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Motor-related signals in the auditory system for listening and learning

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In the auditory system, corollary discharge signals are theorized to facilitate normal hearing and the learning of acoustic behaviors, including speech and music. Despite clear evidence of corollary discharge signals in the auditory cortex and their presumed importance for hearing and auditory-guided motor learning, the circuitry and function of corollary discharge signals in the auditory cortex are not well described. In this review, we focus on recent developments in the mouse and songbird that provide insights into the circuitry that transmits corollary discharge signals to the auditory system and the function of these signals in the context of hearing and vocal learning.

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Introduction

Sensation often begets movement, pointing to a flow of information within the brain from sensory to motor regions. Perhaps less obviously, most behaviors also engage information flow in the opposite direction, in the form of motor-related corollary discharge signals that infiltrate sensory regions of the brain [1–4] (Figure 1). In the auditory system, corollary discharge signals are theorized to facilitate normal hearing by suppressing the responses of auditory neurons to movement-related auditory feedback [1]. Moreover, corollary discharge signals that accurately predict the expected auditory consequences of one's own movements (as posited for forward models of speech learning) can be compared with movement-related feedback to generate error signals, which are critical for learning to make movements with precise acoustic outcomes, including speech and music [5–7]. Despite clear evidence of corollary discharge signals in the auditory cortex and their presumed importance for hearing and auditory-guided motor learning, major questions regarding the form and function of corollary discharge signals in the auditory cortex remain unresolved.

What are the synaptic and circuit mechanisms by which movement-related corollary discharge signals modulate auditory cortical activity? Auditory cortical activity is often suppressed during movements including vocalization, but it is unknown whether suppression is due to increased inhibition, withdrawal of excitation, or some combination of both.

What are the circuits that convey corollary discharge signals to the auditory cortex? Although evidence for movement-related modulation of auditory cortex is pervasive, the source of movement-related signals that can be detected in the auditory cortex have remained a matter of speculation.

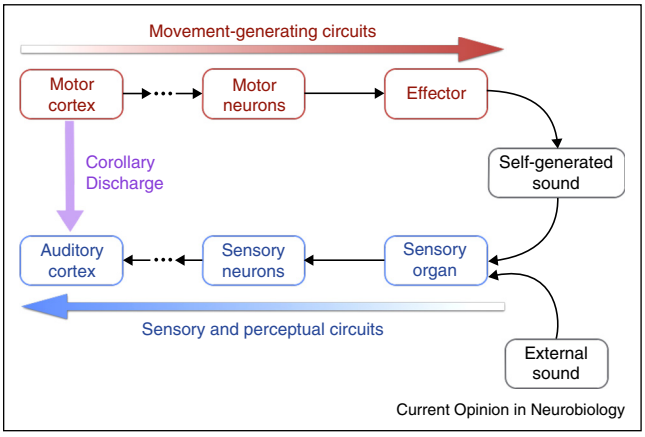
How do corollary discharge signals in the auditory system facilitate motor learning? Corollary discharge signals in the auditory cortex likely serve many roles, including helping us to learn complex acoustic behaviors, yet the causal role for corollary discharge signals in auditory-guided motor learning remains untested.

Recent studies in mice and songbirds have begun to provide answers to these questions, aided by advances in techniques for monitoring synaptic activity in freely behaving animals, improved behavioral quantification, and the experimental capacity to manipulate activity within defined neuronal populations. In particular, work in the mouse has begun to uncover the synaptic and circuit mechanisms by which motor and auditory signals are integrated in the brain, while studies using songbirds have shed light on how error-related information arising from forward interactions impinges on error correction circuitry to facilitate motor learning. In this review, we focus on recent developments in the mouse and songbird that provide a better understanding of how corollary discharge signals in the auditory system function during naturalistic behaviors.

Neural signatures of movement in the auditory cortex

Movement-related signals are likely to modulate auditory processing at many levels of the auditory neuraxis and even at the auditory periphery, as evidenced by the contraction of middle ear muscles during vocalization [8]. Despite the distributed nature of these signals, several reasons

Figure 1



The auditory system processes environmental sounds as well as sounds generated by our own movements. Motor-related corollary discharge signals that modulate the auditory cortex during movement are speculated to facilitate the detection of environmental cues and the learning of complex auditory-guided behaviors.

motivate a focus on corollary discharge signals at the cortical level, including the important role of cortical regions in speech and language [9–11], the pronounced capacity of cortical circuits for learning-related plasticity [12–14], and the strong suspicion that dysfunctional corollary discharge circuits in the cortex give rise to auditory hallucinations and certain forms of tinnitus [15]. In support of this focus, auditory cortical activity in humans and non-human primates is often suppressed during and before vocalization [1,5], manual musical gestures [16,17•,18], and non-musical movements [19,20], consistent with a motor origin. Notably, responses to vocalizations are most strongly suppressed when the sounds that the subject hears match the expected consequences, suggesting an acoustic specificity to corollary discharge signals at the level of the cortex [21]. Recent studies reveal that movement-related changes in auditory cortical activity in mice bear close parallels to those observed in humans and other primates. In both head-fixed and unrestrained freely behaving mice, spontaneous and tone-evoked firing rates of auditory cortical excitatory neurons are suppressed prior to and during movement, the latter indicating a divisive normalization of sound-evoked responses during movement that spans the mouse hearing range [22••,23•]. Moreover, many different types of movements, including grooming, locomotion, and vocalization, trigger changes in auditory cortical activity and sensory responsiveness [22••]. Therefore, in mice and humans, many behaviors, and not only vocalization, can modulate auditory cortical activity.

Synaptic and circuit mechanisms of corollary discharge in the auditory cortex

In addition to recapitulating key aspects of movement-related modulation of auditory cortical activity first observed in humans and other primates, studies in mice open the door to a range of experimental techniques that can shed light on the circuit and synaptic mechanisms through which corollary discharge signals suppress the auditory cortex during movement. In fact, recent studies using intracellular and extracellular recording combined with optogenetic methods in freely behaving mice provide evidence that movement-related signals actively suppress auditory cortical activity through a combination of mechanisms including increased activity in local inhibitory circuits [22••] and decreased excitatory drive from the thalamus (Williamson R *et al.*, Annual Meeting of the Society for Neuroscience (Washington, DC, 2014), submitted for publication) and from within the auditory cortex [23•].

Unlike extracellular recordings, intracellular recordings can resolve the activity of a neuron's synaptic inputs and enable measurement of a cell's input impedance and intrinsic excitability, all of which can be used to elucidate circuit mechanisms through which corollary discharge signals act in the auditory cortex. Intracellular recordings in head-fixed and unrestrained mice reveal that prior to and throughout movement, the membrane potential of auditory cortical excitatory neurons becomes much less variable, and these changes are accompanied by a decrease in input impedance and intrinsic excitability [22••]. These alterations in membrane properties are all signatures of postsynaptic inhibition, suggesting that corollary discharge signals drive activity in local inhibitory networks. In the auditory cortex of the mouse, parvalbumin-positive (PV+) inhibitory interneurons are known to provide strong inhibitory input onto excitatory neurons, providing a potential source of postsynaptic inhibition during movement [24]. However, whereas some studies indicate that PV+ interneurons show increased activity during movement ([22••]; McGinley MJ *et al.*, Annual Meeting of the Society for Neuroscience (Washington, DC, 2014), submitted for publication), another study concluded that PV+ interneurons decrease their activity during movements [23•]. These discrepancies may reflect the different time windows over which PV+ neural activity was measured: Schneider *et al.* detected transient increases in PV+ firing rates that began prior to movement and persisted into early stages of a locomotor bout, whereas Zhou *et al.* detected decreased PV+ firing rates when activity was averaged throughout an entire locomotor bout. One possibility is that transient increases in PV+ activity near the time of movement onset may induce more prolonged suppression of excitatory neurons, and that PV+ activity may rebalance with decreased levels of recurrent excitatory drive during later stages of sustained locomotion. In fact, rebalancing of excitatory and inhibitory currents has been observed in the auditory cortex during locomotion, consistent with this idea [23•].

Although local inhibition accounts for decreased responsiveness to acoustic stimuli within the auditory cortex,

withdrawal of excitatory drive from the auditory thalamus may also play a role in suppressing auditory cortex during movement (Williamson R *et al.*, submitted for publication). To distinguish the relative contributions of cortical and subcortical suppression, Schneider *et al.* used an optogenetic approach to selectively activate auditory thalamic inputs to the cortex and compared how movement affected cortical responses to thalamic terminal activation, which are likely to be influenced only by movement-related signals acting in the cortex, and to tones, which are potentially influenced by movement-related signals acting at many sites along the auditory neuraxis. These experiments revealed that slightly more than half of the suppression could be accounted for by local cortical mechanisms, indicating that movement-related signals act at both cortical and subcortical loci to suppress auditory cortical responses to acoustic stimuli [22••].

Functions of suppressive corollary discharge signals in the auditory cortex

A critical unresolved issue is the functional significance of these suppressive signals for hearing and auditory-dependent behaviors. At face value, movement-related suppression of auditory cortical activity may reduce the mouse's ability to detect sounds when it is moving, an idea that has gained support from psychophysical experiments (McGinley MJ *et al.*, submitted for publication). Perhaps the brain of the moving mouse is committing limited resources to a strategy favoring evasion at the expense of auditory sensitivity. Alternatively, auditory cortical sensitivity could actually increase if spontaneous firing rates decrease more than tone-evoked firing rates during movement, resulting in an increased signal-to-noise ratio [23•]. In fact, such a boost in signal-to-noise ratios occurs in the auditory system of rodents performing auditory discrimination tasks that require attention (Williamson R *et al.*, submitted for publication; [25]), suggesting that this mechanism may also be exploited during movement. Additionally, movement-related suppression in the mouse auditory cortex may reflect a predictive mechanism that facilitates the distinction between reafferent and exafferent sounds, as has been described in the auditory cortex of vocalizing primates [1]. An important goal of future experiments will be to test these ideas.

Sources of corollary discharge signals in the auditory cortex

The sources of movement-related signals in the auditory cortex are potentially numerous, given that auditory cortex receives convergent input from various motor-related centers along with other brain regions, including neuromodulatory cell groups. Using a suite of viral tracing strategies in the mouse, Nelson *et al.* described a projection from both deep and superficial layers of the secondary motor cortex (M2) to the auditory cortex, finding that M2 axons course across all cortical layers and make synapses onto both excitatory and inhibitory neurons, including PV+ interneurons [26•]. M2 neurons that project to the auditory cortex (i.e., $M2_{ACtx}$ neurons) are active during movement and a subset of these neurons extend axons both to the auditory cortex and, via the pyramidal tract, to various brainstem structures including the periaqueductal gray, providing an architecture through which copies of movement-related signals can be transmitted to the auditory cortex [26•]. Notably, selectively activating M2 projections to the auditory cortex of resting mice can recapitulate movement-like dynamics and sensory responsiveness of auditory cortical neurons [22••]. Conversely, optogenetically silencing M2 neurons in moving mice rapidly switched auditory cortical dynamics and responsiveness to a rest-like state, even though movement persists [22••]. Therefore, $M2_{ACtx}$ neurons are an important source of movement-related signals that can be detected in the auditory cortex of the mouse.

These experiments establish M2 as an important source of movement-related signals in the auditory cortex, but do not exclude the possibility that motor to auditory cortical interactions occur either in parallel with or under the control of other brain regions. For example, pharmacological and optogenetic experiments in the mouse visual and auditory cortices reveal that locomotion-related changes in membrane potential dynamics are influenced by movement-related changes in cholinergic and noradrenergic tone, underscoring a role for neuromodulatory cell groups in movement-related modulation of sensory processing (McGinley MJ *et al.*, submitted for publication; [27•,28,29]). Neurons in the mesencephalic locomotor region — a brain region important for initiating locomotion — excite cholinergic neurons in the basal forebrain during movement, which in turn project to the visual cortex, where they disinhibit visual cortical pyramidal cells [27•,30]. Indeed, cholinergic neurons in the basal forebrain also project to the auditory cortex, raising the possibility that signals from M2 and the basal forebrain are integrated in the auditory cortex during movement and that both types of inputs function cooperatively to modulate auditory cortical processing. Moreover, cholinergic projections from the basal forebrain to the auditory cortex can induce plasticity in cortico-cortical synapses [31], raising the possibility that increased levels of acetylcholine in the auditory cortex during movement could help to 'train' motor cortical inputs to generate predictive signals important for auditory plasticity and auditory-guided motor learning.

Auditory-guided motor learning

Beyond a role in maintaining sensitivity to exafferent sounds during movement, corollary discharge signals that function predictively also have been invoked as a central element in forward models of speech learning [21]. Unfortunately, those organisms for which we have the deepest understanding of how movement modulates the

auditory cortex — mice and marmosets — are not vocal learners. In contrast, songbirds such as zebra finches learn to vocalize and thus may provide a unique model for testing how corollary discharge signals in the auditory system function as part of a mechanism for vocal learning. Male zebra finches learn to sing during a juvenile sensitive period by memorizing a tutor song and then using auditory feedback to match their own vocalizations to the memorized model [32]. Notably, using singing-triggered noise to disrupt auditory feedback in adult zebra finches can reversibly destabilize song [33], pointing to both a continued reliance on auditory feedback and the presence of a stable, internal vocal target against which feedback continues to be compared. In addition, analogues of auditory cortical neurons in the zebra finch exhibit hallmarks of predictive corollary discharge signals, including elevated action potential activity prior to vocal onset and enhanced action potential activity when auditory feedback is altered during vocalization [34]. Recent studies have helped to better illuminate sources of corollary discharge signals in the zebra finch auditory 'cortex,' identify regions that may contain auditory memories against which auditory feedback is compared, delineate pathways that convey resultant error signals, and define sites where error correction signals important for vocal plasticity may first arise.

Sources of corollary discharge in the songbird forebrain

The central circuits for singing include the song premotor nucleus HVC, which contains separate pools of projections neurons that innervate either a song motor nucleus (robust nucleus of the arcopallium, RA) essential for song production or a basal ganglia homologue (Area X) important to auditory-dependent vocal plasticity. Furthermore, HVC receives auditory input from secondary regions of the auditory cortex, with the consequence that many HVC neurons display both premotor and auditory properties, such as selectivity for certain songs and auditory — vocal mirroring [35,36]. Although the flow of information from auditory to vocal motor regions in the songbird brain has long been viewed as a one way street, emerging evidence points to a third projection neuron type within HVC that extends axons into a part of the secondary auditory cortex (a small region known as Avalanche, or Av), reminiscent of the projections certain M2 neurons make to the auditory cortex of the mouse [37•]. These HVC_{Av} cells are a likely source of motor-related signals in the songbird auditory cortex, as they receive excitatory input from HVC_{RA} cells and are active during singing, even in deafened birds. Moreover, selectively killing HVC_{Av} cells with targeted genetic methods disrupts juvenile song learning, while similar manipulations in adults have little effect on their previously learned songs [37•]. Together, these findings support the idea that HVC_{Av} cells transmit corollary discharge signals to the auditory cortex that are important to vocal learning but not to acute aspects of song motor control. One possibility is that HVC_{Av} cells provide a motor-related contextual signal that gates auditory feedback signals in the auditory cortex, thus facilitating feedback-dependent error detection.

Internal models for auditory-guided motor learning

Adult zebra finches depend on auditory feedback to maintain stable songs, indicating the presence of an internal song model. Some auditory cortical neurons in or near Av are selectively active when a singing bird experiences distorted auditory feedback, consistent with error signals that reflect a mismatch between an internal model and observed sensory outcomes [34]. A critical unsolved puzzle is the neural circuitry that mediates the comparison between singing-related auditory feedback and the memory of the song model, the solution to which rests in part on understanding how the song model is represented in the songbird's brain. A variety of correlative and causal evidence implicates both secondary auditory cortical regions (i.e., caudomedial nidopallium, abbreviated as NCM) and HVC in the formation of tutor song memories, raising the possibility that the memory is distributed across a relatively large auditory and sensorimotor network [38••,46–48]. Notably, Av is reciprocally connected with both NCM and HVC and thus could provide the anatomical bridge for such a distributed encoding mechanism.

Recent experiments have tested the importance of NCM to maintaining an internal song model in adult birds by delivering aversive feedback (e.g., white noise) when the pitch of a target note falls above (or below) a threshold [38••]. With NCM intact, adult zebra finches avoid this pitch-contingent aversive feedback by adaptively shifting the pitch of the target note away from the threshold, and when the aversive feedback is turned off, their songs recover back to baseline. Interestingly, large lesions of NCM in adult finches do not block adaptive vocal plasticity induced by pitch-contingent noise, but they do slow or prevent recovery back to the original song structure once the aversive stimulus is discontinued. These findings suggest that partially distinct pathways mediate adaptive vocal plasticity and recovery while also lending further support to a role for NCM in encoding an internal representation of the vocal target.

Error detection and correction

Regardless of the exact location of an internal song model and the circuit mechanisms that enable error detection, the output of such circuitry must ultimately interact with pathways important to error correction. A region of songbird forebrain known as Aiv (ventral portion of the intermediate arcopallium) receives input from a wide variety of auditory cortical regions, including NCM and Av, and contains a subset of neurons that project to the ventral

tegmental area (VTA) [39•]. During singing, a subset of Aiv_{VTA} neurons respond strongly to perturbed auditory feedback, a property that supports their role in an error-correction circuit and may be inherited from their auditory cortical afferents [39•]. Moreover, lesions placed in Aiv or in the dorsal region of the arcopallium (Aid) [40] disrupt juvenile song learning and lesions placed in Aiv also substantially slow the time course of deafening-induced vocal plasticity in adult finches [39•]. One possibility is that error signals propagating from the arcopallium to the VTA lead to phasic activity in dopaminergic neurons in the VTA [41], which in turn reinforces certain variations in vocal output that are adaptive either with respect to internal models or external contingencies. Future experiments measuring the activity and function of VTA neurons during learning and during song perturbation will be critical for testing this idea.

One of VTA's major projections is to Area X, a striatal component of a cortico-basal ganglia circuit that is critical for vocal learning, and thus the Aiv–VTA–Area X pathway may be critical for linking error-detection and error-correction circuitry. The patterns of action potential activity of neurons in Area X and other parts of the cortico-basal ganglia circuit are critical for regulating vocal variability, — a key ingredient in reinforcement models of song learning — and these patterns can be influenced by dopamine signaling, pointing to VTA inputs to Area X as a potential driver of vocal change [42,43]. However, a major challenge has been to understand whether variability signals first arise in Area X or in its premotor afferents, which include the song premotor nucleus HVC as well as LMAN, the output nucleus of this cortical-basal ganglia pathway. In a compelling series of experiments, Woolley *et al.* established that singing-related variability emerges within Area X, rather than at earlier or later stages of the pathway [44••]. Therefore, the pathway spanning the VTA and Area X may be the site where auditory feedback-dependent error signals are converted into error correction signals important to vocal learning. Interestingly, although basal ganglia circuits are important for the maintenance and modification of song's spectral features, song's temporal features appear to be controlled through separate neural circuits, possibly involving inputs HVC receives from midbrain dopamine neurons distinct from those in the VTA [45].

Conclusions and future directions

Recent experiments in the mouse and zebra finch have identified how local and long-range circuits modulate auditory cortex during movement and how corollary discharge signals in the auditory cortex influence behavior. These findings pave the way for future experiments that can resolve longstanding questions regarding how corollary discharge signals function in behaving animals. A hallmark of forward models is the specificity with which corollary discharge signals suppress or cancel predictable reafferent sounds, yet the neural circuitry that creates an acoustically specific negative image in the auditory cortex remains to be unraveled. Is movement-related suppression in the mouse auditory cortex part of such a predictive mechanism? Do predictive corollary discharge signals adapt when the sensory consequences of a movement undergo a persistent change? The auditory cortex receives motor-related input from sources other than M2 (e.g., primary motor cortex) and motor-related signals are likely to arrive in the auditory cortex coincident with neuromodulatory inputs. Future experiments must therefore determine how motor and neuromodulatory inputs interact during behavior, and determine whether these interactions are important to experience-dependent changes in auditory cortical properties. Finally, disrupted auditory feedback can drive singing behavior away from a stable and stereotyped motor plan. How do error signals act on motor circuitry to modify a behavior that in turn produces a desired sensory outcome? Answering these questions will depend on synaptic and circuit analysis, as well as genetic manipulation of neural activity, in auditory — motor networks in freely behaving animals as they discriminate auditory targets and learn new auditory-guided behaviors.

Conflict of interest statement

Nothing declared.

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The authors make intracellular recordings in freely behaving and head-restrained mice to show that a variety of movements are accompanied by decreased synaptic responses to sensory input. They show that approximately half of the sensory-evoked suppression observed during movement is due to local inhibition within the cortex. Optogenetic manipulations, physiological and optical recording experiments reveal that M2 provides a motor-related corollary discharge signal to the auditory cortex that recruits PV+ interneurons to suppress excitatory neurons.

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By making whole-cell voltage-clamp recordings in the auditory cortex of behaving mice, the authors characterize changes in excitatory and inhibitory input to auditory cortical pyramidal neurons during periods of action versus rest. They find that auditory cortical sensory responses are suppressed during locomotion and that both excitatory and inhibitory inputs are decreased relative to rest.

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The authors describe a population of deep and superficial M2 neurons that project to the auditory cortex, where they synapse onto excitatory and inhibitory populations. Using both slice and *in vivo* preparations, the authors show that optogenetic stimulation of ChR2+ M2 terminals in the auditory cortex drives strong feedforward inhibition, in part through direct excitation of PV+ interneurons. This study provides a structural diagram of a corollary discharge circuit in the auditory cortex.

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•• Canopoli and colleagues test the idea that a higher-order auditory area of the songbird forebrain, NCM, is important for maintaining song memory. They show that lesions to NCM do not prevent song from changing when acoustic feedback is perturbed, but slow or prevent the recovery of song back to baseline when acoustic feedback perturbation is discontinued. This blockade of recovery hints that NCM may be an important region for song memory.

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