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Rejuvenation of plasticity in the brain: opening the critical period

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Cortical circuits are particularly sensitive to incoming sensory information during well-defined intervals of postnatal development called 'critical periods'. The critical period for cortical plasticity closes in adults, thus restricting the brain's ability to indiscriminately store new sensory information. For example, children acquire language in an exposure-based manner, whereas learning language in adulthood requires more effort and attention. It has been suggested that pairing sounds with the activation of neuromodulatory circuits involved in attention reopens this critical period. Here, we review two critical period hypotheses related to neuromodulation: cortical disinhibition and thalamic adenosine. We posit that these mechanisms co-regulate the critical period for auditory cortical plasticity. We also discuss ways to reopen this period and rejuvenate cortical plasticity in adults.

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Introduction

Learning and memory involve the acquisition and storage of sensory information. These cognitive processes occur throughout life. However, children and adults learn differently: children learn faster and more efficiently than do adolescents and adults. These observations triggered the idea of 'critical periods', which are optimal periods of development when brain circuits acquire and store information [1–5]. One example of this concept is language acquisition. Learning a second language after puberty is much more conscious and labored than the automatic acquisition occurring in young children as a result of mere passive exposure [5,6].

Acoustic information in the form of auditory patterns is most likely represented in the primary auditory cortex (ACx) [7]. Similar to other sensory cortices, the ACx is topographically organized [8,9]: neurons with different preferred sound frequencies are spatially distributed in the ACx, forming tonotopic maps [10]. This information is inherited from tonotopic organization of the cochlea and delivered to the ACx through thalamocortical (TC) projections emanating from the auditory thalamus [11]. In animals, the ACx is plastic throughout the lifespan. This plasticity is observed at the level of tonotopic maps, as individual neurons' responses shift to reinforced sound frequencies [12]. Plasticity in sensory cortices is believed to be the cellular correlate of perceptual learning [13–16] (however, see [17,18]).

Auditory plasticity is thought to optimize neural circuits for processing species-specific vocalizations, including language in humans [5,19]. As with language acquisition in humans, ACx plasticity differs between young and adult animals. In rodent pups, passive sound exposure induces ACx plasticity [20–23] but only for a few days after hearing onset [postnatal day (P)11–P15]. In adults, passive sound exposure is substantially less effective in inducing ACx plasticity [20–22,24].

These studies and those of other sensory cortices demonstrate the existence of critical periods for cortical plasticity [24,25]. Most concepts about the mechanisms of cortical plasticity originated from visual cortex studies [26]. Although in some cases the assumption of similarity between cortices holds true, ACx plasticity is distinct from visual cortex plasticity because of physiological and structural differences [27]. Herein, we review recent advances in cortical plasticity research in rodents, particularly from the perspective of the primary ACx.

Neuromodulation of ACx plasticity

The concept of a critical period for ACx plasticity implies that developmental events impede adults from learning in a passive mode. Studies of adult ACx plasticity commonly report the requirements of attention and alertness. ACx plasticity is well documented in mature animals when pairing specific sounds with associative cues (e.g. reward or punishment) [14,16,28–31].

Attention, vigilance, and alertness are mediated, at least in part, by neuromodulatory drive to the neocortex, which receives cholinergic, noradrenergic, and dopaminergic inputs from the nucleus basalis (NB), locus coeruleus

(LC), and ventral tegmental area (VTA), respectively [32•,33,34,35]. Aversive or rewarding stimuli activate these networks and promote the release of transmitters onto downstream regions [36,37•,38,39,40••]. Such stimuli activate NB cholinergic neurons with high speed and precision [37•]. In adult rodents, pairing sounds with neuromodulatory circuit activation causes robust associative ACx plasticity [12,32•,41] and heightened auditory perception [40••,42], despite closure of the critical period.

In young pups, the ACx learns from the surrounding acoustic milieu: in this exposure-based model of plasticity [43], neuromodulation is less necessary. However, the ability of the adult ACx to learn from sensory exposure alone is curbed, making it difficult for that information to alter neuronal circuits. The adult ACx becomes an 'associative learner' (i.e. circuits are modified when sensory information is behaviorally relevant). In this reinforcement-based mode of plasticity [43], neuromodulator-mediated attention and alertness augment sensory information and store that which applies to important tasks or experiences [44].

Developmental events that control critical periods most likely are not fully engaged during the critical period, but once implemented, they close the critical period by restricting cortical plasticity. Removing these restrictions may extend the critical period and rejuvenate cortical plasticity in adults, as suggested for deleting chondroitin sulfate proteoglycans or Nogo receptors in the visual cortex [45,46] or Icam5 in the ACx [20]. Although these molecules control the critical period, whether they engage the same mechanisms as neuromodulators to rejuvenate adult cortical plasticity remains unknown. Here we discuss two theories of the critical period for ACx plasticity that are mechanistically connected to neuromodulation—the long-standing theory of 'cortical disinhibition' and a recent theory of 'thalamic adenosine'.

Cortical disinhibition

Because the theory of cortical disinhibition has been reviewed extensively [32•,47,48•], we will present only its main points and recent developments. Glutamatergic and GABAergic neuronal activity in the neocortex sets the appropriate ratio of excitation to inhibition, known as 'E:I balance'. The notion that GABAergic interneurons restrain learning has been comprehensively investigated [32•,48•]. Initially, delayed maturation of inhibitory neurons during the critical period was proposed, implying that the E:I balance is not established early in life and cortical plasticity could occur [47]. However, in the P17–P24 rat ACx, *in vivo* whole-cell recordings showed that excitation and inhibition are balanced and tuned to the same frequencies [49]. Another study demonstrated a fully established E:I balance in thalamorecipient layer (L) 4 neurons of the rat ACx as early as P12 [50]. Recording from neurons in multiple cortical layers, another study demonstrated that immediately after the onset of hearing (P12), inhibition is strong but more poorly tuned than excitation. By P21, E:I balance is achieved as excitation and inhibition tuning become highly correlated [51]. Discrepancies among these studies may stem from variability of E:I balance between neurons at different cortical layers, even within the same animal [51]. Together, these works suggest that during the critical period, the E:I balance is achieved, at least for thalamorecipient L4 neurons.

The E:I balance can be transiently disrupted by repeated pairing of a tone with electrical stimulation of cholinergic neurons in the NB [52]. In adult rats, immediately after the pairing protocol, neurons shift their tuning toward the pairing tone. This is accompanied by a rapid reduction in inhibition, which alters the E:I balance. This reorganization lasts for approximately 2 hours even after a brief pairing and may prime the ACx for plasticity. NB neurons are activated by foot-shocks, and subsequently release acetylcholine onto L1 interneurons in the ACx [53]. Nicotinic receptor–dependent depolarization of L1 inhibitory interneurons occurring within 50–60 ms of the shock inhibits parvalbumin (PV)–positive L2/3 interneurons and subsequently disinhibits excitatory neurons. This disinhibition mechanism likely underlies ACx plasticity associated with fear learning [48•,53]. These studies point to L1 inhibitory neurons as a possible hub of sensory cortical disinhibition. Of L1 interneurons, vasoactive intestinal peptide (VIP)–positive (L1/VIP) interneurons may assert disinhibitory control through PV-positive and somatostatin (SOM)-positive interneurons in deeper cortical layers [54••] (Figure 1). Interestingly, L1/VIP neurons in the ACx and visual cortex are activated in response to various salient stimuli (e.g. air puffs, water reward [54••], or locomotion [55]).

Can we extend the critical period into adulthood by manipulating cortical disinhibitory circuits? Deletion of Lynx1, an endogenous inhibitor of nicotinic receptors that has higher expression in adult mice than pups, extends cortical plasticity in the visual cortex to P60 [56]. Lynx1 is expressed in L1 interneurons, which also express 5-HT_{3A} receptors (but not VIP) [57••]. These L1/5-HT_{3A} interneurons receive cholinergic inputs that activate α4 nicotinic receptors and disinhibit the ACx through PV-positive L4 neurons (Figure 1). Silencing L1/5-HT_{3A} interneurons abolishes critical period plasticity in acute slices from pups [57••].

These studies suggest that cortical disinhibition helps control the critical period of ACx plasticity. However, it is not sufficient to achieve input specificity, an important feature of ACx plasticity [12]. For instance, a salient unconditioned stimulus such as foot-shock achieves cortical disinhibition by activating L1 neurons broadly throughout the ACx and visual cortex [53]. Moreover,