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Commentary

Corticolimbic Circuits in Learning, Memory, and Disease

Hadley C. Bergstrom[1]* and Courtney R. Pinard[2]

[1]Department of Psychological Science, Program in Neuroscience and Behavior, Vassar College, Poughkeepsie, New York
[2]The American Association of Immunologists, Rockville, Maryland

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Changing environmental circumstances demand a high degree of flexibility in behavioral responsivity. Corticolimbic brain networks orchestrate flexible responding, especially when stimuli elicit defense or approach behaviors. The corticolimbic system processes a broad range of behavioral and cognitive functionality that includes motor programming and control, decision making, mnemonic function, and emotional regulation.

Environmental factors, including stress- and fear-inducing stimuli, all have the potential to modify the corticolimbic system. The prefrontal cortices, amygdala, and hippocampus, which make up the corticolimbic system, are highly interconnected with the hypothalamic-pituitary-adrenal axis, rendering them particularly susceptible to the chronic effects of stress (Vyas et al., 2002; Radley et al., 2004). In addition, alterations in corticolimbic circuitry are associated with various neuropsychiatric and neurological disorders. For example, the corticolimbic system processes traumatic fear memories, which have the potential to persist and become dysregulated, representing a central symptomatic dimension of fear-regulatory disorders such as posttraumatic stress disorder (PTSD) (Bergstrom, 2016). Likewise, addictive drugs preferentially target the corticolimbic system, strengthening patterns of compulsive and habitual behaviors that define addiction (Robbins and Everitt, 2002). Various components of the corticolimbic system can degenerate, resulting in devastating neurological conditions such as Alzheimer and Parkinson disease and profound learning and memory deficits.

Despite significant progress unraveling the neuroanatomy and functionality of the corticolimbic system, much remains unknown. This *In Focus* issue of *The Journal of Neuroscience Research* aims to highlight new perspectives and data on the anatomical organization and functional interactions of corticolimbic circuits in learning, memory, and disease. A special emphasis is placed on corticolimbic networks involved in processing emotional learning and memory. We brought together a diverse group of leading neuroscientists studying various aspects of the corticolimbic system, including amygdalohippocampal interconnectivity and long-range GABAergic projection neurons (McDonald and Mott, 2017), the temporal dynamics of systems-level memory consolidation processes in hippocampocortical circuits (Jasnow et al., 2017), cholinergic influence on corticolimbic circuitry during Pavlovian conditioning (Wilson and Fadel, 2017), and medial prefrontal control of Pavlovian-instrumental learning (Halladay and Blair, 2017).

McDonald and Mott (2017) review the complex neuroanatomy of amygdalohippocampal interconnections, including those involving GABAergic projection neurons. The involvement of reciprocal connections between discrete amygdala nuclei and distinct layers of the hippocampal/parahippocampal regions in the temporal lobe memory system is well established. Less understood is how long-range GABAergic neurons are uniquely positioned to enhance the emotional contribution to declarative memory. The potential role of GABAergic amygdalohippocampal projections in both coupling synchronized oscillations and facilitating the synaptic plasticity involved in mnemonic function is highlighted. Memory disorders in relation to altered amygdalohippocampal circuitry are discussed, including PTSD, temporal lobe epilepsy, and Alzheimer disease. In their review, McDonald and Mott set the stage for designing new electrophysiological and behavioral experiments that selectively target different components of the amygdalohippocampal circuit.

Rarely do circumstances in the environment reoccur. For organisms to respond to changing environmental circumstances in an adaptive way, Jasnow et al (2017) discuss how the nervous system has adapted mechanisms to

*Correspondence to: Hadley C. Bergstrom, Department of Psychological Science, Program in Neuroscience and Behavior, Vassar College, Poughkeepsie, NY.

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"generalize" conditioned behavioral responsivity to stimuli that resemble the original conditioned stimuli. One important property of memory generalization is that it can magnify with time, making generalization "a temporally dynamic process." The article focuses on the time-dependent nature of contextual fear memory generalization and recent neuronal circuit data showing that the anterior cingulate cortex and ventral hippocampus support contextual fear memory generalization over time (Cullen et al., 2015). A novel, sex-dependent role for the gonadal hormone estradiol in contextual fear memory precision over time is also discussed (Lynch et al., 2013). As generalization is thought to play a critical role in anxiety-related disorders (Dunsmoor and Paz, 2015), a call for more research into how the temporal control of contextual fear memory generalization expression contributes to anxiety disorders is made.

Wilson and Fadel (2017) review what is known about the role of basal forebrain cholinergic neuronal input to the hippocampus, amygdala, and prefrontal cortex in fear conditioning and extinction. The growing literature on the specific contribution of cholinergic mechanisms to the consolidation of these learning responses is discussed. The authors compare anatomical, pharmacological, and neurochemical evidence demonstrating that activating muscarinic cholinergic receptors in corticoamygdalar and corticohippocampal circuits contributes to the acquisition of fear extinction. Pharmacological studies addressing the role of cholinergic processes in mediating cued fear responses in delay conditioning protocols are summarized. Gaps in research are identified, such as the relatively low number of optogenetic and local field potential studies examining the regulation of synchrony by cholinergic neuronal input to neurons in the CA1 area of the hippocampus, infralimbic cortex (IL), and lateral amygdala. This review of cholinergic regulation of fear learning and extinction is distinct from other reviews on the topic because of its systematic and brain region–specific focus on Pavlovian contextual and cue-conditioned fear responses and extinction.

The IL region of the medial prefrontal cortex has been linked with behavioral flexibility in Pavlovian and instrumental responding. How the IL interacts in the defensive action selection consisting of two competing Pavlovian conditioned defensive responses consisting of freezing or flight is unknown. This question has clinical relevance because dysregulation of medial prefrontal circuits has been implicated in anxiety disorders (Milad et al., 2006). Halladay and Blair (2017) investigated this question by pairing an aversive unilateral periorbital unconditioned stimulus (US) with a tone-conditioned stimuli. This preparation results in either conditioned motor behavior (flight) or conditioned motor suppression (freezing) that depends on when the rats encountered the US. Pharmacological manipulation of the IL with either muscimol ($GABA_A$ agonist) or picrotoxin ($GABA_A$ antagonist) augmented flight, but not freezing responses. These data suggest that the IL plays a role in defensive action selection that includes a broad action space consisting of potentially dichotomous responsivity. These findings further our understanding of how corticolimbic circuits orchestrate flexible behavioral output in the face of variable environmental circumstances including threat imminence.

In the last decade, the advent of new neuroscience tools for visualizing long-range neuronal circuits with cell type–specific resolution and reversible gain/loss of function circuit manipulation at high-speed has opened new vistas on corticolimbic structure and function. It is anticipated that a continued systems-level neuroscience focus of corticolimbic networks will advance our understanding of the nervous system, in both normative and disease states.

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