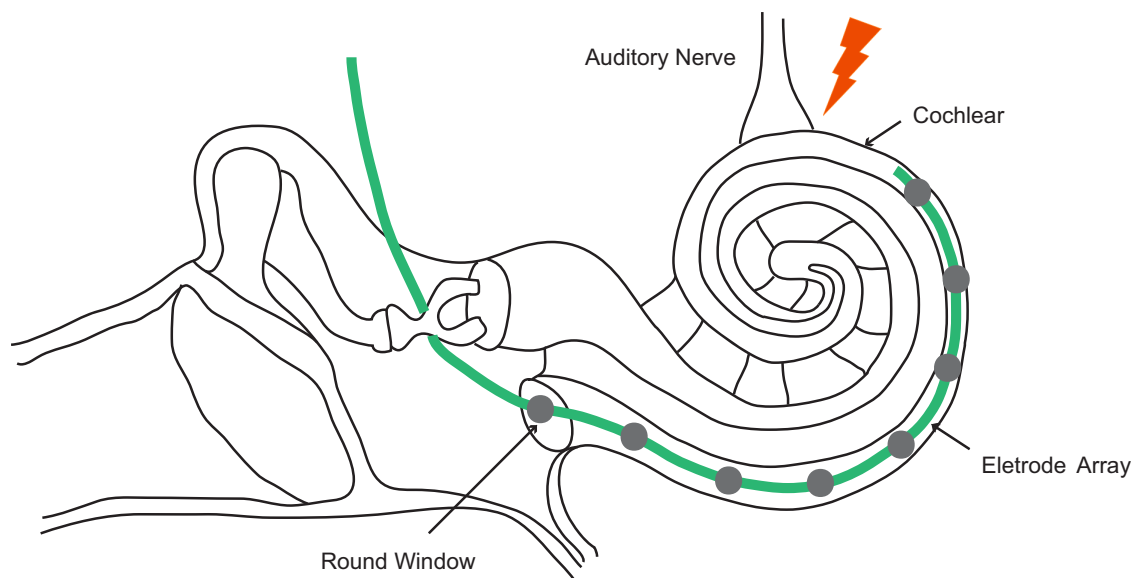
Sensory and Motor Systems

Tracking Down Nonresponsive Cortical Neurons in Cochlear Implant Stimulation

 Charlotte Amalie NavntoftDOI:<http://dx.doi.org/10.1523/ENEURO.0095-17.2017>

Department of Biomedicine, Basel University, Basel, 4056, Switzerland

Visual Abstract



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Significance Statement

The cochlear implant (CI) can restore a sense of hearing to deaf people. Although it works well in quiet situations, most CI users still struggle to follow conversations in noisy environments and perceive music. One challenge in CI stimulation is that the brain must resolve and interpret the signal to generate meaningful and goal-oriented hearing. How efficient this process is and how the underlying neuronal circuits respond, or fail to respond, to such input compared with normally transmitted sound is essentially unknown. Understanding these central auditory mechanisms is crucial for the further development of CIs. In a recent study published in *The Journal of Neuroscience*, [Johnson et al. \(2016\)](#) investigated how CI stimulation engages the auditory cortex in awake marmosets. There were two main findings: first, CIs are surprisingly inefficient in activating cortical neurons that normally respond to sound; second, CI-responsive neurons are functionally different from non-CI-responsive neurons. Here, we discuss the results and hypothesize how inhibition could be involved the brain's response to CIs.

Sound travels from its source to the ear, and further on eventually to the brain, through a chain of biological mechanisms that convert vibrations in the air into nerve impulses. In deaf people, the link between sensory hair cells and the auditory nerve in the cochlea is often broken (or the terminals of the auditory nerve are simply gone), and the auditory input therefore never reaches the brain. Cochlear implants (CIs) bypass this missing link by directly stimulating the auditory nerve. To date, this approach has restored hearing sensation to >300,000 severely and profoundly deaf people.

Present-day design of CIs is based on a bottom-up approach in which the goal is to reproduce normal patterns of neural activity at the auditory periphery. In a recent study published in *The Journal of Neuroscience*, Johnson et al. (2016) used another way of thinking about CI design that includes mechanisms from the central auditory system, and not only its periphery. In such a top-down approach, one asks what input the central auditory system needs to perform optimally in a given situation (Wilson et al., 2011).

The common marmoset (*Callithrix jacchus*) is a valuable model of how the human brain processes auditory information: it is a highly vocal, communicative, and social nonhuman primate, and its hearing range and organization of the auditory cortex (AC) are similar to those of humans (de la Mothe et al., 2006; Osmanski and Wang, 2011). Furthermore, the use of marmosets makes possible the determination of single-neuron responsiveness, which is extremely difficult or impossible to obtain in humans.

Johnson et al. used a novel unilateral CI model, implanting an eight-electrode array in one ear of the marmoset and leaving the other ear intact. Taking advantage of the binaural properties of AC—neurons in one hemisphere are excited by inputs from both ears—the authors precisely located the primary auditory cortex (A1) and characterized the acoustic features and selectivity of A1 neurons to CI stimulation (Fig. 1A, B).

First, the authors investigated how efficient a CI is in transmitting information to the AC compared with acoustic stimuli. They recorded 1408 single neurons from the AC and classified them as either acoustic-driven (the neuron responded to tones or bandpass noise) or CI-driven (the neuron responded to electric stimulation of the implant). It is important to highlight that acoustic and CI stimulation are two different quantities (Wilson and Dorman, 2009), and the authors therefore carefully optimized stimuli parameters to match them as well as possible. One

striking finding of the work is that CI stimulation was surprisingly inefficient at activating as many neurons as comparable acoustic stimulation. Why are some neurons, and not others, activated by a CI?

One possible explanation is related to the differences between contralateral and ipsilateral stimulation, with contralateral stimulation typically being much more effective and precise (Lui et al., 2015). Because their novel unilateral model allowed for testing each neuron's response to both acoustic and CI stimulation, Johnson et al. could compare acoustic properties of nonresponsive and CI-driven cells. The assumed binaurality is a limitation of the paper. It may have been difficult to “functionally localize” responsive neurons, via acoustic stimulation, in the hemisphere contralateral to the implant because the response to ipsilateral acoustic stimulation is different. To address this issue, the authors could have recorded the cortical response first to contralateral acoustic stimulation and then to contralateral CI stimulation after CI insertion in the same ear.

A second possible explanation is that the CI has been activated only with a standard stimulation protocol and not a test battery of additional CI pulse variables (e.g., different pulse wave form shapes, pulse durations, pulse stimulation rates, amplitude modulation), which potentially could engage neurons in a more similar way (higher number of activated neurons, more focused response in the tonotopic map, higher firing rate, etc.). A third possibility is lack of cortical adaptation to CI stimulation, discussed below.

The response of a neuron to pure tones of varying frequency and level, known as its frequency response area (FRA), is a fundamental receptive field measure in the auditory system (Sutter et al., 1999). Neurons with so-called V-shaped FRAs respond to more frequencies with increasing sound levels, whereas O-shaped FRAs are narrowly tuned to sound frequency and level (Sadagopan and Wang, 2008). That CI stimulation mainly engaged neurons with V-shaped FRAs while nonresponsive cells typically had O-shaped FRAs supports the authors' argument that CI stimulation differs in some fundamental ways from the stimulation that results from actual sounds (Johnson et al., 2016).

Why do neurons with small and selective receptive fields not respond to CI stimulation? Are they simply not activated, or are they suppressed? It is well established that the interaction between inhibition and excitation plays a crucial role in shaping and refining the brain's representation of sensory stimulus attributes (Wehr and Zador, 2005). Nonresponsive cells were mainly located in upper cortical layers and CI-responsive cells in middle thalamo-recipient layers, suggesting that the CI signal is received by cortical structures but does not progress to further intracortical processing. In A1, so-called sideband inhibition helps to sharpen the tuning of local neuronal responses and appears as suppression of A1 neurons by off-frequency components (Sutter et al., 1999; Wang et al., 2000; de la Rocha et al., 2008). A big issue with CI stimulation is that the applied current spreads over a wide area, stimulating a large neuronal population (Lands-

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Correspondence should be addressed to Charlotte Amalie Navntoft, Department of Biomedicine, Basel University, Klingelbergstrasse 50-70, Room 7014, 4056 Basel, Switzerland. E-mail: charlotte.navntoft@unibas.ch.

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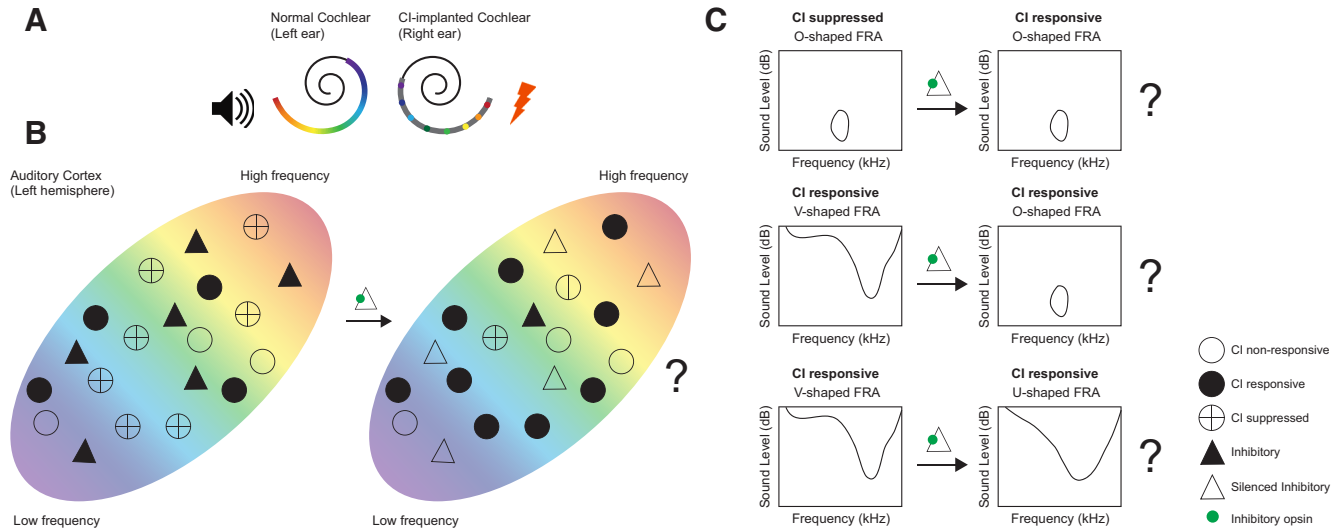


Figure 1. A, The setup used in Johnson et al., 2016. A CI implant with eight electrodes is implanted in the right ear, and the left ear is left acoustically intact. The perception of different frequencies is elicited by stimulating different electrodes along the tonotopic axis in the cochlea (color gradient). This strategy allows Johnson et al. to measure the response of single neurons in the left auditory cortex to both acoustic and CI stimulation in an awake marmoset, and thereby to examine the characteristics of neurons that respond, or fail to respond, to CI stimulation. Acoustic and CI stimuli were matched whenever possible. For CI stimulation, the response of a neuron is tested across different electrode positions and at multiple current levels, and analogously for acoustic stimulation, across a range of frequencies and at multiple sound levels. The CI electrode/frequency producing the significantly largest firing rate response is defined as the best electrode or best frequency of the neuron, for CI and acoustic stimulation, respectively. The receptive field of a neuron is described by electrode/frequency tuning curves across all current/sound levels. **B**, Hypothesis: interneurons, particularly PV interneurons, are important for effective cortical response to CI stimulation. Left, CI stimulation is surprisingly inefficient in activating A1 neurons (black circles) because many neurons are suppressed (crossed circle) by inhibitory interneurons (filled triangles). Right, decreasing inhibitory GABAergic interneuron activity using either optogenetics or pharmacology will increase the effectiveness of CI stimulation, and in particular, likely yield more O-shaped neuron activity either from previously suppressed (top) or evolved from V-shaped neurons (middle; see text). However, decreased GABAergic inhibition would likely come at the cost of broader V-shape tuning in already CI-responsive cells (bottom). Filled circle, CI responsive neuron; open circle, CI nonresponsive neuron; crossed circle, suppressed neuron; filled triangle, active inhibitory neuron; open triangle, inactivated inhibitory cell; green circle, inhibitory opsin or pharmacological blockage.

berger et al., 2012), so the authors proposed that this spread activates an off-frequency component suppressive to neurons. Using broadband acoustic noise to mimic the broad CI stimulation and a two-tone suppression protocol to probe sideband inhibition, they found that CI nonresponsive neurons were also suppressed by broadband stimuli and more easily in the two-tone protocol than in CI-only driven cells. Taken together, the results suggest that the widespread current after CI stimulation activates neighboring off-frequency components that eventually suppress neuronal response to the incoming signal.

These results provide valuable insight into how CI only partially engages the brain at the level of single neurons. Below, I place the findings into perspective and propose future experiments.

The finding that CI-mediated inhibition overwhelms excitation leaves many questions unanswered. Is this misbalance related to the strength of—or the timing between—excitation and inhibition? Which cell types and circuits are involved? Will less inhibition improve efficiency and selectivity of CI stimulation, and eventually improve perception of CI input?

To address the first question, one could look at the temporal dynamics of O- and V-unit population responses on CI stimulation as in Sadagopan and Wang (2010). That

study examined how FRA shape changes over the duration of the response to played sound using population-average FRAs in small time bins. In addition to the well-documented short-latency sideband suppression, they uncovered long-latency suppressions caused by single-tone stimulation. Interestingly, such long-latency suppressions also included monotonically increasing suppression with sound level both on–best frequency (BF) and off-BF. As the CI mainly activated V-unit neurons with monotonic acoustic rate-level functions, this suppressive effect could contribute to the lack of CI efficiency. Sadagopan and Wang (2010) also observed that over time a V-unit response evolved to an O-unit-like response. Further analysis of the present data could therefore investigate whether CI stimulation might fail to promote this process.

In the AC, synaptic inhibition is known to be involved in shaping receptive fields, controlling gain, and promoting temporal precision (Moore and Wehr, 2013; Aizenberg et al., 2015). The overall inhibitory tone is orchestrated by locally acting GABAergic interneurons. The most common types are parvalbumin-positive interneurons (PVs) that target the pyramidal cell bodies and gate feedforward thalamocortical auditory output of layer III/V neurons (Hamilton et al., 2013). In particular, PV activity is thought to be crucial for intensity tuning and to contribute to

sideband inhibition and response timing (Moore and Wehr, 2013; Aizenberg et al., 2015). We therefore hypothesize that PV interneurons might play key roles in the observed inefficient cortical response to CIs. This hypothesis can be explored optogenetically via fast and efficient control of targeted cell types and, importantly, the opportunity to probe causal relations between various actors and actions of interest. A chronic optogenetic model has recently been developed in marmosets (MacDougall et al., 2016), and viral targeting of interneurons in marmosets is in its early phases (Dimidschstein et al., 2016). In the near future, it should be possible to optogenetically manipulate PV activity in AC while recording in AC of a CI-implanted animal (Fig. 1). If PV interneurons contribute to the lack of CI response, inhibiting PV interneurons should increase the effectiveness of CI stimulation and, in particular, might yield more O-unit activity either previously suppressed or evolved from V-shaped neurons. Until such an experiment is feasible, blocking all interneurons pharmacologically (GABAergic inhibitor) on CI stimulation in awake marmosets could be an interesting first step in understanding the role of interneurons (not just PV) in A1. Nonetheless, decreased GABAergic inhibition would likely come at the cost of broader V-shape tuning in already CI-responsive cells, as previously reported (Wang et al., 2000). Indeed, a finely tuned balance between inhibition and excitation is needed to produce an optimal cortical response after CI stimulation.

Hearing with a CI takes time and practice, because the auditory system must adapt to reinterpret the new auditory input as meaningful sound (Fallon et al., 2008; Kral and Sharma, 2012). Therefore, an important caveat of the work by Johnson et al. (2016) is that although recordings were made up to 14 mo after CI implantation, animals received only passive stimulation during the experimental sessions and not during engagement in a task, communication with conspecifics, or any other interaction with the surrounding environment. The results might thus relate to mechanisms in a recently implanted CI user, before any experience and behavioral-dependent plasticity takes place, rather than in an experienced CI user whose brain has adapted to make sense of CI stimulation.

The authors found that neurons sharply tuned to frequency and sound level (O-shaped FRAs) are poorly activated by CI stimulation, but whether this is a result of (1) cortical CI-evoked response or (2) lack of plastic changes is difficult to tell. In favor of the first statement, many CI users face challenges hearing in dynamic and noisy environments, which is partially due to limited dynamic range (5–15 dB compared with 0–120 dB in normal hearing) and a poor ability to discriminate steps in amplitude of a sound (Moore, 2003; Wilson et al., 2011). As these phenomena require fine and robust representation of sound level, it is likely that a general lack of O-unit response could underlie these perceptual limitations.

On the other hand, supporting the second statement, Polley et al. (2006) have shown that behavioral training in rats caused overrepresentation of the target-specific sound

level in the AC (Polley et al., 2006), and plasticity is known to reorganize receptive fields in the AC (Froemke, 2015). Taken together, these data suggest that the marmoset AC in the study by Johnson et al. (2016) has a history of experience with real sounds but not the kind of stimulation produced by CIs. Future experiments using the CI marmoset model could test the hypothesis that O-units are important for CI performance in noisy surroundings. This approach might also reveal whether general experience and behavioral testing with chronic CI stimulation can engage more O-units, and if so, how this would impact perception of CI stimulation. Finally, using the top-down approach described by Wilson et al. (2011), future experiments could use a test battery of other CI parameters (e.g., different carrier rate, asymmetric or ramped pulse shapes, coding intensity via duration instead of amplitude, amplitude modulation) to precisely target and engage more O-units.

Altogether, Johnson et al. (2016) provide solid insight into how the brain responds, or fails to respond, to CI stimulation. The findings will provide crucial guidance for the development of next-generation CIs that target neuronal circuits normally engaged by sound and eventually have potential to improve the outcome of CIs.

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