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Auditory cortical plasticity in cochlear implant users

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Abstract

Cochlear implants are one of the most successful neuroprosthetic devices that have been developed to date. Profoundly deaf patients can achieve speech perception after complete loss of sensory input. Despite the improvements many patients experience, there is still a large degree of outcome variability. It has been proposed that central plasticity may be a major factor in the different levels of benefit that patients experience. However, the neural mechanisms of how plasticity impacts cochlear implant learning and the degree of plasticity's influence remain unknown. Here, we review the human and animal research on three of the main ways that central plasticity affects cochlear implant outcomes.

INTRODUCTION

Hearing loss is a disabling condition affecting many tens of millions of people worldwide [1]. Deafness can impact quality of life beyond loss of a sensory system fundamental to social communication, and is now identified as a risk factor for a number of conditions including dementia and Alzheimer's disease [2,3]. Human subjects with profound deafness can be treated with cochlear implants, which are neuroprosthetic devices that directly electrically stimulate the auditory nerve [4]. However, there is a large amount of variability in learning rates and peak levels of speech perception across individual cochlear implant users [5-7]. Learning to hear with cochlear implants is proposed to require plasticity within

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the central auditory system [8-12], but the mechanisms by which real-world experience or explicit behavioral training enables plasticity and improves outcomes is poorly understood.

Cochlear implants were developed in human subjects over a period of decades, evolving from a single wire to the multi-electrode devices of today [13]. Thes devices are placed within the cochlear and interface directly with the spiral ganglia of the auditory nerve, bypassing any earlier deficits in the hearing pathway such as hair cell damage or conductive hearing loss. However, our understanding of how cochlear implants interface with the auditory system beyond the auditory nerve, how they activate the higher-level central auditory neuraxis, and how these neural systems adapt over time to reinterpret the signals as meaningful sounds is still limited. Central auditory processing is required for patients to be able to use the auditory information provided through cochlear implants [14], and experience-dependent adaptation to cochlear implant input is important for patient outcomes. Most patients require months or even years to reach maximal perceptual performance [5, 15-18], and targeted training improves both speech and music perception in patients [19], suggesting that neural plasticity is a major determinant of patient outcomes. Additionally, for patients with sub-optimal outcomes, few predictive markers exist, and there are no widely accepted methods to affect those outcomes once patient performance has plateaued.

The neural and perceptual adaptation to cochlear implants can also be studied in animals, to reveal fundamental mechanisms and principles by which training affects auditory processing and perception in a way that cannot easily be examined in human subjects. To identify neurobiological factors contributing to successful implant use and inter-subject variability in learning and performance, animal models of cochlear implants have been developed [20-22]. There is a wide body of literature implicating neuroplasticity in cochlear implant performance in both humans and animals. This plasticity can be broken down into either adaptive or cross-modal. Adaptive plasticity is how the central auditory system changes in response to the cochlear implant. Cross-modal plasticity is the idea that one sensory modality can activate a separate sensory system’s central processing areas, in particular when one type of sensory input has been reduced such as in deafness or blindness. Cross-modal plasticity occurs after a period of auditory deprivation, such that the auditory cortex is is re-organized to support other sensory processes, including visual and somatosensory input. Much of the research on cross-modal plasticity in deaf patients focuses on visual stimuli evoking activity in the central auditory system. Depending on the extent of this reorganization and the capacity of the auditory cortex to revert to primarily auditory processing, this can be detrimental to cochlear implant outcomes. Furthermore, cross-modal plasticity occurs differentially in prelingually deaf patients (who have had no auditory experience) and postlingually deaf patients, whose auditory system development was normal. In contrast to the unclear benefits and even potentially disruptive effects of cross-modal plasticity, training and experience with the cochlear implant is important in adaptation to the new form of auditory stimulation. Speech perception performance improves with time, even when there is a reduction of residual unaided hearing, suggesting an adaptive process in the central auditory system. These types of plasticity that occur and interact surrounding cochlear implant use are the topic of this review.

ADAPTIVE PLASTICITY

Following loss of auditory input and cochlear implantation, the central auditory system and perhaps other parts of the brain need to change post-operatively in order to adapt to the electrical input provided by cochlear implants. This is of particular importance when hearing loss occurs in the mature auditory system, which has experience with previous auditory signals. In addition to the spectral degradation of the information provided by cochlear implants, there is presumably some degree of “frequency mismatch” in stimulation. This mismatch refers to the fact that most cochlear implants only cover the most basal turn of the cochlea and thus may not stimulate neurons with low characteristic frequencies. Instead, low frequency stimuli stimulate cochlear locations that are more basal (higher frequency) than the locations that were stimulated by the same sound prior to hearing loss [23]. Over time, the perception of this frequency shift can normalize. Studies using normal hearing subjects listening to acoustic models of cochlear implants suggest that gradual introduction of the shift over several training sessions can result in faster adaptation and perhaps better generalization to new talkers [24-26]. The adaptation of the auditory system over time with cochlear implants has been observed in a longitudinal positron emission tomography (PET) study in both pre- and postlingually-deaf patients. Postlingually-deaf patients. Postlingually-deaf patients showed an increase in PET activation of Broca’s area during speech perception post-implantation, but this was not observed in prelingually-deaf patients. The observation was coupled with increasing speech perception capabilities in the postlingually-deaf group, but not the prelingually deaf [27]. These findings are supported by an earlier study that Broca’s area activation by speech-reading in cochlear implant patients increases with time post-implantation [28]. In a unique case study, intracranial electrocorticographic recordings were conducted in a bilateral cochlear implant user with refractory epilepsy. Results showed activation of the auditory cortex comparable to that of normal hearing patients in this experienced cochlear implant user, but lacking in tonotopicity (or “electrodopicity”) [29].

However, neuroimaging approaches pose some limitations, such as slow temporal dynamics and poor spatial resolution on human studies of adaptation to hearing loss and cochlear implantation. Therefore, several models of hearing loss and cochlear implantation in animals have been developed. These include established procedures for cochlear implantation in the cat, ferret, guinea pig, and marmoset, as well as newer studies of cochlear implants in rodents. These rodent systems present the added utility of transgenic animals for examining mechanisms of plasticity [30,31*].

Auditory studies conducted in ferrets have shown that following monaural deprivation, plasticity is engaged in order to adapt to the new and altered cues for sound localization. Extracellular recordings in the ferret auditory cortex showed that there were distinct neural processes underlying reweighing and remapping localization cues, which mirrored the different types of behavioral adaptations observed in intermittently monaurally deprived humans [32]. Furthermore, the ferret has been used to study sound localization after bilateral cochlear-implantation [33]. Bilaterally implanted animals with early onset deafness had more difficulty with sound localization than those with lateonset hearing loss. However, multisensory training improved performance in implanted ferrets with early-onset hearing loss, and this improvement was correlated with increased responsiveness of the auditory cortex (Figure 1) [34**]. The benefits of training with the implant are further highlighted by studies in congenitally deaf cats, where behavioral training combined with cochlear stimulation induces more improvement in temporal processing than stimulation alone in the primary auditory cortex, but not in the inferior colliculus [35*].

Marmosets have been useful for studying the neural mechanisms of cochlear implant use, as they are non-human primates with sophisticated vocal communication abilities [36]. Furthermore, technical advances enable chronic recordings in behaving animals and possible transgene expression [37,38]. In unilaterally deafened cochlear implanted marmosets, tone-evoked and implant-evoked auditory cortical responsiveness were monitored. A large proportion of neurons that responded to acoustic stimuli did not respond to cochlear implant stimulation (Figure 2) [39**]. Notably, primates in this study received no training with the implant, which might in part account for the limited cortical activation. This was also the case for temporally modulated electrical and acoustic stimuli. Single-unit recordings revealed that cochlear implant electrical stimulation produced both stimulus-synchronized and nonsynchronized firing, with individual units responding similarly to acoustic and electrical stimulation [40].

PRELINGUAL CROSS-MODAL PLASTICITY

Cross-modal plasticity can be categorized based on the cochlear implant users experience with sound. Early evidence of cross-modal plasticity came from studies on congenitally deaf patients, whose auditory system had no acoustic input prior to cochlear implantation. A link between the degree of cross-modal plasticity and speech perception outcomes after cochlear implantation has been suggested. Lee et al. showed early evidence of cross-modal plasticity using PET in a small study of congenitally deaf children [41,42]. Hypometabolism of the pre-operative auditory cortex (measured bilaterally) was positively correlated with cochlear implant outcomes, suggesting that activity in the auditory cortex by other sensory inputs is maladaptive for ultimate auditory processing. In follow-up studies, the degree of auditory cortical PET activation by visual stimuli was negatively correlated with cochlear implant outcomes, but only in the right hemisphere. Decreased visual responsiveness of the auditory cortex post-implantation was positively correlated with behavioral outcomes [42,43]. Separate EEG studies conducted post-implantation showed that visually-evoked potentials, measured as the negative-going evoked potential N1, in auditory cortical areas of cochlear implant patients were correlated with speech perception [44-46]. However, the effect was observed only in the right hemisphere, and sometimes in terms of N1 amplitude (but not latency) or in other cases N1 latency (but not amplitude). These studies suggested a link between cross-modal plasticity and performance with cochlear implants in the pre-lingually deaf population. A recent study examined differences in visually evoked potentials and auditory evoked potentials between normal hearing and congenitally deaf children. Auditory N1 latency and amplitude, as well as visual N1 latency were reduced, but these changes were not associated across sensory modalities, indicating intra-modal rather than cross-modal plasticity [47].

To understand the changes that are occurring in congenitally-deaf patients, animal studies have been conducted to assess the changes in the auditory system due to sensory deprivation.

Developmental hearing loss results in hyperexcitability and decreases in inhibitory synaptic strength in the auditory cortex, changes which persist into adulthood, as shown by studies of conductive hearing loss in gerbils [48]. In neonatally deafened cats with no sensory restoration, there was a loss of tonotopy in the auditory cortex, but if cochlear implant intervention was used after an extended period of deafness (6 months), this tonotopy could be rescued [8,49]. However, even if auditory input was fully restored, there were deficits in performance on auditory tasks [50].

Animal studies have confirmed the presence of cross-modal plasticity after developmental hearing loss. Congenitally deaf cats exhibited enhanced performance on a range of visual psychophysical tasks. This improvement in visual behavior in deafened animals seemed to depend on activity in the auditory cortex [51]. However, the degree to which cross-modal plasticity is detrimental to cochlear implant outcomes is not clear. In congenitally deaf cats with cochlear implants, there was an increase in visual responsiveness in higher order auditory cortical areas However, the activation of auditory cortex by cochlear implants was similar between congenitally deaf and normal hearing cats [52]. Furthermore, auditory evoked potentials in visual areas could be evoked in congenitally deafened cats both implanted late in deafness [53**]. While this does not rule out the possibility that speech comprehension could be negatively impacted by cross-modal plasticity it does question the interpretation that increased visual activation of the auditory cortex reduces the ability of the auditory cortex to respond to future auditory stimuli.

POSTLINGUAL CROSS-MODAL PLASTICITY

Cross-modal plasticity likely occurs in postlingually deafened patients as well, but the degree to which it occurs and the effects on performance are less understood. Limitations of neuroimaging techniques restrict the necessary longitudinal studies to fully characterize these effects. Magnetic resonance imaging (MRI) can be used only with significant limitations in cochlear implant users, as the implanted magnet introduces imaging artifacts. The invasiveness of PET limits its utility. The recent development of functional near-infrared spectroscopy (fNIRS) has helped advance imaging in cochlear implant users, overcoming these invasive/electrical interference issues. This may help clarify issues surrounding cross-modal plasticity in postlingually deaf patients, as it will allow more intra-subject tests to compare cortical activity pre and post implantation [54-56]. The spatial resolution of fNIRS is quite limited, however, more so than that of MRI. In order to address the limitations of individual imaging modalities, more recent studies simultaneously used different techniques, such as EEG and fNIRS to increase resolution [57*].

A series of EEG studies in human subjects showed evidence that cross-modal activation (visually evoked potentials in the auditory cortex) negatively correlated with speech outcomes in post-lingually deafened cochlear implant users, as was observed in pre-lingually deaf cochlear implant users [58-60]. Additionally, increased coupling between the occipital lobe and the temporal lobe as measured by fMRI may predict poor cochlear implant outcomes [61*]. Conversely, studies using alternative neuroimaging techniques proposed that this cross-modal plasticity was not maladaptive, but instead can be beneficial post-implantation by optimizing audiovisual integration [28,62,63**]. Another potential hypothesis is that the type of cross-modal plasticity is important. Visual activation of the auditory cortex may be maladaptive, but auditory activation of the visual cortex promotes performance [64]. Perhaps this distinction reflects that visual inputs to auditory cortex are abnormal, whereas auditory cortical inputs to the visual cortex are normal and serve some adaptive function in healthy subjects.

Over the past several decades, various animal models of adult onset deafness to investigate the cortical changes that occur after sensory deprivation, overcoming some of the limitations of human imaging studies. Cortical reorganization occurs even when sensory input is deprived after normal auditory development, across model organisms. Changes in tonotopy, best frequency, and spontaneous and evoked activity have been observed [65]. For instance, in cochlear ablations and noise-induced trauma in cats, a tonotopic reorganization of the auditory cortex towards intact frequencies was observed [66,67]. In ferrets with adult onset deafness, extensive cross-modal reorganization was observed, with the auditory cortex becoming responsive to somatosensory input [68]. It seems that changes in cortical inhibition underlies many of the functional changes observed. Scholl and Wehr found that acoustic trauma led to complex changes in cortical inhibitory and excitatory responses across frequency tuning curves [69]. A recent study in mice investigated the effects of reduced inhibitory signaling and hyper excitability of the auditory cortex after peripheral auditory nerve damage on recovery of sound processing, revealing that excitability returned to baseline, but the reduction in inhibitory signaling was sustained [70**]. However, in the same study that showed negative impacts on inhibitory synapses in developmental hearing loss, adult onset hearing loss showed no long-term impacts on inhibitory function [48].

CONCLUSIONS

The success of the cochlear implant is evident through the restoration of hearing and speech perception across patient populations. However, an increased ability to predict outcomes is needed to help understand and address the persistent variability in outcomes [6]. The central auditory system seems to first adapt to the loss of sensory input and then to the restoration of auditory input. It is clear that early intervention in prelingually-deaf patients improves the possibility for functional use of cochlear implants, and is related to enabling normal auditory development and reducing development of potentially maladaptive cross-modal activation of the auditory cortex. In a normally-developed auditory system, the adaptive or maladaptive nature of cross-modal plasticity is poorly understood, and further longitudinal studies that include pre- and post-implant time points are necessary. Human studies are complemented by emerging animal models of cochlear implant use that reveal mechanisms of adaptation and plasticity. Knowledge of the optimal or suboptimal conditions for engaging plastic mechanisms can be potentially harnessed to predict and improve outcomes in cochlear implant patients.

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HIGHLIGHTS

- There is a period of adaptation after cochlear implantation that impacts ultimate utility of the implant.
- In prelingually deaf patients, there is visual activation of central auditory areas, but there is limited evidence that this has negative effects on cochlear implant performance.
- Cross-modal activation is present in postlingually deaf patients, but this may provide benefits in cochlear implant use.

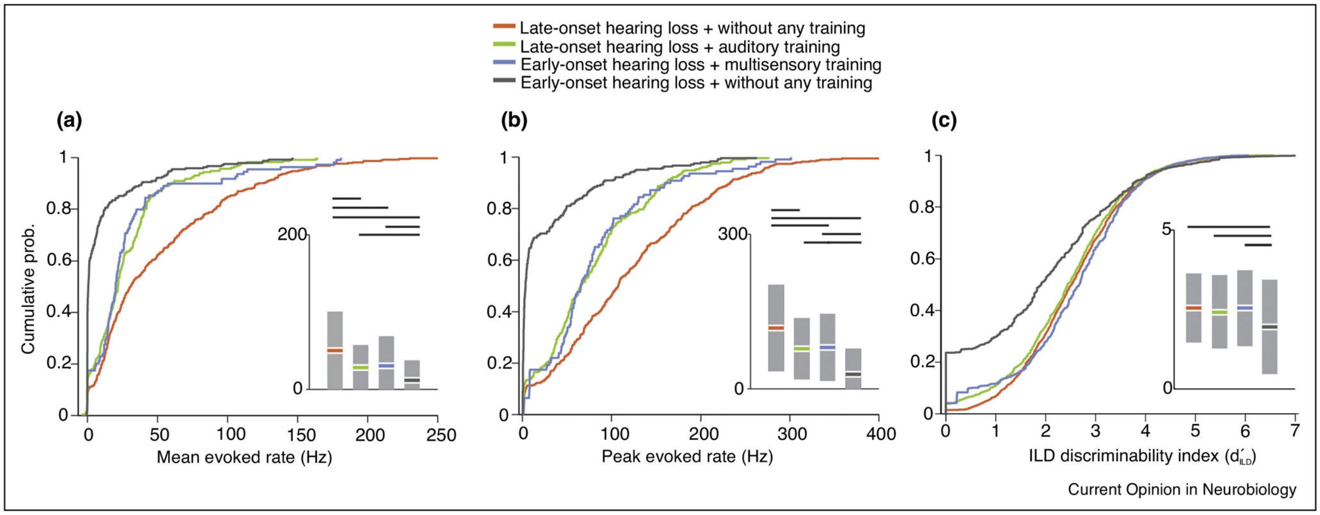

Figure 1.

Cumulative probability functions showing the relative magnitude of the stimulus-evoked responses of A1 neurons, grouped by age of onset of hearing loss and training history in animals with BiCIs. A, Mean sound-evoked firing rates. B, Peak sound-evoked firing rates. C, ILD discriminability index computed from rate-level functions. Insets, Modified box-plots showing the means and 95% confidence intervals of each spike rate measure, grouped in the same fashion as the probability functions. The probability functions and bars indicating that the means have been color-coded to identify the different groups. The horizontal lines indicate significant intergroup differences, as revealed by Tukey HSD tests for post-ANOVA pairwise comparisons. Figure is from Ref 34, with permission.

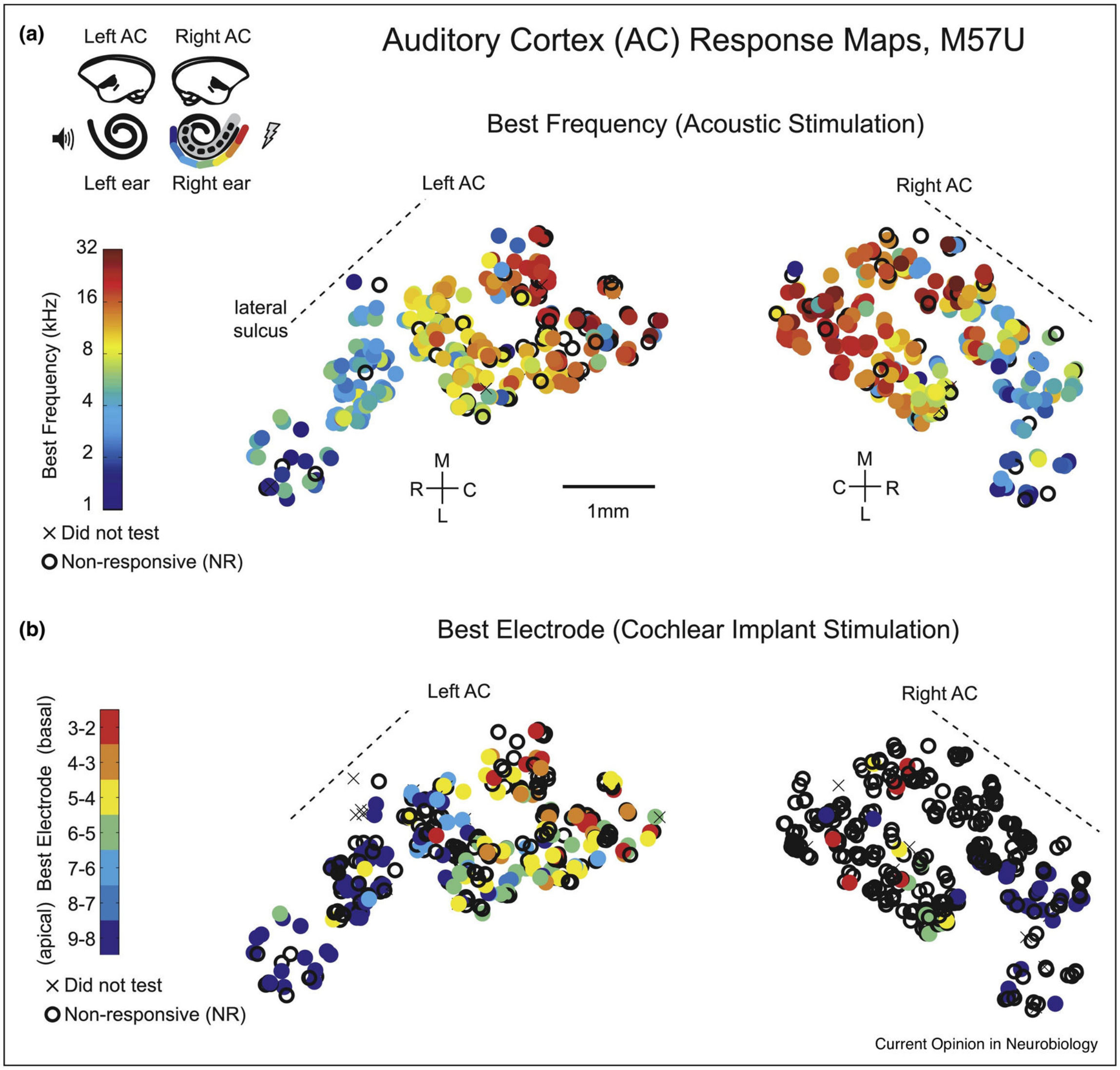

Figure 2.

Topographic maps of auditory cortex responses to acoustic and CI stimulation. A, Acoustic BF maps of left and right auditory cortex (AC) of a marmoset implanted unilaterally in the right cochlea with a CI electrode array (inset plot). Dashed lines indicate approximate positions of the lateral sulcus. Each circle represents a single neuron recorded at that cortical surface location, color-coded by its BF. Black open circles represent neurons nonresponsive (NR) to acoustic tones and bandpass noise. Crosses indicate neurons only tested with CI. B, CI best electrode maps show the same neurons as in A, with color corresponding to CI best electrode. Stimulation was between adjacent contacts in the electrode array, indicated by the pair of numbers on the y-axis. Symbols are the same as in A. Crosses indicate neurons only tested with acoustic stimulation. Figure is adapted from Ref 37, with permission.