The basolateral amygdala is a subdivision of the amygdala that is located in the medial temporal lobe (1). The basolateral complex can be divided into lateral and basal nuclei of the amygdala, which receive inputs from the prefrontal cortex, auditory cortex, thalamus, ventral pallidum, ventral tegmental area, locus coeruleus, dorsal raphe, and stria terminalis and send prominent outputs to the central nucleus of the amygdala, the prelimbic and infralimbic prefrontal cortices, the entorhinal cortex, the bed nucleus of the stria terminalis, the hippocampus, and the nucleus accumbens (1). The central nucleus of the amygdala can be divided into lateral and medial divisions.

The basolateral amygdala has long been associated with connecting salient stimuli to behavioral outputs in the domain of fear conditioning (2). As such, the basolateral amygdala plays a key role in the formation, storage, and retrieval of conditioned fear memories (2). However, the basolateral amygdala also plays a role in mediating appetitive conditioning. Neural connections between the lateral and basolateral amygdala and the nucleus accumbens have been hypothesized to generate goal-directed behavior in response to conditioned reward-predictive cues.

Particularly compelling have been the data showing that the basolateral amygdala mediates conditioning associated with the rewarding effects of drugs of abuse. Neuropharmacological disconnection studies implicated the basolateral amygdala connection to the nucleus accumbens core in cocaine seeking. The removal of a small population of neurons by ablating or sending prominent outputs to the central nucleus of the amygdala (i.e., neurons that are recruited during conditioning) blocked the expression and consolidation of cocaine-induced conditioned place preference (3). As discussed by Hsiang et al. (3), functional magnetic resonance imaging studies in humans with a history of cocaine use showed that the presentation of cues that were previously associated with cocaine craving also increased activity in the amygdala.

In the current issue of Biological Psychiatry, Puaud et al. (4) used a projection-specific Cre-dependent DREADD (designer receptor exclusively activated by designer drugs)-mediated causal approach in Sprague Dawley rats to test the hypothesis that direct projections from the basolateral amygdala to the nucleus accumbens core are required for the acquisition of cue-controlled cocaine-seeking behavior. The authors used a sophisticated behavioral task that measures drug-seeking behavior, combined with a chemogenetic microcircuit approach to show that a specific pathway from the basolateral amygdala to the nucleus accumbens core mediated cocaine craving.

Cre-mediated expression of the inhibitory DREADD hM4D(Gi) in nucleus accumbens core-projecting basolateral amygdala neurons selectively prevented the impact of cocaine-associated conditioned reinforcement on cocaine seeking under a second-order schedule of reinforcement. This effect was reversible and absent in clozapine N-oxide–treated rats that expressed an empty control virus, suggesting that the effects were attributable to the chemogenetic inhibition of basolateral amygdala neurons that project to the nucleus accumbens core. Chemogenetic inhibition of the anterior insula, which receives collateral projections from nucleus accumbens core-projecting basolateral amygdala neurons, had no effect. Following extensive training under a second-order schedule when cue-controlled cocaine seeking was well established, chemogenetic inhibition of the basolateral amygdala–nucleus accumbens core pathway, which completely prevented the impact of cocaine-related cues on conditioned reinforcement, had no effect. These data demonstrate that the acquisition of cue-controlled cocaine seeking that depends on the conditioned reinforcing effects of cocaine cues requires the activity of direct projections from the basolateral amygdala to the nucleus accumbens core.

This was a well-designed and well-executed study that brought together a large body of literature into a coherent microcircuit framework. A particular strength was the use of a behavioral paradigm that builds not only on face validity but also on construct validity. Second-order schedules are ubiquitous in the human world of drug addiction and have been shown to provide an effective means of understanding the motivational circuitry that mediates the role of stimuli that are paired with drug reward. Critically, the response output in these schedules is largely independent of any motor or sedative actions of the drug itself.

However, as with any important advance, many questions remain unanswered. Paralleling the extensive work in the fear conditioning domain, one wonders if using a second-order schedule would allow exploration of the “engram” hypothesis in fear conditioning to appetitive conditioning and drug conditioning, based on the dynamic function and circuitry interactions of the basolateral amygdala with the nucleus accumbens. In other words, is there a craving engram? Indeed, the authors suggested that because chemogenetic inhibition of the basolateral amygdala–nucleus accumbens core pathway did not disrupt responding following extensive training under a second-order schedule when cue-controlled
Intrinsic circuitry may be the site of conditioning, much evidence links projections from the basolateral complex to the central nucleus of the amygdala complex. Some have argued that this neurocircuitry that links the basolateral amygdala with fear conditioning and appetitive conditioning associated with drug craving.

Figure 1. Neurocircuitry that links the basolateral amygdala with fear conditioning and appetitive conditioning associated with drug craving. (A) For fear conditioning, much evidence links projections from the basolateral complex to the central nucleus of the amygdala complex. Some have argued that this intrinsic circuitry may be the site of “fear engrams.” For conditioned fear, a repeated motif of connectivity between the basolateral amygdala medial intercalated cells (ICM) and central nucleus of the amygdala neurons has been hypothesized (8). Here, principal basolateral amygdala neurons are hypothesized to influence central nucleus of the amygdala neurons via either a direct glutamatergic projection or indirectly by exciting intercalated GABAergic (gamma-aminobutyric acidergic) cells that then generate feedforward inhibition in central nucleus of the amygdala neurons. Ultimately, learned fear is hypothesized to be regulated by modifying the relative efficacy of the direct vs. indirect components of this microcircuit (8). For appetitive conditioning, data to date provide evidence of glutamatergic projections from the lateral and basolateral amygdala to the shell and core of the nucleus accumbens. There is also evidence of such inputs to both GABA interneurons and medium spiny neurons (MSNs) in the core of the nucleus accumbens in appetitive conditioning (9). The nucleus accumbens core (AcbC) and nucleus accumbens shell (AcbSh) have intrinsic cholinergic interneurons and dynorphin neurons and many similar inputs. However, they have different inputs from the prefrontal cortex, insula, hippocampus, and lateral hypothalamus (LH), none of which are shown here. The outputs of the core and shell also differ with core projections predominantly to motor regions that are important for executing action, such as the ventral pallidum and subthalamic nucleus, and the shell sends projections predominantly to areas that are associated with emotional processing, such as the LH, ventral tegmental area, bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala, and ventromedial ventral pallidum. Both the core and shell respond to the onset of a salient event, such as the delivery of an infusion of cocaine, but the core is more likely to encode information about reward-predictive cues. The shell is more likely to encode outcome-selective information about such reward-predictive cues relative to a given motivational state (incentive salience). Although still highly speculative, one could hypothesize that interactions between intrinsic and external connections form the basis of a “craving engram.” If one were able to modify such an engram, then would one have a key to reversing craving and preventing relapse in addiction. The diagrams were redrawn from Duvarci et al. (10). BA, basal nuclei of the basolateral amygdala; CeL, lateral central nucleus of the amygdala; CeM, medial central nucleus of the amygdala; LA, lateral nuclei of the basolateral amygdala.

cocaine seeking was well established, “the engram of the instrumental association potentiated by the conditioned reinforcing properties of drug-paired cues may be distributed across amygdalo-striatal systems” (Figure 1) (4).

In fear conditioning, early studies showed that lesions of the basolateral amygdala blocked innate responses to an aversive unconditioned stimulus. Lesions of either the basolateral or central nucleus of the amygdala prevented the acquisition and expression of learned defensive responses to a conditioned stimulus (2). The amygdala also plays a key role in the extinction of conditioned fear (2). Here, during extinction, the ability of the conditioned stimulus to activate intra-amygdala pathways from the basolateral amygdala to the central nucleus of the amygdala is reduced, resulting in a failure to engage central nucleus of the amygdala-dependent conditioned defensive reactions, such as freezing (2).

An intriguing extension of the role of the basolateral amygdala in fear conditioning is the hypothesized role of the basolateral amygdala in fear engrams (5). An engram can be defined as “the combined set of physical changes that occur within the brain as a result of a particular experience, and that enable the animal to memorize elements of that experience in order to inform future behavior” (5). Engram cells allegedly exhibit synaptic and cell-intrinsic plasticity that allow the storage of information without a need for the continuous firing of action potentials (5). Evidence of a role of the basolateral amygdala in fear engrams ranges from the fear memory being completely and permanently stored within the basolateral amygdala to fear memory being completely outside the basolateral amygdala and the basolateral amygdala modulating fear engrams elsewhere (5).

In a further interaction with fear conditioning circuitry, the basolateral amygdala–nucleus accumbens circuit may also play a key role in conditioning that is associated with conditioned withdrawal. Here, lesions of the basolateral amygdala blocked the acquisition of conditioned opioid withdrawal (6). Additionally, one could extend such negative valence conditioning studies to studies that use animal models of cocaine seeking, in which an aversive tautant response that is hypothesized to reflect a negative emotional-like state in anticipation of cocaine predicts cocaine seeking (7). Do the circuits that mediate the reward-driven “craving engram” overlap with the hyperkatalifeia-driven craving engram? Such fundamental knowledge, gained by utilizing modern Brain Research through Advancing Innovative Neurotechnologies (BRAIN) techniques combined with sophisticated behavioral paradigms, may allow...
one to generalize knowledge of the mechanisms of different domains (e.g., conditioned fear vs. conditioned reward) to provide a key to understanding of long-lasting neuro-adaptations associated with addiction.

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