Neuromodulatory influence of norepinephrine during developmental experience-dependent plasticity

Randall M. Golovin1,2 and Nicholas J. Ward2,3,4
1Neuroscience Graduate Program, Vanderbilt University, Nashville, Tennessee; 2Vanderbilt Brain Institute, Vanderbilt University, Nashville, Tennessee; 3Vanderbilt Vision Research Center, Vanderbilt University, Nashville, Tennessee; and 4Department of Psychology, Vanderbilt University, Nashville, Tennessee

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Golovin RM, Ward NJ. Neuromodulatory influence of norepinephrine during developmental experience-dependent plasticity. J Neurophysiol 116: 1–4, 2016. First published December 9, 2015; doi:10.1152/jn.00461.2015.—Critical periods represent phases of development during which neuronal circuits and their responses can be readily shaped by stimuli. Experience-dependent plasticity that occurs within these critical periods can be influenced in many ways; however, Shepard et al. (J Neurosci 35: 2432–2437, 2015) recently singled out norepinephrine as an essential driver of this plasticity within the auditory cortex. This work provides novel insight into the mechanisms of critical period plasticity and challenges previous conceptions that a functional redundancy exists between noradrenergic and cholinergic influences on cortical plasticity.

auditory cortex; critical period; neuromodulation; norepinephrine; plasticity

BRAIN DEVELOPMENT AND MATURATION requires incredible plasticity, the ability to change at both structural and functional levels. This plasticity is especially active during critical periods, specific times of life in which environmental and internal factors have an enhanced ability to manipulate neural circuitry. These critical periods are crucial for proper sensory system development and remain the best point for early intervention in sensory disorders such as amblyopia and congenital hearing disorders such as asymmetric hearing loss and auditory neuropathy spectrum disorder. In addition, early disruption of neural signaling can impair adult plasticity, which may have implications for complex neurodevelopmental disorders (Greenhill et al. 2015). Attempts to harness the potential of critical periods and reopen a period of youthful plasticity may give rise to better intervention in neuropsychiatric and neurodegenerative diseases, in which neural structures are altered or damaged (Hensch and Bilimoria 2012). It is important to study the mechanisms mediating critical periods, because they represent unique ways by which the brain is able to adapt, for better or worse, to its environment.

Early studies demonstrated critical period plasticity in the ocular dominance columns of cat (Wiesel and Hubel 1963) and monkey (LeVay et al. 1980) primary visual cortex (V1). A hint at the mechanism for this anatomical shift was later provided by the work of Kasamatsu and Pettigrew (1976), who demonstrated the necessity of norepinephrine (NE) for ocular dominance plasticity in V1. This work, however, was challenged when it was shown that only the combined depletion of acetylcholine (ACh) and NE could block experience-dependent plasticity in V1 (Bear and Daniels 1983). Despite the apparent redundancy of this signaling, the intracellular mechanism by which ACh and NE act to facilitate critical period plasticity remains unknown. However, great strides have been made in understanding critical period plasticity through study of the role that local inhibitory neurons play in balancing circuit excitability (Toyoizumi et al. 2013). In their recent study, Shepard et al. (2015) provide evidence that NE is necessary for experience-dependent plasticity of the auditory cortex. In this work, we analyze evidence for the necessity of NE in critical period plasticity of auditory cortex, suggest strategies for deconstructing the influence of NE on this cortical circuit, and link this study’s findings to novel concepts of the role of neuromodulation and excitatory/inhibitory balance in critical period plasticity.

In their studies, Shepard et al. (2015) found that mice lacking NE failed to reorganize auditory cortex in response to prolonged sound exposure. To eliminate NE, the authors used a transgenic mouse line lacking dopamine β-hydroxylase (Dbh−/−), the enzyme that converts dopamine to NE. The auditory cortex is organized in a tonotopic pattern such that neurons that fire best for a particular frequency are grouped together. Shepard et al. took advantage of this organization to detect shifts in the best responding frequency (BF) by exposing mice to 8-kHz pure tones at moderate intensity (80 dB) and duration (16–18 h per day from postnatal day 7 to 21). Multiunit in vivo electrophysiology was then used to determine the outcome of sound exposure on Ddh−/− and Ddh+/+ mice. Throughout the study, heterozygous mice (Ddh+/−) were used as controls because their auditory brain stem responses and NE levels were similar to those of wild-type animals. The authors organized their study by starting with a comparison of basal assessments of hearing and auditory cortex organization of Ddh−/− and Ddh+/+ mice, which was followed by their primary goal of assessing any variation in experience-dependent plasticity.

First, Shepard et al. (2015) showed that the tonotopic maps of auditory cortex did not differ in size or response properties between genotypes before sound exposure. Next, the authors tested whether a quiet environment drove differential map reorganization between mice with or without NE. They found that there was no significant change in the map organization for either genotype. These results set the experimental foundation to show that Ddh−/− mice, unlike controls, did not show experience-dependent plasticity in response to repeated 8-kHz exposure during the critical period.
After sound exposure of each group of mice, Shepard et al. (2015) assessed previously established metrics of plasticity for auditory cortex: BF area and tuning bandwidth. Exposure of Dbh−/− mice to 8-kHz pure tones resulted in an increased area with BF close to 8 kHz (6.3–10.1 kHz) when compared with unexposed mice of the same genotype. In contrast, Dbh+/− mice showed no significant change between exposed and unexposed animals. This result affirmed previous studies showing only areas close to the experimental frequency were affected by sound exposure (Edeline et al. 2011). As with the frequency map, the bandwidth of sounds to which a recorded area of cortex responded was narrower in sound-exposed compared with baseline control mice, whereas bandwidth was unaltered in Dbh−/− animals. Altogether, Shepard et al. provide physiological evidence that NE is needed for critical period plasticity in BF and tuning bandwidth.

This study implicates NE as a necessary driver of critical period plasticity of the auditory cortex. In contrast, previous findings in V1 suggested functional redundancy of noradrenergic and cholinergic influences on plasticity; that is, neither system’s removal alone was sufficient to eliminate plasticity (Bear and Singer 1986). It is important to consider, then, how modular these plasticity mechanisms are across different sensory cortices. This current work therefore prompts a reexamination of prior NE depletion studies in which noradrenergic neurons were destroyed using a potentially incomplete and nonspecific ablation by 6-hydroxydopamine (Bear and Daniels 1983; Bear and Singer 1986; Kasamatsu and Pettigrew 1976). It may be useful to complement older ablation studies by examining visual cortex in Dbh−/− mice, which would clarify the degree to which plasticity mechanisms in visual and auditory cortices are similar. Such studies could also aid in the resolution of whether or not noradrenergic and cholinergic inputs exhibit a functional redundancy in this cortical plasticity.

Interpretation of results from knockout studies such as those performed by Shepard et al. (2015) may be confounded by the difficulty of separating out primary vs. secondary effects of the knockout. The authors attribute the loss of plasticity in Dbh−/− mice to the primary NE deficiency; however, this assumes the knockout causes only negligible alterations to the levels or function of other neuromodulatory ligand and receptor systems. In terms of establishing the necessity of NE in auditory cortex plasticity, future studies should involve attempts to rescue plasticity in Dbh−/− mice. Prior work by Kasamatsu et al. (1979) demonstrated that in the visual cortex of NE-depleted cats, ocular dominance plasticity can be rescued by administration of NE. In auditory cortex, a similar pharmacological rescue of critical period plasticity in Dbh−/− mice would help determine if NE is both necessary and sufficient for this plasticity. Furthermore, use of genetic or pharmacological suppression of specific adrenergic receptor subtypes would help link functional changes to a molecular mechanism.

As Shepard et al. (2015) point out, an ideal way to analyze the role of NE in developmental auditory cortex plasticity would be to produce a mouse with Dbh knockout specific for auditory cortex during the critical period. Unfortunately, this would be technically difficult, because auditory cortex receives noradrenergic innervation from the locus coeruleus (LC), which provides a widespread projection system to many brain areas. It would likely be challenging to target only those noradrenergic neurons that project to the auditory cortex while excluding all others. Perhaps the most tractable approach would be to not focus on both spatial and temporal specificity of this knockout at the same time, but rather examine induced Dbh knockout within a time window relevant to the critical period. Achieving postnatal Dbh knockout in this manner would involve using a system similar to the tamoxifen-inducible Dbh-Cre mice developed by Stubbsch et al. (2011). Such an approach would avoid potential confounds of the Shepard et al. study by 1) allowing for typical fetal development that does not require supplementation with an NE precursor, 2) avoiding early developmental compensatory changes in other neuromodulatory systems, and 3) ensuring specificity of the knockout for the critical period.

In terms of advancing this field of research, it is important to evaluate not only whether NE is necessary for critical period plasticity but also how NE modulates the brain’s response to sensory information during the critical period. One possible mechanism is that shifts in excitatory/inhibitory balance might connect NE to critical period plasticity. Prior studies have demonstrated that shifts in excitatory/inhibitory balance alter ocular dominance plasticity in the developing visual cortex (Hensch 2005). During cortical plasticity events, NE may shift excitatory/inhibitory balance by exerting a disinhibitory influence on the circuitry. In support of this idea, Martins and Froemke (2015) have shown that in adult primary auditory cortex (A1), disinhibition by LC activation permits BF tuning plasticity. From a developmental standpoint, these effects of NE may function in the background of maturing GABAergic inhibition. Early in development, GABAergic synapses switch from depolarizing to hyperpolarizing current, which allows them to function as the major inhibitory input to the nervous system. The timing of this shift is important in critical period dynamics, because a threshold level of GABAergic inhibition is needed for opening the critical period (Fagiolini and Hensch 2000). Toyozumi et al. (2013) have presented evidence that this maturation of inhibitory neurons facilitates critical period plasticity by preferentially suppressing spontaneous cortical activity, allowing external sensory input to serve as the primary driver of plasticity. If NE is necessary for critical period plasticity, as suggested by Shepard et al. (2015), how does it tie in with this shift in excitatory/inhibitory balance?

We hypothesize that NE acts similarly in both development and adulthood to facilitate experience-dependent plasticity. To affect long-lasting changes in response to sensory experience, sensory signals must overcome two types of inhibition: a tonic inhibition that reduces spontaneous activity in the system and a phasic inhibition that limits the response to a given stimulus. NE is known to act on neuronal circuits to enhance excitatory drive in a broadband fashion by reducing tonic inhibition (Froemke 2015; Martins and Froemke 2015). During the critical period, enhancement of sensory input to the cortex might then occur by a reduction of spontaneous excitatory activity by GABAergic neuron maturation accompanying a broadband boosting of responses to stimuli that activate the adrenergic system. Martins and Froemke (2015) propose support for this idea behaviorally and electrophysiologically by showing that in adult A1, pairing sounds with LC stimulation leads to a transient broadening of frequency tuning followed by a long-lasting sharpening at the paired sound frequency. It is likely that NE comodulates such processes along with other neuro-
modulators like ACh; however, Shepard et al. (2015) indicate that NE exhibits a unique, necessary role in auditory cortex plasticity. Taking the next steps to understand this privileged influence that NE exhibits over auditory critical period plasticity may therefore involve delving into the disinhibitory effects it exerts within cortex.

Although Shepard et al. (2015) have shown that NE is necessary for developmental plasticity in the auditory cortex, it almost certainly does not act alone. NE and ACh can both elicit synaptic plasticity in cortical slices via phospholipase C (PLC; Choi et al. 2005), which may act as a cellular integrator to sum modulatory activity within a neuron. The manner in which cholinergic and noradrenergic signals modulate critical period plasticity may entail distinct pathways with separate functions or, alternatively, a convergence of signals on a biochemical integrator.

To interrogate potential intracellular convergence of ACh and NE signaling on a molecule such as PLC, it would be useful to gain control of this signaling pathway. A subset of cholinergic and adrenergic receptors are G protein-coupled receptors (GPCRs) that use Gq, a G protein subunit, to activate PLC. Gaining control of PLC could be accomplished by using engineered versions of GPCRs known as DREADDs (designer receptors exclusively activated by designer drugs). DREADDs are unresponsive to endogenous ligands but can be activated by synthetic small molecules so as to allow specific control of GPCR signaling. The influences of PLC signaling on auditory plasticity could therefore be examined by using tissue-specific expression of a Gq-coupled DREADD. For instance, if ACh and NE both activate PLC, then use of a Gq-coupled DREADD should produce effects similar to application of ACh and NE. To address questions regarding the contested functional redundancy of NE and ACh in plasticity, it will be imperative for future studies to examine any convergence of intracellular signaling pathways that lead to plasticity in cortical circuits.

The advent of optogenetic methods may present a powerful set of tools for deconstructing the inputs that converge to modify cortical structure. These techniques allow for light-mediated control of specific neuron populations, which have been genetically modified to express light-sensitive ion channels. A promising approach would be to combine optogenetics with pharmacology to isolate the role of particular neuromodulatory receptors in circuit function. For example, LC activation could be placed under optogenetic control by genetically inducing expression of a light-sensitive ion channel within noradrenergic LC neurons. Implantation of optical fibers would allow for light-mediated LC neuron stimulation, which would be paired with presentation of auditory stimuli to induce A1 plasticity. This paired stimulation can be accompanied by simultaneous recordings of neuronal responses in A1 to track plasticity. Using paired stimulation and broad antagonism of α-adrenergic receptors, Martins and Froemke (2015) implicated these receptors in LC–A1 plasticity. We propose the use of more selective adrenergic antagonists in this paired stimulation protocol to isolate the specific types of α- and/or β-receptors involved in modulating A1 responses. A similar approach could be used with ACh and the nucleus basalis to identify the types of cholinergic receptors responsible for modulation of A1 responses.

Because science is an iterative process, it is important to revisit previous results as new techniques are developed. Using a novel transgenic approach to NE depletion, Shepard et al. (2015) tested the role of NE in critical period plasticity. Despite inconsistent reports of the role of NE in V1 developmental plasticity, Shepard et al. found that NE is necessary for critical period plasticity of BF response in the mouse auditory cortex. Moving forward from these studies, it will be important to leverage new tools for activating specific neural circuits to examine if this result can be generalized to other sensory cortices and translated into an explanatory mechanism at circuit and cellular levels. Such findings will push research addressing critical periods toward effective translational breakthroughs that may help combat developmental, neuropsychiatric, and neurodegenerative diseases.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

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