



Corticofugal modulation of audition

Diego Elgueda¹ and Paul H Delano^{2,3,4,5}

The mammalian brain is connected to the ear through corticofugal pathways. These neural circuits link non-auditory regions of the cerebral cortex like frontal and visual areas with the auditory cortex or the inferior colliculus, which send descending pathways that reach the cochlear receptor through olivocochlear neurons. Recent evidence has demonstrated that top-down circuits are functional and relevant for behavior and cognition. For instance, the corticofugal modulation of peripheral auditory responses aids in ignoring irrelevant stimuli during selective attention. The neural mechanisms involved in these modulations include sensory gain control and oscillatory changes of neural and cochlear activity. Whether these corticofugal effects are a general mechanism to filter auditory responses during cognitive and emotional processes remains to be confirmed.

Addresses

¹ Departamento de Patología Animal, Facultad de Ciencias Veterinarias y Pecuarias, Universidad de Chile, 8820808, Santiago, Chile

² Departamento de Otorrinolaringología, Hospital Clínico de la Universidad de Chile, 8380456, Santiago, Chile

³ Departamento de Neurociencia, Facultad de Medicina, Universidad de Chile, 8380453, Santiago, Chile

⁴ Centro Avanzado de Ingeniería Eléctrica y Electrónica, AC3E, Universidad Técnica Federico Santa María, 2390212, Valparaíso, Chile

⁵ Biomedical Neuroscience Institute, BNI, Facultad de Medicina, Universidad de Chile, 8380453, Santiago, Chile

Corresponding author: Delano, Paul H (pdelano@med.uchile.cl)

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Introduction

The auditory system allows animals to detect pressure changes in the environment, which are perceived as sounds, and are essential for acoustic communication, modifying behavior for important functions such as survival and reproduction. This sensory function is often thought of as a unidirectional process, going from the cochlear receptor to central auditory structures. However, the auditory pathways include descending neural circuits, connecting the brain with the cochlea in a bidirectional

manner [1]. Importantly, top-down circuits are not limited to the auditory pathways, but to the whole nervous system, including cognitive, emotional and sensory regions of the brain [2–4]. In this article, we review evidence that the corticofugal modulation of audition involves different neural networks, which through connections with the auditory cortex and subcortical auditory nuclei can even modulate the most peripheral structures of the auditory pathway: the cochlea and auditory nerve.

Corticofugal pathways from the brain to the inner ear

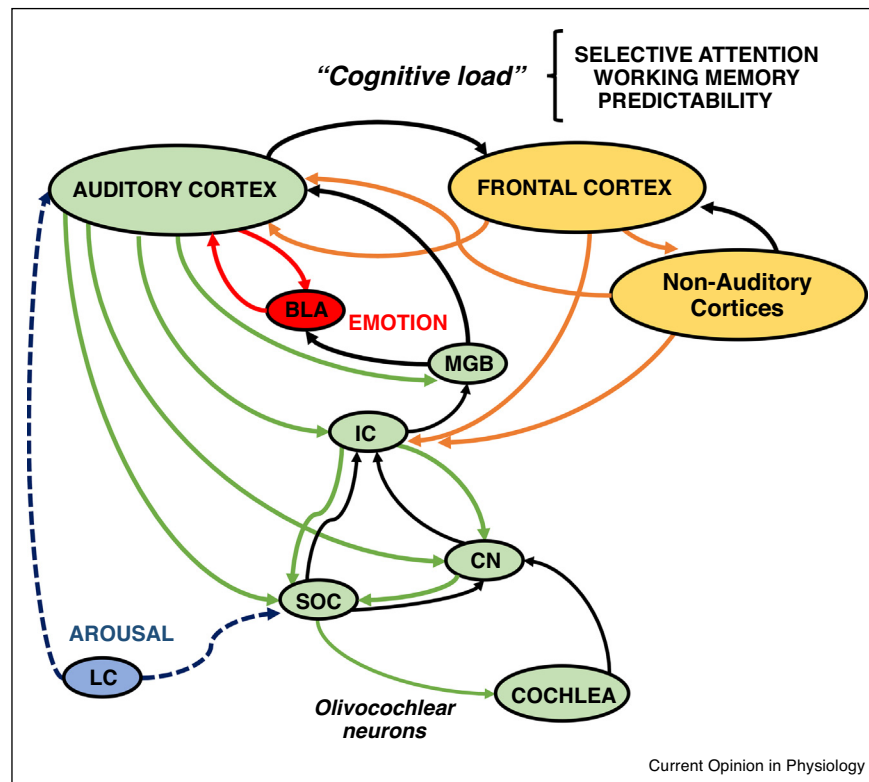
The deep layers of the auditory cortex (V and VI) send prominent corticofugal projections to several subcortical nuclei of the auditory pathway, including the thalamus, inferior colliculus (IC), superior olivary complex (SOC) and cochlear nucleus, reaching the cochlear receptor through olivocochlear neurons [5,6]. There are two types of olivocochlear neurons in the SOC: medial and lateral olivocochlear neurons, which make cholinergic synapses with the outer hair cells (OHC) of the cochlea and with auditory-nerve fibers, respectively [7,8].

In addition, the auditory cortex is vastly interconnected through top-down and bottom-up circuits with frontal and temporo-parietal regions of the brain [2,3]. Importantly, corticofugal projections have also been described from the frontal, somatosensory and visual cortices to the IC [9•]. The auditory efferent network is also interconnected with emotional and arousal circuits: the amygdala receives direct afferent projections from the auditory thalamus and efferent connections from the auditory cortex [4,10], while locus coeruleus neurons make synapses with olivocochlear neurons [11,12] and auditory cortex [13]. A summary of cognitive, emotional and arousal brain networks that could influence auditory efferents is presented in [Figure 1](#).

Corticofugal modulation of the olivocochlear reflex

Medial olivocochlear (MOC) neurons are activated by ipsilateral and contralateral sounds, through a brainstem reflex [14] that has been implicated in protection to loud sounds and antimasking of auditory stimuli in background noise [7]. Importantly, physiological studies have shown that the MOC reflex can be modulated by auditory-cortex descending projections [15,16]. Dragicevic *et al.* [15] using electrical microstimulation of the auditory cortex in chinchillas, showed that the auditory cortex sets an optimal strength of contralateral sound suppression on auditory-nerve responses of about 1–2 dB. A similar paradigm in mice with a genetic deletion in the MOC

Figure 1



Top-down connections from the brain to the cochlear receptor. Black arrows represent ascending connections in the auditory pathways and brain connectivity. Green ovals and arrows represent auditory structures and auditory efferent pathways. Orange ovals and arrows represent top-down connections from frontal and other non-auditory cortices to the auditory cortex and inferior colliculus. Red represents emotional connections between the auditory system and basolateral amygdala, while blue shows connections from the locus coeruleus to olivocochlear neurons and auditory cortex, which might be involved in arousal modulation of SOC activity. The auditory cortex and the inferior colliculus are key structures connecting non-auditory regions of the brain with the auditory efferent network. Other structures (i.e. claustrum) are not shown for simplicity. BLA: basolateral amygdala; CN: cochlear nucleus; IC: inferior colliculus; MGB: medial geniculate body; LC: locus coeruleus; SOC: superior olivary complex.

cholinergic receptor of OHCs ($\alpha 9$ -nicotinic receptor knock-out) demonstrated that the corticofugal effects on auditory-nerve responses are mediated by the cholinergic MOC synapses on OHC [16]. These studies in animal models show that the auditory cortex can modulate the MOC reflex strength. This conclusion is also supported by human experiments in which cortical ablation of the temporal superior gyrus reduced the strength of the MOC reflex [17], while electrical microstimulation of the auditory cortex diminished the amplitude of otoacoustic emissions (a measure of cochlear hair cell function) [18]. Interestingly, MOC feedback is absent in subjects with cochlear implants, which has motivated the implementation of coding strategies to improve speech-in-noise performance of bilateral cochlear implant users [19]. Future cochlear implants could go further and develop closed loops that mimic the cortical modulation of the MOC reflex [15,20].

Top-down projections from frontal, visual, and association areas to the auditory cortex

Previous reviews on corticofugal modulation of audition consider the auditory cortex as the origin of the auditory efferent system [1,5,6]. Although this could be true for the auditory modality, our brain is always functioning with multisensory influences, which are also modulated by our cognitive and emotional states [4,21,22]. Along this line, the neuroanatomy of the connections between the auditory cortex and other regions of the brain are vast and bidirectional, forming different processing loops that allow both bottom-up and top-down modulations of auditory neural representations, which may be the substrate for the integrative computations required for auditory perception and cognition [3,23].

Auditory cortices are reciprocally connected with higher-order cortical areas beyond the auditory domain, many of

which are considered to be part of the cortical attentional network [24], such as areas in the frontal and parietal lobes. In primates and carnivores top-down connections from these regions emerge and terminate at non-primary auditory areas [3,25,26]. On the other hand, anatomical and physiological evidence in rodents shows significant connectivity of primary auditory cortex (A1) with orbito-frontal cortex [27–29], which could explain top-down facilitative changes of A1 receptive fields by pairing of sounds with orbitofrontal electrical activation in mice [28]. In addition, the auditory cortex receives indirect inputs from other sensory and non-sensory cortical areas through connectivity with claustrum [30], a subcortical gray matter structure acting as a hub for cortical inputs. Auditory cortex is also modulated by visual and somatosensory stimulation, and receives direct connections from somatosensory [31,32] as well as from visual areas [21,33]. Neuroanatomic evidence has shown that the primary auditory cortex of mice is the target of direct connections from extrastriate visual cortex [34], which modulate the activity of the deep layers (V and VI) of A1 [35**]. As stated above, pyramidal neurons of layers V and VI are the origin of the corticofugal projections to auditory subcortical nuclei, a fact emphasizing that top-down projections from different brain regions to the auditory cortex could interact with the descending pathways that comprise the auditory efferent system. Therefore, neural networks involved in cognition, emotion, or other functions can influence the cochlear receptor activity through the auditory efferent system.

Corticofugal modulation of audition during cognitive tasks

Goal directed cognitive tasks can modulate the activity of the auditory cortex, subcortical nuclei and even of the auditory nerve and cochlear receptor. However, the vast majority of past studies have focused on separate aims: (i) cortico-cortical mechanisms or (ii) the modulation of peripheral auditory responses. Only a few studies have

combined techniques to assess how cortico-cortical and peripheral effects interact [36,37,38**,39]. Table 1 describes different methodologies that could be combined for exploring cortical and peripheral auditory functions simultaneously.

Top-down modulation of auditory cortex activity during cognitive tasks

Neurophysiological recordings in auditory and frontal cortices of ferrets performing auditory discrimination tasks have revealed that encoding of non-acoustical sound features, such as task-related meaning or category, emerges in the frontal cortex and cascades back to auditory non-primary and primary cortical fields. Attention-related enhancements of single-unit responses to task-relevant sounds have been shown to increase in secondary auditory cortex relative to A1 [40], and recently, further attentional enhancement and sustained short-term memory activity encoding sound task-meaning have been shown in a tertiary auditory area of ferrets performing the same auditory task [41*]. In addition, a recent study revealed that neural correlates of sound task categories emerge in the frontal cortex and later appear in secondary and primary auditory cortex responses, suggesting a top-down cascade of categorical information from the frontal lobe to non-primary and primary auditory fields [42**]. An enhanced representation of attended sounds in non-primary auditory cortex has also been shown recently in intracranial recordings performed in neurosurgical patients, where attended speech representations were selectively enhanced in the superior temporal gyrus -a collection of tertiary auditory areas- while primary auditory responses in Heschl's gyrus were influenced by attention to only a limited extent [43*]. Together, animal and human studies show that during cognitive tasks, such as goal-directed attention, the frontal cortex exerts top-down modulation of the activity of primary and secondary auditory cortices.

Table 1

Methodologies to study brain and peripheral auditory function

	Brain	Auditory peripheral
Recording techniques	Electroencephalogram Electrocorticogram Auditory evoked potentials Local field potentials [15,38**,43*,53] Magnetic resonance imaging [54] Single and multi-unit recordings [41*,42**]	Otoacoustic emissions [37,38**] Electrocochleography [44] Laser Doppler vibrometry [55] Volumetric optical coherence tomography vibrometry [56] Auditory-nerve single unit recording [57] Cochlear implants [19]
Activity-modulatory techniques	Ultrasonic brain imaging [26] Electrical microstimulation/Cortical inactivation (cryoloops, lidocaine) [15,53] Optogenetics [58]/Chemogenetics [51] Magnetic transcranial stimulation [60]	Optical stimulation [59]

Top-down modulation of auditory peripheral responses

Cochlear and auditory-nerve responses can be modulated during selective attention to auditory or visual stimuli [37,38^{**},44]. However, this type of modulation is not always observed, suggesting that in the case of experiments performed with otoacoustic emissions, these corticofugal effects could be related to motion artifacts [45]. One important caveat is that the modulation of the most peripheral auditory responses is not necessary to accomplish a cognitive task, but it aids in filtering out irrelevant stimuli during attention tasks [46]. Data from mice, chinchillas and humans show that the recruitment of the MOC system during attention paradigms is only necessary when the task is challenging [38^{**},44,46], suggesting that MOC neurons are not activated when the attention task is relatively easy.

Another important issue that may explain negative results in cognitive experiments exploring auditory efferent effects is the limited type of analyses that have been used for searching corticofugal effects, which are mainly restricted to the gain control of the auditory response amplitudes. One exception is the work performed by Dragicevic *et al.* [38^{**}], in which electroencephalogram (EEG) and distortion product otoacoustic emissions (DPOAE) signals were analyzed in the frequency domain. In this work, subjects had to alternate between auditory and visual attention. This study provided, during periods of selective attention, the first evidence of interaction between cortical regions (frontal, vertex and occipital EEG electrodes) and the cochlear receptor in an infrasonic frequency band (<10 Hz), including delta and theta EEG waves. Moreover, in this work the amplitude and temporal order of brain and cochlear oscillations were inverted depending on whether the subject attended to the auditory or visual modality. Future studies on the corticofugal dynamics of the auditory efferent system should use combined approaches, and in addition to the response amplitudes, analyze the frequency domain, use causal inference, or artificial intelligence techniques, such as deep learning to reveal patterns of activity altered by task demands [47].

A recent work [48^{**}] used functional magnetic resonance imaging (fMRI) in humans to study subcortical auditory nuclei activation during an auditory detection task in background noise. The SOC and locus coeruleus were the only subcortical nuclei activated during the auditory task. The locus coeruleus is a well-known brainstem noradrenergic structure related to arousal level, while its dysfunction is involved in anxiety disorders [13,49]. Neuroanatomical evidence in rats and guinea pigs has identified direct connections from the locus coeruleus to olivocochlear neurons [11,12], adding an important connection to the auditory efferent network. Auditory

Box 1 Future directions and questions in corticofugal modulation of audition.

- Corticofugal studies on the modulation of audition should include the whole brain, as the auditory efferent system works in tightly coupled collaboration with other regions of the nervous system. Importantly, the auditory cortex and inferior colliculus are known to receive inputs from visual, somatosensory and frontal areas (see Figure 1).
- More studies in animal models and humans that combine brain and peripheral techniques are needed. Candidate tools include optogenetics, EEG, fMRI for brain measurements, and laser interferometry, otoacoustic emissions, electrocochleography for cochlear function (see Table 1).
- Corticofugal dynamics should be studied with different approaches, targeting not only the 'gain mechanisms', but also analyzing interactions in the frequency domain and utilizing artificial intelligence.
- The dynamics of causal influences of non-auditory regions of the brain on auditory cortical and subcortical representations remain to be elucidated.
- An open question that future studies should answer is whether cognitive modulation of the peripheral auditory responses by corticofugal pathways is restricted to selective attention or is a more general cognitive mechanism.
- One missing point in the literature is the possible corticofugal emotional influence on the cochlear receptor. Because of clinical conditions such as Meniere's disease, this is an important open question to address, as it is known that Meniere's episodes are associated with emotional disturbances.
- Auditory prostheses, like cochlear implants, lack efferent control. Future developments must include multiple feedback loops. Combined cortical and cochlear implants could be implemented in the near future.

circuits are also influenced by limbic and emotional networks [4,10]. The best studied connections are those that connect auditory thalamus with basolateral amygdala, which is reciprocally connected with auditory cortex. These circuits are essential for the identification and association underlying auditory fear conditioning [50,51], but how they might interact with the auditory efferent network is, as yet, completely unknown.

Importantly, evidence shows that other cognitive functions, such as working memory and predictability, can also activate top-down auditory networks [39,52]. For instance, Sorqvist *et al.* [52] showed that a verbal visual working memory task modulates the amplitude of auditory midbrain responses (wave V from auditory brainstem responses), while Riecke *et al.* [39] reported that auditory predictability altered the amplitude of DPOAE. Taking all this evidence together, we propose a more general cognitive function for the auditory efferent system, which is to reduce or filter cochlear responses during highly demanding cognitive tasks, including selective attention, working memory or prediction, by activation of top-down cortical networks from the frontal cortex and other non-auditory regions to the cochlear receptor.

In conclusion, the auditory corticofugal system allows the brain to sculpt responses in every cortical and subcortical processing stage of the auditory system, permitting the modulation of sounds' neural representations depending on their behavioral relevance, environmental context and the brain state. However, there are still many open questions that should be addressed in the future (Box 1) to better understand the role of top-down networks that modulate audition.

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Conflict of interest statement

Nothing declared.

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