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Review article

Impact of peripheral hearing loss on top-down auditory processing

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ABSTRACT

The auditory system consists of an intricate set of connections interposed between hierarchically arranged nuclei. The ascending pathways carrying sound information from the cochlea to the auditory cortex are, predictably, altered in instances of hearing loss resulting from blockage or damage to peripheral auditory structures. However, hearing loss-induced changes in descending connections that emanate from higher auditory centers and project back toward the periphery are still poorly understood. These pathways, which are the hypothesized substrate of high-level contextual and plasticity cues, are intimately linked to the ascending stream, and are thereby also likely to be influenced by auditory deprivation. In the current report, we review both the human and animal literature regarding changes in top-down modulation after peripheral hearing loss. Both aged humans and cochlear implant users are able to harness the power of top-down cues to disambiguate corrupted sounds and, in the case of aged listeners, may rely more heavily on these cues than non-aged listeners. The animal literature also reveals a plethora of structural and functional changes occurring in multiple descending projection systems after peripheral deafferentation. These data suggest that peripheral deafferentation induces a rebalancing of bottom-up and top-down controls, and that it will be necessary to understand the mechanisms underlying this rebalancing to develop better rehabilitation strategies for individuals with peripheral hearing loss.

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Contents

1. Introduction

We effortlessly navigate a world filled with complex sounds. Even under challenging listening situations, our auditory systems routinely extract the meanings of signals corrupted by noise. One cue that may be used to perform this operation is the linguistic or acoustic context within which a sound exists. For example, high-level information about the nature of ambiguous speech sounds

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can dramatically enhance the ability of an organism to recognize these sounds (Davis and Johnsrude, 2007; Liberman and Whalen, 2000; Remez et al., 1981). As such, most real-world hearing is necessarily an inferential process. That is, comprehension of external sounds involves a combination of the detection of the bits and pieces of partially degraded external sound sources, combined with sets of expectations and prior knowledge stored by the listener. It is not yet clear how changes in bottom-up signals from the peripheral auditory system (i.e., in the setting of peripheral hearing loss) alter the top-down mechanisms that influence hearing in noisy environments.

The inferential process of using top-down information to disambiguate noisy signals has been most well described in the domain of speech processing. Here, multiple levels exist in which context can influence the understanding of speech: syntactic, semantic, phonemic and others (Obleser, 2014). Unlike reading tasks, where individuals can control the rate of degraded input by reading more slowly, in hearing, perceptual judgements must be made in real-time, increasing the dependence on contextual information for this process. Therefore, speech perception requires the rapid integration of bottom-up (i.e., signal-related) with top-down (i.e., perceiver-related) factors. Unfortunately, little is known about how bottom-up and top-down signals are integrated in the brain. Nor is it known how loss of bottom-up signals influences the activity of top-down signals. Given the topic of this special issue of *Hearing Research* on plasticity following hearing loss and deafness, this review will focus on the latter, attempting to integrate what is known in the human speech processing literature with the animal literature on sensory system loss. Developing a better understanding of the mechanisms of rebalancing of bottom-up and top-down processing strategies after hearing loss is critical since these strategies will be important in developing new approaches to rehabilitation after hearing loss.

For clarity, we will use the term “top-down” to refer to the cognitive and behavioral manifestations of the use of high-level or contextual information to facilitate sensory processing. The term “descending projection” will be used to refer to anatomical projections originating from sites at upper levels of the sensory hierarchy that project to structures lower in the hierarchy (e.g., from the cortex to the thalamus). One assumption made in this review is that descending projections are important for top-down modulation. This assumption is supported by findings that elimination or stimulation of descending projections dramatically alters receptive field properties of neurons in lower structures (reviewed in (Bajo and King, 2011; Gilbert and Li, 2013; Sillito et al., 2006; Stebbings et al., 2014; Suga, 2012)), as well as altering both their temporal and spatial context-dependent responses (Felsen et al., 2002; Jones et al., 2015). Despite these suggestive findings, there are yet few direct studies available examining the hypothesis that descending projections within sensory systems support behavioral manifestations of top-down modulation. However, given their privileged position to directly modify bottom-up processing based on high-level information, descending projections provide an ideal substrate to mediate top-down cognitive processes. In addition, descending projections are ubiquitous in sensory systems. In some brain structures, such as the thalamus, descending projections outnumber ascending projections by at least 3:1 (Erişir et al., 1997; Van Horn et al., 2000). Descending projections have been described at virtually every level of all sensory systems, ranging from short-range intracortical, to long range from cortex to the brainstem, and, in many cases, extend to the sensory periphery (Guinan, 2006; Heinricher et al., 2009; Matsutani and Yamamoto, 2008; Moga et al., 1990; Repérant et al., 2006). These data suggest that descending projections have the ability to provide high-level cues to influence the earliest stages of sensory processing. See Fig. 1 which summarizes what is known about the organization of descending subcortical projections across sensory systems.

2. Speech perception

It has been known for many decades that speech that is corrupted by noise is made more intelligible by the addition of context (Miller et al., 1951). Fig. 2 shows an intelligibility curve for speech corrupted by noise. This curve may be shifted to the left by any factors that provide some clues to the listener about the nature of the target sound. For example, having heard the sentence prior to it being used as a test item, providing lexical or semantic cues, or limiting the number of choices available to the listener all shift this curve to the left, permitting quantification of contextual advantages (reviewed in (Obleser, 2014)). Another approach to quantify top-down influences on speech perception is to measure the ability to recover missing information in a stream of coherent speech, such as in the phonemic restoration effect. In this effect, phonemes in speech are replaced by noise bursts. Listeners perceive the missing phoneme, often not realizing that these phonemes were replaced by noise. Similar to the speech intelligibility effects described above, the perceived phoneme is dependent upon the context provided by the other phonemes present, and previously stored representations (Shinn-Cunningham and Wang, 2008; Srinivasan and Wang, 2005). It is important to note that paradigms such as the enhancement of word intelligibility by sentence context or phonemic restoration effects, which are commonly attributed to top-down modulatory effects, may also have bottom-up components. For example, coarticulation may alter subtle bottom-up cues for words spoken in sentences and therefore alter their intelligibility (Bonte et al., 2006; Strange, 1989). In addition, the gaps in speech introduced in phonemic restoration paradigms introduce distortions that are mitigated by noise filler, thus providing a bottom up cue to enhance intelligibility (Huggins, 1964). Mitigating these concerns are findings that listener expectation and broader sound context substantially modifies phonemic restoration, suggesting that performance on this task requires top-down modulation (Bashford et al., 1992; Samuel, 1981; Warren and Sherman, 1974).

3. Changes in top-down systems after deafferentation in humans

In the human scientific literature, data describing the influences of bottom-up signals on top-down modulation are derived primarily from studies on two groups of patients with hearing loss: patients with aging-related hearing loss and patients with cochlear implants. Even in the absence of frank hearing loss (measured with pure tone threshold shifts), patients may have auditory deafferentation (e.g., of primarily high-threshold fibers) leading to central reorganization. Such reorganization may lead to auditory perceptual disturbances such as tinnitus and hyperacusis, and top-down mechanisms have been implicated here as well (Song et al., 2015).

Aging is associated with both peripheral hearing loss (Cruickshanks et al., 1998; Moscicki et al., 1985) as well as central changes in auditory processing (Martin and Jerger, 2005; Pichora-Fuller, 2003). Several studies have examined the ability of older listeners with hearing loss to utilize top-down cues to interpret ambiguous or corrupted sounds. These studies have shown a number of effects. First, even when using non-ambiguous speech sounds, aging is associated with disruption of central processing that is not accounted for by a simple decrease in signal to noise ratio of the input sound (Oates et al., 2002; Tremblay et al., 2003).

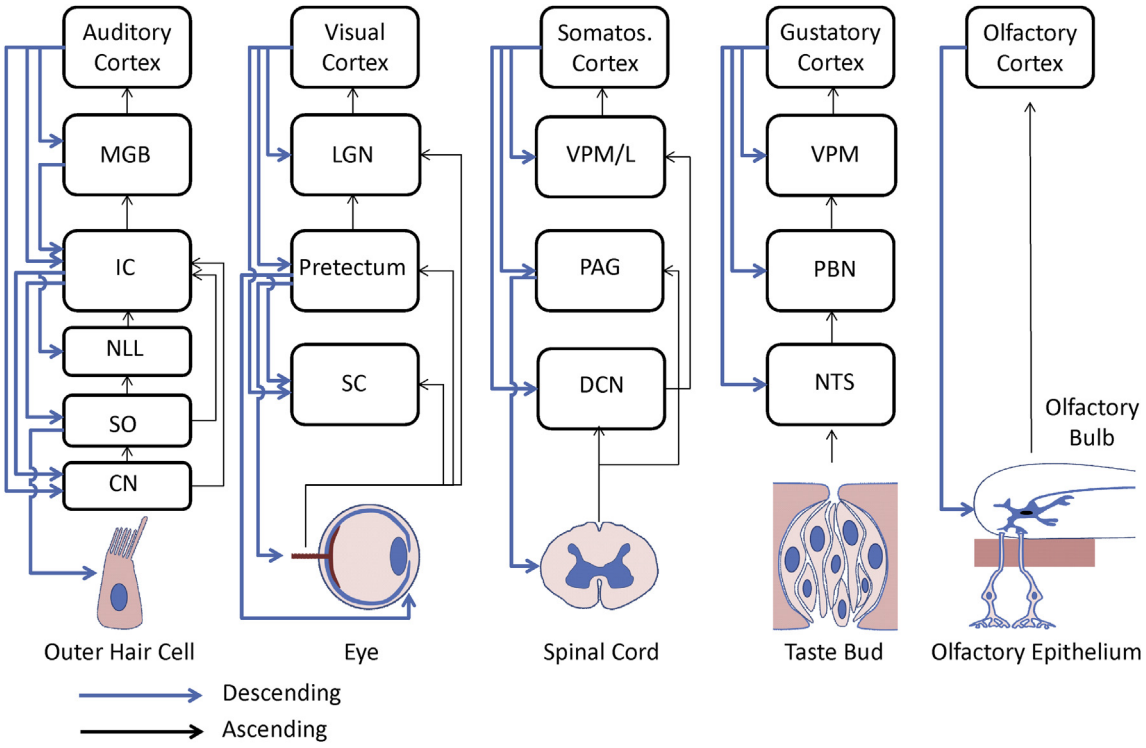

Fig. 1. Schematic diagram illustrating subcortical top-down projections across the five sensory systems. Black arrows = bottom-up projections. Blue arrows = top-down projections. CN = cochlear nuclei, DCN = dorsal column nuclei, IC = inferior colliculus, LGN = lateral genicular nucleus, MGB = medial geniculate body, NLL = nuclei of the lateral lemniscus, NTS = nucleus tractus solitarius, PAG = periaqueductal gray, PBN = parabrachial nuclei, SC = superior colliculus, SO = superior olive, VPL = ventral posterior lateral nucleus of thalamus, VPM = ventral posterior medial nucleus of thalamus.

Second, even when older adults' performances on challenging auditory tasks may appear normal, the extra cognitive effort required to maintain performance on these tasks impairs their performance on other cognitive tasks (i.e., the effortfulness hypothesis) (McCoy et al., 2005). Third, several studies have shown relative preservation of speech perception in noise in older individuals, and in some cases enhanced use of context, compared to the performance that would be expected based on the degree of peripheral hearing loss (reviewed in (Pichora-Fuller, 2008)). For example, Sheldon et al. examined the ability of younger listeners and older listeners with impaired peripheral hearing to use supportive context to identify sentence target words in noise-vocoded speech. Both older and younger listeners showed substantial improvement (i.e., a leftward shift of the psychometric curve analogous to Fig. 2) when either simple semantic context or priming cues were used. However, older listeners showed a statistically significant greater leftward shift than younger listeners (Sheldon et al., 2008). This is consistent with earlier work demonstrating increased use of supportive context in older listeners with hearing loss during challenging listening tasks (Sommers and Danielson, 1999). These studies suggest that peripheral hearing loss may require, or at least facilitate, the greater use of contextual cues by older individuals in challenging listening situations. This strategy, however, has limitations: overreliance on contextual cues can lead to perceptual errors ("false hearing") when low-probability events are used as targets. These types of errors are frequently observed in older listeners (Rogers et al., 2012).

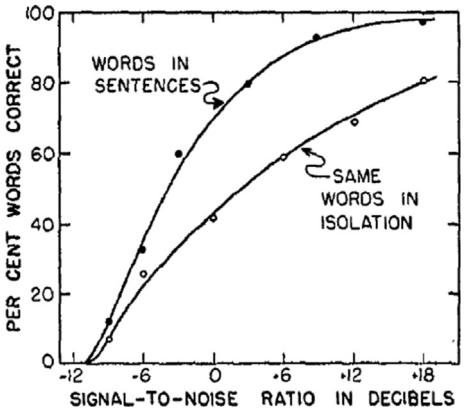

Fig. 2. Psychometric curve illustrating the improvement in speech intelligibility when words in noise are given in context. This improvement is seen as a shift to the left of the psychometric curve (obtained with permission from Miller et al., 1951).

Patients with aging-related hearing loss may also have other aging-related cognitive changes, which may confound any study of the use of top-down strategies by older adults. Therefore, another approach to study the impact of hearing loss on top-down modulation involves the study of a younger group of subjects with cochlear implants. These patients have profound peripheral hearing loss, but do not exhibit the aging-related cognitive changes seen in older adults. A recent study from Bhargava et al. suggests that under certain conditions, cochlear implant users may have an increased ability to utilize top-down cues in a phonemic restoration paradigm. In their study, cochlear implant users were compared to normal hearing listeners who were presented with 8-channel noise-band vocoded speech. The subjects were presented with meaningful speech interrupted by noise bursts and the degree of intelligibility was measured. The investigators found that at a 75% duty cycle (i.e., gaps represented 25% of the signal), cochlear implant users were able to benefit from the phonemic restoration effect to a greater drop in signal to noise than did normal listeners

(see Fig. 3). However, this benefit was restricted; decreasing the intelligibility by decreasing the duty cycle to 50% diminished the phonemic restoration benefit in both cochlear implant users and normal listeners (Bhargava et al., 2014). These data suggest that under certain conditions, chronic impairment of bottom-up information, as seen in cochlear implant users, can enhance use of top-down strategies for the understanding of speech relative to normal listeners. Alternative explanations exist. For example, the noise vocoding used with normal listeners may have increased the difficulty of their task relative to cochlear implant users, accounting for the differences in the groups (personal communication, P. Bhargava).

Other literature has suggested that the use of contextual cues in speech may be impaired in cochlear implant users. For example, Conway et al. found that ambiguous words placed late in a sentence, and hence most able to be facilitated by contextual cues, were not more likely to be intelligible in cochlear implant users (Conway et al., 2014). In Eisenberg et al. the intelligibility benefit of words placed in sentences was seen in most, but not all, cochlear implant users (Eisenberg et al., 2002). Several potential explanations exist for the disparate findings on the use of context by cochlear implant users. First, the use of contextual cues for speech perception in hearing impaired users is dependent on the degree of hearing loss; the effect is largest when the hearing loss is mild (Başkent et al., 2010). Second, domain non-specific cognitive impairment can be seen in cochlear implant users (Kral et al., 2016; Pisoni et al., 2010), and this cognitive loss correlates with the inability to use contextual cues (Conway et al., 2014). Third, the use of contextual cues depends on one's vocabulary and experience with language, two factors which are highly variable in cochlear implant users (Connor et al., 2006). Finally, multiple paradigms have been used in these studies (words in sentences, word order, phonemic restoration), possibly contributing to the disparate results.

The data presented above suggest that top-down modulatory systems that are engaged to enhance speech perception are sensitive to changes in the patterns of afferent input arriving from the peripheral auditory apparatus, and may show plastic effects after hearing loss. The neural instantiations of these top-down changes are not yet known. A broad network of cortical areas, including areas of the superior temporal gyrus and sulcus, angular gyrus, as well as prefrontal cortex are engaged during tasks involving use of contextual cues in challenging listening tasks (Obleser and Kotz, 2009; Obleser et al., 2007). How these networks and their modulatory projections are altered during hearing loss is not known with any specificity. It may be that older listeners or listeners with cochlear implants may rely more heavily on top-down effects without there being structural changes in this pathway. Alternatively, loss of bottom-up input may induce reorganization of descending pathways, permitting an increased efficiency of their use. It is not possible to answer this question in humans by inducing a manipulation of bottom-up inputs and systematically assessing the impact of this intervention on top-down modulatory processes. Studies have shown that animal models also have the ability to use top-down cues to disambiguate noisy signals (Braaten and Leary, 1999; Petkov et al., 2003; Sugita, 1997), raising the possibility that animal models may provide some insights about the underlying mechanisms. In the subsequent sections, we explore the impact of peripheral sensory loss on descending projection systems.

4. Changes in descending systems after hearing loss in animal models: olivocochlear efferents

The olivocochlear system is the most peripheral of the descending auditory pathways and is thought to enhance signal discriminability in noise and to protect the cochlea from acoustic trauma (Guinan, 2010). Fibers originating in the lateral superior olive comprise thin, unmyelinated axons and primarily innervate ipsilateral spiral ganglion cells that contact inner hair cells, while the medial efferent fibers comprise thick, myelinated axons and synapse contralaterally on outer hair cells. The medial system mediates a frequency-specific olivocochlear reflex to diminish cochlear amplification after exposure to loud sounds, while the function of the lateral system is less well understood, and has the potential to both enhance and suppress cochlear signals (Guinan, 2006). While olivocochlear neurons are ideally positioned to exert influence at the auditory periphery, their location also makes

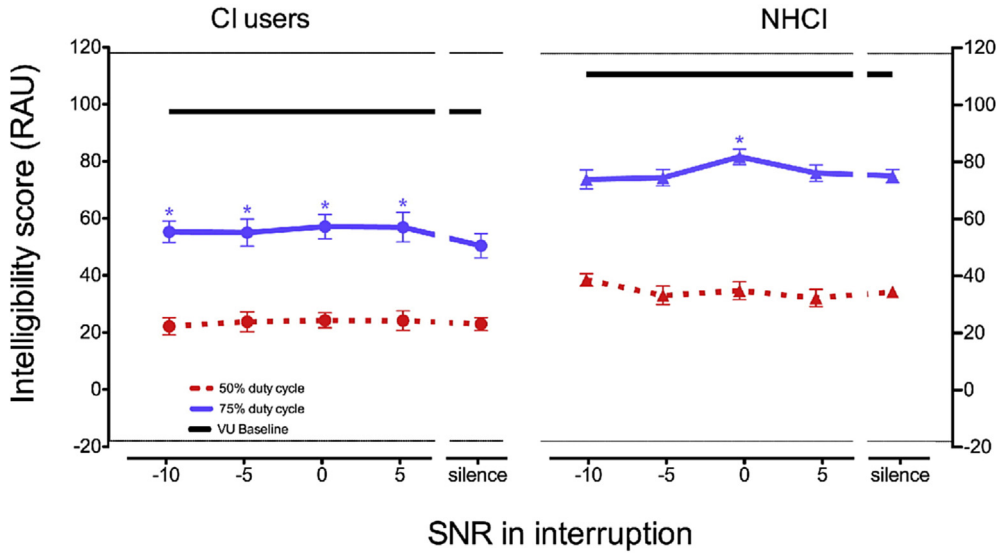

Fig. 3. Intelligibility (in rationalized-arcsine-unit, or RAU, scores) vs. signal to noise (SNR) in cochlear implant (CI) users and normal hearing users listening to noise-vocoded speech (NHCI). Sound is presented as either intact (VU, or Vrij University, baseline in black) or degraded, retaining 75% duty cycle (blue) or 50% duty cycle (red). Sounds are presented either with silence in the gaps (rightmost part of x-axis) or noise with varying SNR (leftmost part of x-axis). Asterisk = $p < 0.05$. (obtained and modified with permission from (Bhargava et al., 2014)).

them vulnerable to changes induced by acoustic trauma. Multiple investigators have characterized the extent of deafening-induced efferent fiber degeneration with contrasting results. McFadden et al. used gentamycin and ethacrynic acid injections to completely destroy inner and outer hair cells in the adult chinchilla. They found that both medial and lateral efferents in the basal regions of the cochlea degenerated first, with a clear base to apex progression of loss over several weeks. Four weeks after injection, efferent fibers were completely absent from the basal half of the cochlea and were reduced by 88% in the apical half, while lateral efferents had fully degenerated in both regions (McFadden et al., 2004). In contrast to this dramatic degeneration, Glueckert et al. observed "excellent survival" of efferent fibers, particularly lateral efferents, for up to 47 days in the guinea pig following similar gentamycin and ethacrynic acid treatments. There was, however, significant loss of medial efferents, especially in basal regions of the cochlea where scar tissue had formed (Glueckert et al., 2008).

To determine whether olivocochlear neurons are able to survive severe cochlear damage, Kraus and Illing retrogradely labeled olivocochlear neurons in rats prior to complete cochlear ablation. Cochleotomy destroys the axons of olivocochlear cells, which is known to induce degeneration and cell death in other populations. The authors found that axotomy led to a 75% reduction in the lateral olivocochlear cell population, but did not affect medial olivocochlear neurons. This differential affect is likely attributable to the presence of surviving axon collateral axonal branches: medial olivocochlear neurons send collateral axonal branches to the ventral cochlear nucleus, and a subpopulation of lateral olivocochlear neurons also project to the inferior colliculus. Interestingly, over half of the surviving lateral olivocochlear cells were shown to express the molecular markers c-Jun and Growth Associated Protein 43 (GAP-43), which are known markers of plasticity and regeneration. These results indicate that lateral olivocochlear neurons may have an innate potential for regeneration that could be exploited given proper environmental conditions, e.g., in the presence of a peripheral nerve graft (Kraus and Illing, 2005).

In a subsequent study, these authors found that GAP-43 is also expressed in the rat ventral cochlear nucleus following cochleotomy or noise-induced hearing loss. Partial cochleotomy gave rise to GAP-43 expression only in regions of the ventral cochlear nucleus that correspond tonotopically to the lesion site. The expression was localized to pre-synaptic terminals and was absent in animals that received injections of kainic acid into the superior olivary complex, indicating that the observed GAP-43 is synthesized in medial olivocochlear neurons. Analysis using electron microscopy revealed profiles matching the morphology of growth cones and showed that GAP-43 stained processes were immature, unmyelinated axons. These results suggest that at least some of the GAP-43 positive terminals result from deafening-induced axonal sprouting and synapse formation, rather than the modification of existing synapses. Furthermore, the GAP-43 positive synaptic terminals selectively formed on post-synaptic profiles that led to ipsilateral excitation and contralateral inhibition, which could help compensate for the loss of excitatory input ipsilateral to the acoustic trauma. Overall, these data suggest that medial olivocochlear inputs to the ventral cochlear nucleus sprout and are altered following hearing loss, and that these changes may specifically help restore the bilateral balance of excitation (Illing et al., 2005).

Other studies further support the idea that cholinergic olivocochlear collaterals to the ventral cochlear nucleus are upregulated following cochlear damage. Jin et al. quantified choline acetyltransferase activity, which is a marker for acetylcholine-based neurotransmission, in the rat auditory brainstem following cochlear ablation. They found that choline acetyltransferase activity increased by 30–50% bilaterally in the ventral cochlear nucleus, but decreased ipsilaterally in the lateral superior olive and bilaterally in the ventral nucleus of the trapezoid body. The decrease in choline acetyltransferase activity is thought to reflect axotomy-induced death of lateral and medial olivocochlear neurons in these regions. The increased activity in the ventral cochlear nucleus, however, is likely due to sprouting and upregulation of existing cholinergic olivocochlear collaterals (Jin et al., 2005). The physiological data of Sumner et al. also support this hypothesis. Following ossicular disruption, they observed an immediate and lasting increase in the proportion of ventral cochlear nucleus neurons exhibiting excitatory responses to contralateral noise stimulation. This long-latency response was similar to responses occasionally seen in normal hearing animals, indicating the upregulation of an existing, multisynaptic pathway. The collateral projection from the ventral nucleus of the trapezoid body to the ventral cochlear nucleus is a likely candidate underlying this contralateral excitation. Other potential sources could include descending glutamatergic inputs from the inferior colliculus or from the contralateral cochlear nucleus (Sumner et al., 2005).

5. Changes in descending systems after hearing loss in animal models: corticofugal projections

Projections from the cortex to subcortical structures (corticofugal projections), particularly to the thalamus and inferior colliculus, are numerous, heterogeneous and have substantial physiological impact on their target structures (Bajo and King, 2011; Bajo et al., 1995; He, 2003; Llano and Sherman, 2008; Ojima, 1994; Prieto and Winer, 1999; Slater et al., 2013; Stebbings et al., 2014; Suga, 2012; Villa et al., 1991). Despite this, far less is known about how hearing loss affects corticofugal projections than about brainstem descending projections; much of this information must be extrapolated based upon changes in layer V and VI of the auditory cortex, in which corticocollicular and corticothalamic cells bodies reside. The layers of the primary auditory cortex, like other sensory cortices, receive distinct thalamic and cortical inputs and are hypothesized to be activated sequentially, such that after thalamic inputs activate layer IV, supragranular layers send projections to infragranular layers, which then project to subcortical targets (Douglas and Martin, 2004). To examine the layer-specific functional deficits of the auditory cortex in deafness, Kral et al. used the deaf white cat as a model for congenital deafness. These animals are completely devoid of inner and outer hair cells by the typical age of hearing onset, but, unlike pharmacologically deafened animals, do not exhibit profound degeneration of primary afferents. Furthermore, despite their complete lack of auditory experience, the brainstem of the deaf white cat largely retains normal connectivity, and the auditory cortex has been shown to contain a rough tonotopic arrangement. Therefore, these animals serve as a good model to assess functional consequences of auditory deprivation in the face of a relatively normal central anatomy. The authors compared the effect of stimulation via cochlear implants in deaf white cats and normal controls on auditory cortical field potentials at multiple depths. They found that the temporal pattern of activation for the supragranular layers was delayed in deaf white cats, indicating a deviation from the canonical pattern of cortical activation; furthermore, the amplitude of the activation in the infragranular layers was significantly reduced (See Fig. 4 for their summary of these effects in the cortex). The authors attributed this attenuation to abnormal or immature activation of the input from the supragranular (layers II and III) to the infragranular (layer V and VI) layers. Since the cells in layer V and VI of the auditory cortex give rise to the descending projection systems, it is

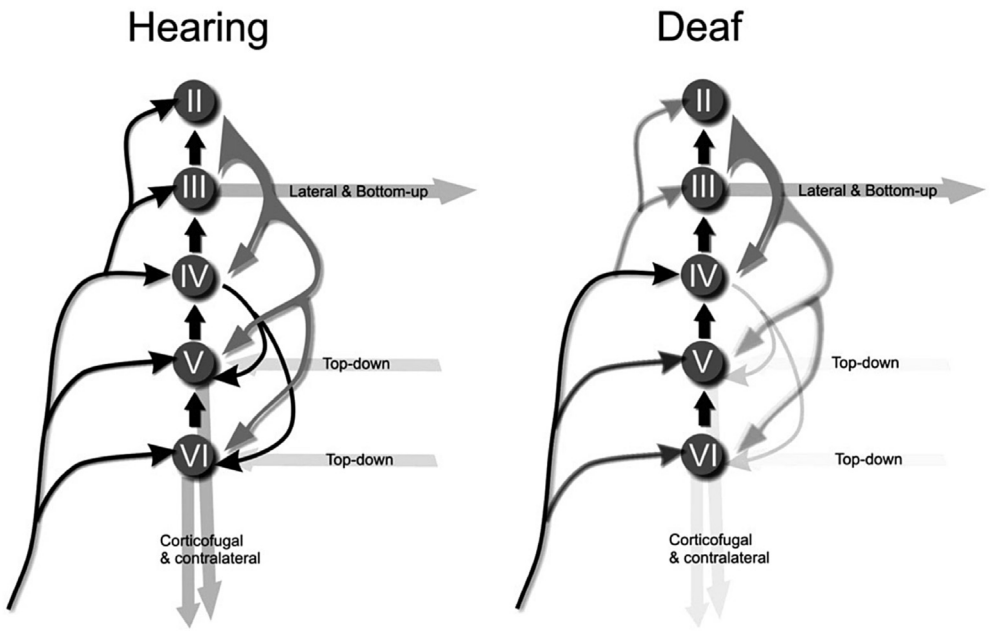

Fig. 4. Layer-specific functional organization of the auditory cortex in normal (left) and congenitally deaf white cats (right). Intracortical transmission deficits in the congenitally deaf white cat likely affect corticofugal pathways in addition to callosal and hierarchical cortico-cortical networks (obtained with permission from (Kral and Eggermont, 2007)).

likely that these pathways to the auditory thalamus, midbrain, brainstem, and other targets are also compromised (Kral et al., 2000).

Other studies have employed methods that reversibly occlude the ear canal, such that auditory input can be altered or attenuated for a particular experimental time window and subsequently restored. Bajo et al. used such an experimental paradigm to investigate how temporary unilateral occlusion affects sound localization ability in ferrets. Normally, ferrets with an earplug will initially experience difficulty in localizing sound, but, with training, can adapt to the altered cues and improve performance to control levels. The authors specifically wanted to test the hypothesis that the auditory corticofugal pathway mediates these learning-induced changes. In an experimental group of ferrets, this pathway was selectively destroyed via injection of a retrograde tracer to label the corticocollicular pathway and then subsequent chromophore-targeted laser photolysis. Following ablation of the cortico-collicular pathway, these ferrets were comparable to control animals in terms of their ability to localize sound. However, following unilateral occlusion, these animals could not re-learn to localize sounds from the contralateral hemifield. These results broadly suggest that descending pathways are involved in adaptation in degraded sensory environments, and specifically show that the corticocollicular pathway is involved in learning-induced auditory plasticity (Bajo et al., 2010).

6. Insights from the visual system

Far more is known about anatomical changes in corticofugal projections following deafferentation in the visual system than in the auditory system, particularly with regards to the visual corticocollicular projection. The cortical input to the superior colliculus is conserved across species and appears to be involved in coding for directional selectivity and binocularity, among other properties (Swadlow, 1983). García del Caño et al. investigated how removal of the retina within the first 48 postnatal hours affected the topography of corticocollicular projections to the superior colliculus in rabbits. After a 45–50 day period post-lesion, they injected the tracer phytohemagglutinin-L (PHA-L) into the contralateral striate cortex of enucleated and control animals to label projections to the superficial layers of the superior colliculus. They found that the terminal field in the lesioned animals was significantly larger than in controls. The central position of the labeling, however, was similar for both groups, indicating that positional cues were not disrupted. They also saw a marked increase in the number of synaptic terminals in the stratum zonale of lesioned animals. The authors hypothesized that the increase in fibers and synaptic terminals in medial areas of the superior colliculus could be caused by a compensatory mechanism, since these areas are typically innervated by retinal inputs. Under normal conditions, these fibers might be eliminated due to competitive interactions with retinal inputs (García Del Caño et al., 1997).

In a later publication, these authors performed similar enucleation experiments in both newborn and adult rats. Their anterograde tract-tracing data for the newborn rats was consistent with their previous findings in rabbits: whereas labeling in control rats was organized into a discrete column, the terminal fields in enucleated animals expanded across nearly the entire collicular surface (Fig. 5A, B). It was unclear whether this expansion reflected active sprouting mechanisms caused by visual deprivation, or simply a maintenance of the typical immature pattern into adulthood. Adult enucleated rats showed no terminal field expansion, indicating that the plastic mechanisms giving rise to axonal sprouting/deactivated pruning are restricted to a developmental window (Fig. 5C). Interestingly, the adult enucleated animals also showed increased synaptic terminal density in the stratum zonale, suggesting that the plastic processes involved in reactive synaptogenesis are maintained into adulthood (García Del Caño et al., 2002).

Depending upon the species being studied, the retinal projection may reach the superior colliculus before birth (Bunt et al., 1983; Godement et al., 1984; Williams and Chalupa, 1982). It is possible, then, that postnatal enucleation studies are not entirely representative of the topography of corticocollicular termination patterns in the absence of retinal input. Studies that have examined the visual corticocollicular projection in anophthalmic mice are

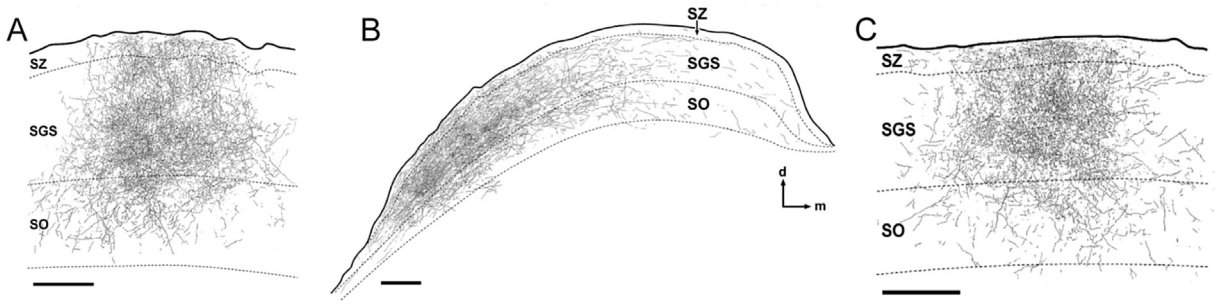

Fig. 5. A) Terminal field of a control rat. B) Expanded terminal field of rat enucleated in early postnatal life. C) Terminal field of rat enucleated in adulthood, demonstrating a lack of expansion (obtained with permission from (García Del Caño et al., 2002)). SG = stratum griseum superficiale, SO = stratum opticum, SZ = stratum zonale.

largely in agreement with the aforementioned enucleation studies. Additionally, these studies have shown that the corticocollicular axons in anophthalmic mice reach the superior colliculus later and their rate of growth within the colliculus is slower in comparison to controls. Furthermore, while a rough topographical arrangement is present in anophthalmic mice, it never reaches full refinement (Khachab and Bruce, 1999).

The distribution and number of visual corticocollicular cells bodies within the cortex has also been investigated in instances of deafferentation. Rhoades et al. bilaterally enucleated newborn hamsters and performed retrograde tract-tracing studies 120–180 days later. They found essentially no difference between the enucleated hamsters and controls in terms of the number and distribution of both corticocollicular and corticothalamic projections. They did, however, see abnormal layer specificity for callosal projections in the enucleated animals (Rhoades and Fish, 1983). Retrograde tracing studies in monocularly enucleated newborn opossums, however, showed differing results in terms of the distribution of corticocollicular cell bodies. Djavadian et al. performed bilateral injection of two different retrograde tracers in the right and left superior colliculus three months after the enucleation surgery. Both tracers labeled cells ipsilaterally in layer V of the striate cortex. The number of labeled cells, however, was greatly reduced (65% reduction) on the side ipsilateral to the lesion in comparison to control animals (Djavadian et al., 2001). It is unknown why these two studies differ in their results, though species-specificity or differences in post-operative survival time may account for some of the variation.

Cellular changes have also been reported in the corticothalamic pathway in instances of visual deprivation. Fukuda et al. performed enucleation experiments on different groups of rats at postnatal day 1 or 3. At 3–5 months, the rats received injections of a retrograde tracer either in the lateral geniculate nucleus or the visual cortex. The area of the retrogradely-labeled corticothalamic and thalamocortical cells was then measured. The rats that were enucleated at postnatal day 1 showed significant increases, between 15 and 47%, in cell body area compared to controls. However, this effect was largely abolished in the animals that were enucleated at postnatal day 3, with only contralateral layer VI cells showing a mild increase in soma size. Interestingly, this increase in soma size for descending connections was in sharp contrast to the results seen for the thalamocortical cells, which decreased in area for both postnatal groups (Fukuda and Hsiao, 1984).

The timing of corticothalamic innervation also seems to be intimately linked to retinal input. To visualize the development of visual corticothalamic projections, Seabrook et al. used a transgenic mouse in which green fluorescent fusion protein is targeted to neurons with cell bodies in layer VI. In these same mice, they injected the tracer cholera toxin B intravitreally to label developing retinal projections. They found that corticogeniculate fibers begin to enter the lateral geniculate nucleus around postnatal day 3 or 4. At this time point, the retinal projections had already fully innervated the lateral geniculate nucleus. The corticothalamic fibers did not reach full innervation until after eye opening, when the retinal projections had formed distinct eye-dominant domains. The authors also examined how retinal deafferentation affects the development of the corticothalamic projection. They either surgically removed the eye after birth, or genetically bred the mice with a mutant strain in which retinal progenitors fail to develop. In both instances, they found that corticothalamic development was accelerated: the corticothalamic axons began entering the lateral geniculate nucleus at postnatal day 2, and reached complete innervation by postnatal day 8–10. Despite this accelerated anatomical growth, physiological experiments revealed that corticothalamic synapses in genetically deafferented mice functionally matured at the same rate as control mice (Seabrook et al., 2013).

In a follow-up study, the authors uncovered a molecular mechanism controlling the relative timing of retinal and corticothalamic innervation. They found that aggrecan, a repulsive protein found in the extracellular matrix, is temporarily upregulated in the neonatal lateral geniculate nucleus during normal development. Aggrecan expression prevents premature entry of corticothalamic axons into the lateral geniculate nucleus. Retinal inputs are able to control the timing of degradation of aggrecan, and in their absence, aggrecan is prematurely degraded, thus leading to accelerated innervation of corticothalamic inputs (Brooks et al., 2013).

7. Insights from the somatosensory system

Studies in the somatosensory system have investigated the role of corticothalamic feedback on reorganization of thalamic receptive fields in response to sensory deprivation. Krupa et al. measured the responses of single units in the rat ventral posterior medial nucleus of the thalamus to whisker stimulation before and after temporary whisker deafferentation (via injection of lidocaine into the whisker pad). They found that deafferentation led to unmasking of sensory responses to whisker stimulation as well as elimination of existing responses. In another group of deafferented animals, the primary somatosensory cortex was inactivated with muscimol prior to whisker deafferentation. In comparison to the control animals, cortical inactivation reduced the degree of receptive field reorganization by 50% and caused a marked decrease in the size of the unmasked sensory response and the number of neurons exhibiting unmasked responses induced by deafferentation (Krupa et al., 1999).

Chowdhury et al. also investigated the role of top-down somatosensory modulation on thalamic receptive fields after deafferentation. These experiments were conducted in raccoons that had undergone removal of a single forepaw digit. They found that

cortical lesions in control animals led to an immediate 85% increase in the size of receptive fields of neurons in the somatosensory portion of the thalamus (the ventroposterior lateral nucleus). While digit removal caused expansion of receptive fields relative to control animals, cortical lesions in deafferented animals did not significantly alter these receptive fields when the lesion was performed shortly after deafferentation. However, when cortical lesions were induced 4 months after digit removal, an overall 25% expansion in receptive field size was observed. These data indicate that cortical feedback influences receptive field size in the intact animal and after recovery from peripheral injury, but is ineffective during early stages of deafferentation-induced reorganization (Chowdhury et al., 2004).

Other investigators have examined changes in functional connectivity between somatosensory cortex and thalamus following peripheral deafferentation. Jung and Shin recorded single units in the ventroposterior lateral nucleus of the thalamus and the primary somatosensory cortex before and during injection of lidocaine into the forepaw of adult rats. Using spike-triggered cross-correlation analysis, they found that the degree of both thalamocortical and corticothalamic connectivity was significantly reduced during temporary deafferentation. Of the corticothalamic connections that persisted during temporary deafferentation, 9 were suppressed and 23 were enhanced relative to baseline conditions before lidocaine injection (Jung and Shin, 2002), suggesting compensatory upregulation of top-down control after loss of afferent input.

8. Conclusions and implications

Overall, these studies reveal that a loss of bottom-up sensory input produces a variety of changes in descending projections, and may have clinical implications. The human literature suggests that peripheral hearing loss with aging or in cochlear implant users, in certain circumstances, induces a greater ability to use top-down cues than those without such hearing loss. This increased reliance on top-down cues has its limitations and can also induce false percepts. The animal literature suggests a great number of changes occur after peripheral deafferentation across different sensory systems. These changes include structural modulations at the level of cell bodies and terminals, temporal changes in developmental innervation patterns, and physiological alterations in functional connectivity and control of receptive fields. The precise nature of these alterations is dependent upon the timing of sensory deprivation, the experimental animal of choice, and the system of interest; for example, enucleation produces opposite effects in the timing of innervation for corticocollicular and corticothalamic projections. The observed effects are likely caused by a complex interplay of molecular changes and activity-dependent mechanisms. When interpreting the data from the visual and somatosensory deafferentation studies, it is important to recognize major organizational differences between the auditory system and other sensory systems. The auditory system contains multiple subcortical processing structures caudal to the inferior colliculus, many of which are required to stimulus location. Given the needs of the auditory system to compute stimulus location in space, while visual and somatosensory systems rely on their sensory epithelia for this, the auditory system may have a lower tolerance for subcortical plasticity than what exists in visual and somatosensory systems. Therefore while these findings from the visual and somatosensory systems may not be wholly generalizable to the auditory system, they do provide clues about into how hearing loss may affect the analogous auditory corticofugal systems, and may provide insights to develop better strategies to ameliorate the effects of hearing loss on the comprehension of complex sounds.

A greater understanding of the relationship between peripheral hearing loss and top-down modulation may also better inform approaches to auditory rehabilitation. For example, it may be possible to capitalize on the preserved top-down modulatory strategies in older hearing-impaired listeners by utilizing more synthetic- or sentence-based rehabilitation approaches (rather than phoneme-based), or by building up stored representations in anticipation of encountering specific acoustically-challenging situations. Both approaches have been used in the past with some success ((Rubinstein et al., 2000; Stacey and Summerfield, 2008), reviewed in Pichora-Fuller and Levitt, 2012). In addition, specifically addressing domain-general cognitive processes (such as selective attention and sequence learning) which serve as prerequisites for the effective use of top-down cues in speech, may be of particular value in cochlear implant users, who may have impairments here (Kral et al., 2016; Pisoni et al., 2010). Therefore, continued exploration of the relationship between degradation of bottom-up sensory processing and plasticity in descending projections is likely to bear fruit in our ability to enhance the quality of life of patients with hearing impairment.

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