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Conditioned Reinforcement and the Specialized Role of Corticolimbic Circuits in the Pursuit of Happiness and Other More Specific Rewards

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Normal behavior is guided by both primary reinforcers (such as food, drugs, sex, etc.) and secondary or conditioned reinforcers. Conditioned reinforcers are cues that have been repeatedly paired with primary rewards such that they acquire the ability to support behavior even in the absence of those primary rewards (Mackintosh, 1974). Our everyday lives are filled with examples of conditioned reinforcers that drive our behavior. These include examples such as money and corporate icons such as the McDonalds Golden Arches, which acquire an emotional/affective or hedonic value of their own, as well as examples with more specific associations, such as the song that was playing when we met that special someone. Indeed, conditioned reinforcement is pervasive in modern society.

Conditioned reinforcement depends upon a circuit that includes the basolateral amygdala, the orbitofrontal cortex, and the nucleus accumbens (Burns et al., 1993; Cador et al., 1989; Everitt and Robbins, 1992; Parkinson et al., 1999, 2001; Parkinson et al.,; Pears et al., 2001, 2003; Whitelaw et al., 1996). However, our understanding of how these areas interact to mediate conditioned reinforcement is hampered by our limited understanding of underlying associative representations that allow these cues to serve as conditioned reinforcers. Specifically, it is not certain whether conditioned reinforcers are effective because of the affective value they acquire or because of the specific outcomes that they represent and the value that those outcomes have to us. In other words, are the Golden

Arches effective because they predict hamburgers and fries, which we desire, or are they also effective in part because they evoke a more general feeling of happiness directly? Moreover, if both are true, might different brain circuits be specialized to mediate our pursuit of happiness versus our pursuit of more specific rewards? In this chapter, we will outline a new approach we have taken to address these questions.

Basolateral Amygdala, Orbitofrontal Cortex, and Nucleus Accumbens in Reward Processing and Conditioned Reinforcement

Basolateral Amygdala

The basolateral amygdala receives sensory inputs from the environment and is commonly believed to associate neutral sensory cues with information regarding the primary rewarding or aversive outcomes that these cues come to predict (Quirk et al., 1995; Schoenbaum et al., 1998, 1999, 2003). This type of learning is important in adaptive behavior, in which an animal directs its behavior according to the current value of the predicted outcome.

The role of amygdala in this type of learning has been clearly demonstrated in reinforcer devaluation tasks (Hatfield et al., 1996; Malkova et al., 1997). In devaluation (Holland and Straub, 1979), the animal first learns the association between a neutral cue and

a food outcome through a Pavlovian conditioning procedure. After the rat learns this association, it will readily respond to the food cup once the cue comes on in anticipation of the impending outcome. Following learning, the food is devalued by pairing it with illness (or by selective satiation). Subsequently, food cup responding to the cue is assessed in an unrewarded probe session. Normal animals spontaneously decrease conditioned responding to the cue after devaluation, indicating that the cue–outcome association has been formed and can be updated and used to guide food cup responding. Rats with damage to basolateral amygdala failed to alter conditioned responding after devaluation (Hatfield et al., 1996; Malkova et al., 1997). Instead, these rats continued to respond to the cue to the same extent as the rats in which the food is not devalued. This deficit was observed despite normal learning and normal devaluation in earlier training, as well as normal extinction during the probe test. Interestingly, damage to basolateral amygdala made after initial conditioning no longer affects changes in responding after devaluation (Pickens et al., 2003), suggesting that the original deficit reflects a critical role for amygdala in learning the original associations rather than in updating or using that information later in the actual probe test.

Importantly, similar deficits have been found in monkeys with neurotoxic lesions of amygdala (Malkova et al., 1997). In this experiment, monkeys were trained in an object discrimination task where visual objects were paired with different food rewards. Once the monkeys learned the object discriminations, they were allowed to choose between two objects that predicted two different foods. Prior to some sessions, the monkeys were fed to satiety on one of the two foods in order to devalue that particular outcome. Satiation caused normal monkeys to bias subsequent choices away from the object paired with the satiated food, whereas monkeys with amygdala lesions failed to change their choice behavior after selective satiation.

The role of basolateral amygdala in signaling information about predicted outcomes is also evident in a variety of other settings. For example, Dwyer and Killcross used a mediated conditioning procedure to show that rats with basolateral amygdala lesions were impaired in using outcome-specific information evoked by cues to guide their behavior (Dwyer and Killcross, 2006). In this experiment, rats were placed in a Y-maze where each distinctive arm was associated with water, sucrose, or maltodextrin solution. After learning the associations between the contextual cues

contained in the maze arms and the different solutions, the rats were then trained to associate one of the maze arms with illness induced by lithium chloride (LiCl) injections. Subsequently, normal rats reduced their consumption of the solution associated with the target arm. This reduction occurred even though that solution was never directly paired with illness, indicating that rats had activated specific representations of the different solutions when they were exposed to the arms while ill. Rats with damage to basolateral amygdala showed normal behavior during training and devaluation but failed to change their consumption of the solutions in the probe test.

These studies demonstrate a critical role for basolateral amygdala in the process by which neutral cues are able to evoke representations of the outcomes they predict, particularly the value of those outcomes. However, basolateral amygdala has also been implicated in other cue-evoked behaviors, which do not appear to depend specifically upon the value of the predicted outcome. For example, basolateral amygdala supports second-order conditioning (Hatfield et al., 1996; Setlow et al., 2002a). In this Pavlovian procedure, a neutral cue is paired with a reward. Following this, another neutral cue, termed the second-order cue, is then paired with the conditioned stimulus. Although the second-order cue has never been paired directly with reward, a conditioned response develops to this cue. Basolateral amygdala lesions prevent the development of this second-order conditioned response. Interestingly second-order conditioning is not critically dependent on the value of the outcome predicted by the conditioned stimulus (Holland and Rescorla, 1975).

Basolateral amygdala has also been implicated in Pavlovian-to-instrumental transfer (PIT) (Corbit and Balleine, 2005). In this procedure, a cue that has been paired with an appetitive outcome, through Pavlovian conditioning, is able to increase a previously trained instrumental response. This increased responding is termed “transfer.” Transfer occurs despite the lack of any prior pairing between the cue and the instrumental response. As a result, it has been suggested that the effect of the Pavlovian cue is due to its ability to evoke affective or motivational representations. Rats with damage to basolateral amygdala show normal Pavlovian and instrumental conditioning but fail to increase instrumental responding in the presence of the Pavlovian cue. Like second-order conditioning, mentioned above, transfer is not affected by devaluation of the outcome predicted by the conditioned stimulus (Holland, 2004).

These studies suggest that basolateral amygdala also plays a role in allowing cues to evoke representations of general affect that are independent of the specific properties of the predicted outcome, particularly its current value. Again this role seems to be particularly evident prior to learning, since lesions of basolateral amygdala after initial or first-order conditioning no longer affect performance in these settings (Pickens et al., 2003; Setlow et al., 2002a).

Basolateral Amygdala and Orbitofrontal Cortex

The involvement of basolateral amygdala in linking neutral cues to representations of the specific outcomes they predict, particularly the value of those outcomes, depends critically on interactions between basolateral amygdala and orbitofrontal cortex (Baxter et al., 2000; Schoenbaum et al., 2003). Orbitofrontal cortex-lesioned rats, like rats with basolateral amygdala lesions, fail to reduce conditioned responding after changes in the value of the predicted outcome (Gallagher et al., 1999). Similar deficits have been observed in monkeys with orbitofrontal lesions and in monkeys with crossed lesions of orbitofrontal cortex and amygdala (Baxter et al., 2000; Izquierdo et al., 2004). Impairments after crossed lesions demonstrate that proper responding requires serial processing in these two areas.

The role of amygdala and orbitofrontal cortex in signaling outcome representations has also been shown in a human imaging study using a devaluation procedure (Gottfried et al., 2003). In this experiment, subjects were trained to associate visual cues with odors of different foods—food odor “rewards.” After training, the subjects were scanned during presentation of the visual cues before and after being fed to satiation on one of the foods. The cue that signaled the satiated food odor elicited a decreased blood oxygen level-dependent (BOLD) signal in orbitofrontal cortex as well as in the basal nuclei in the amygdala, while signals in these regions to a cue that signaled a nonsatiated food odor were not affected.

The roles of basolateral amygdala and orbitofrontal cortex in responding after devaluation can also be dissociated by manipulating the timing of the lesions. Recall that when lesions of basolateral amygdala are made after conditioning, there is no longer any effect on performance. By contrast, when orbitofrontal cortex lesions are made after initial conditioning, or even after devaluation, there continues to be an impact on devaluation-induced changes in conditioned

responding (Pickens et al., 2003). These results suggest that orbitofrontal cortex plays an ongoing role in the use of cue-evoked representations of the outcome's current value to guide responding.

Whether outflow from basolateral amygdala to orbitofrontal cortex is also important for mediating behaviors based on affective representations is somewhat unclear. Post-training lesions of orbitofrontal cortex affect discriminative responding for second-order cues (Cousens and Otto, 2003). Whether this sort of learning is devaluation-insensitive like Pavlovian second-order conditioning is not certain. Post-training lesions of orbitofrontal cortex have also been reported to impair transfer-like damage to basolateral amygdala (Ostlund and Balleine, 2007). However, lesions made before training had no effect, suggesting that while orbitofrontal cortex may play a role in information acquired when it is intact, it does not contribute critically to the systems that mediate the fundamental processing required for transfer. Thus while the amygdala-orbitofrontal circuit is clearly required for behaviors guided by the cue-evoked value of the predicted outcome, it may not be critical for behaviors guided by cue-evoked devaluation-insensitive, general affective information.

Basolateral Amygdala, Central Nucleus, and Accumbens

The basolateral amygdala also sends strong projections to the central nucleus and to the nucleus accumbens (Kelley et al., 1982; Krettek and Price, 1978; Wright et al., 1996). These outflow pathways appear to be preferentially involved in allowing cues to drive behavior through representations of general affect that are resistant to devaluation of the predicted outcome. As we have described, the basolateral amygdala is implicated in behaviors such as second-order conditioning and PIT (Corbit and Balleine, 2005; Hatfield et al., 1996). As discussed earlier, these behaviors are typically resistant to devaluation of the predicted outcome. Normal performance in these tasks also often depends on central nucleus of the amygdala or the nucleus accumbens (Balleine and Corbit, 2005; Corbit and Balleine, 2005; Holland and Gallagher, 2003; Setlow et al., 2002b). Interestingly, it has been shown that crossed lesions of basolateral amygdala and nucleus accumbens, designed to disconnect the two regions, impair second-order conditioning even when made after first-order conditioning (Setlow et al., 2002b). This contrasts with basolateral amygdala (ABL) lesions, which are most

effective when made before initial conditioning (Setlow et al., 2002a). These results suggest that basolateral amygdala plays a role in acquiring these representations, which nucleus accumbens then employs to guide responding. This is similar to the interactions between amygdala and orbitofrontal cortex in devaluation-sensitive behaviors.

Though deficits in second-order conditioning do not occur after lesions to the central nucleus of the amygdala (Hatfield et al., 1996), damage to this area has been found to affect PIT (Corbit and Balleine, 2005; Hall et al., 2001), as has damage to nucleus accumbens (Balleine and Corbit, 2005; de Borchgrave et al., 2002; Hall et al., 2001). The role of these downstream areas in transfer is complicated by the observation that transfer can be outcome-specific, where both the Pavlovian cue and the lever are associated with the same outcome or transfer can be general when the cue and lever are associated with different outcomes. Unfortunately, these two forms of transfer are typically not elicited by the same training procedures, thus most studies of this phenomenon report on only one or the other. However it appears that basolateral amygdala is required for outcome-specific but not general transfer, whereas central nucleus, and to a lesser extent accumbens, are more strongly implicated in general transfer (Balleine and Corbit, 2005; Corbit and Balleine, 2005; Holland and Gallagher, 2003). One interpretation of these results is that as affective information moves from basolateral amygdala to these downstream areas, it becomes progressively more independent of the specific features of the outcome with which it was originally associated. This idea is consistent with the observation that damage to nucleus accumbens does not impair learned responses after reinforcer devaluation (de Borchgrave et al., 2002) but does affect transfer (Corbit et al., 2001; de Borchgrave et al., 2002; Hall et al., 2001).

Contributions of Reward Circuits to Conditioned Reinforcement

Conditioned reinforcement is the process by which a neutral stimulus, which has been paired previously with a primary reinforcer, is able to support the acquisition and maintenance of a new instrumental response. A large and growing number of studies show that the brain regions involved in reward learning, reviewed earlier, are also critical for normal conditioned reinforcement. For example, Roberts and colleagues have tested the contributions of amygdala and

orbitofrontal cortex in marmosets on a two-schedule, progressive ratio task (Parkinson et al., 2001; Pears et al., 2003). In this task, the marmosets have to execute X number of responses to obtain the conditioned reinforcer and primary reward was delivered after Y presentations of the conditioned reinforcer. The sizes of X and Y were progressively increased until the marmosets stopped responding. Marmosets with bilateral amygdala lesions responded less vigorously and stopped responding on lower schedules than controls (Parkinson et al., 2001). These results show clearly that amygdala—including basolateral amygdala—is important for maintaining responding for conditioned reinforcers. Consistent with this, performance in amygdala-lesioned marmosets, unlike controls, was unaffected by omission of the conditioned reinforcer, suggesting that presentations of the conditioned reinforcers did not maintain the responding on these higher order schedules. Marmosets with orbitofrontal cortex lesions also behaved abnormally in this task; however, unlike amygdala-lesioned animals, they actually responded more and at higher schedules than controls (Pears et al., 2003). This effect points to differences in the role of basolateral amygdala versus orbitofrontal cortex in mediating responding in this complex setting. However, as was the case for amygdala-lesioned animals, the performance of the orbitofrontal-lesioned marmosets was insensitive to omission of the conditioned reinforcer. Thus orbitofrontal cortex is also important for the process by which conditioned stimuli come to support instrumental responding.

Connections between basolateral amygdala and nucleus accumbens have also been implicated in conditioned reinforcement. For example, rats with bilateral basolateral amygdala lesions were impaired in a conditioned reinforcement task (Cador et al., 1989). In this experiment, thirsty rats were conditioned to associate a light/noise with water. After learning, these rats were presented with two levers, one leading to the light-noise cue and the other lever leading to nothing. Rats with basolateral amygdala lesions showed normal Pavlovian conditioning to the light but failed to respond on the lever for presentation of the light cue. This impairment was ameliorated dose-dependently by infusion of D-amphetamine into nucleus accumbens, suggesting that the deficit reflected the loss of normal excitatory drive from basolateral amygdala to accumbens. Additionally, these authors found that these infusions increased responding on the lever that produced the light cue in controls.

Dissociating the Associative and Circuit Basis of Conditioned Reinforcement

The results reviewed earlier suggest that different brain circuits might be involved in conditioned reinforcement due to their respective roles in reward learning. Thus basolateral amygdala and orbitofrontal cortex may support conditioned reinforcement because they allow Pavlovian cues to evoke representations of the outcomes they predict. Similarly projections from basolateral amygdala to central nucleus and nucleus accumbens may support conditioned reinforcement because they allow Pavlovian cues to evoke representations of general affect.

In this model, basolateral amygdala would play a central role in endowing cues with the ability to serve as conditioned reinforcers, since it is required for cues to acquire both affect and outcome representations. This is consistent with observations that although amygdala-lesioned marmosets show normal Pavlovian conditioning, which could be mediated by direct associations between cues and responses, they will not subsequently acquire novel conditioned instrumental responding for those cues. This hypothesis might also account for the somewhat different pattern of results in orbitofrontal-lesioned marmosets, which overresponded on the complex scheduled conditioned reinforcement task described earlier in this chapter. If orbital lesions cause a selective inability to use the conditioned reinforcer to signal the outcome while leaving affective representations largely intact, they might show general overresponding over time because they would be unable to recognize that the outcome is not actually delivered on most trials. Though admittedly one might have expected some impact on responding when the conditioned reinforcer was omitted, it is possible that the complex and prolonged training regime allowed the affective properties of the conditioned reinforcer to transfer to the response in orbitofrontal-lesioned marmosets.

However, whether or not our hypothesis fully explains existing data is to some extent premature, since we do not currently know whether conditioned reinforcers support behavior because of the outcomes they predict or due to some inherent value or “affect” that the cues have acquired. Intuitively one might expect it is both; however, to the best of our knowledge, with the exception of one particular study (Parkinson et al., 2005), this has not been empirically tested. To test this idea, it is necessary to utilize more specific Pavlovian training techniques to create cues

that are biased to trigger or evoke either outcome or affect representations. These cues can then be used to assess conditioned reinforcement. Here we will describe our initial studies aimed at identifying the underlying representations of conditioned reinforcers.

Conditioned Reinforcement Mediated by Devaluation-insensitive Representations of General Affect

To show that conditioned reinforcement can be mediated by devaluation-insensitive representations of general affect, we tested the ability of rats to acquire a novel instrumental response for a Pavlovian cue *after* devaluation of the outcome predicted by the cue (Burke et al., 2007, 2008). The training procedure is shown in Table 2.1. Rats received presentations of a neutral cue paired with delivery of a food outcome in a Pavlovian conditioning procedure. Additionally, a control cue was also presented. For most of the rats, this cue was presented without reward; for some rats, it was “blocked” from forming any association with the outcome (see the section “Conditioned Reinforcement Mediated by Devaluation-sensitive Representations of Specific Outcomes” for explanation). After training, rats were assigned to one of the two groups. Rats in one group underwent reinforcer devaluation, in which the food was paired with illness induced by LiCl injection. Rats in the control group received similar exposure to the food and illness on alternate days. As in prior work (Gallagher et al., 1999; Pickens et al., 2003; Schoenbaum and Setlow, 2005), rats in the paired group significantly reduced their food consumption, while rats in the unpaired group showed no change in their food consumption.

We next tested the ability of these cues to support conditioned reinforcement. For rats in the paired group, responding on one lever/chain resulted in presentations of the cue associated with a devalued food while responding on the other lever/chain led to the control cue. For rats in the unpaired group, one response produced the cue associated with a nondevalued food and the other the control cue. As illustrated in Figure 2.1, rats responded significantly more for either the nondevalued or a devalued cue versus the control cue, with no significant effect of devaluation. This result indicates that a devalued cue was able to support apparently normal conditioned reinforcement. These data show, consistent with prior results (Parkinson et al., 2005), that devaluation-insensitive, general affective properties evoked by Pavlovian cues can support conditioned reinforcement.

Table 2.1 Outline of Events for the Devaluation Procedure Preceding Conditioned Reinforcement

Outline of Events		
Conditioning	Devaluation	Conditioned Reinforcement
Cue 1: Food pellet, Cue 2: Control cue	Paired group: Food pellet–LiCl	R1: Devalued cue, R2: Control cue
Cue 1: Food pellet, Cue 2: Control cue	Unpaired group: No pellet–LiCl	R1: Nondevalued cue, R2: Control cue

Cue 1 [was either a] cue light or house light, counterbalanced. [Cue 2 was either a light cue (cue light or house light) or a noise cue (tone or white noise)] Cue 1, in the paired group, becomes the “devalued cue” while Cue 1, in the unpaired group, becomes the “nondevalued cue.” Cue 2 is a control cue for both groups. R1 and R2 were two identical levers/chains. The food pellet was a 45 mg sucrose pellet (Research Diets, New Brunswick, NJ). LiCl was given in two to three nonconsecutive injections of 0.3 M LiCl (5 mg/kg).

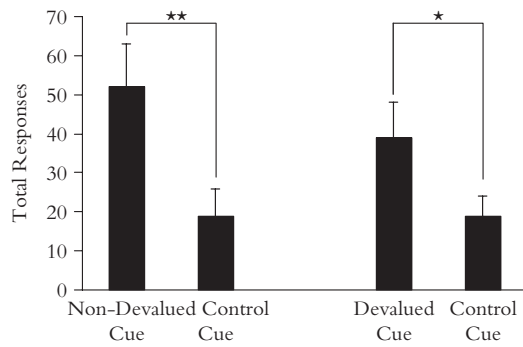


Figure 2.1. Acquisition of a new instrumental response for a cue associated with a devalued outcome. This graph shows the average total number of responses for nondevalued and devalued cues compared to the control cues over three days (i.e., three 30-min sessions) on a VR2 schedule. Responding on the left side of the graph shows responses from rats in the unpaired group, which did not experience food–LiCl pairings. Data on the right side of the graph represents responses from rats in the paired group that did experience food–LiCl pairings. In both groups, rats responded more for the cue associated with the food outcome (whether it was devalued or not) over the control cue, demonstrating no effect of devaluation. (*, $p < 0.05$; #, $p = 0.1$) (Graph modified from Burke et al., 2007.)

Conditioned Reinforcement Mediated by Devaluation-sensitive Representations of Specific Outcomes

To show that conditioned reinforcement can be mediated by outcome representations that are devaluation-sensitive, we used a Pavlovian training procedure termed transreinforcer blocking (Burke et al., 2007,

2008). Blocking refers to the observation that a cue that predicts reward will prevent the formation of associations between that reward and any other cues that are present. Thus, if a rat is trained that a light predicts food and is later presented with that same light and a tone, followed by the same food, the rat will not learn to associate the tone with any of the information evoked by presentation of that food (e.g., its sensory qualities and particular value and the more general affective properties it evokes, which are typically shared with many different outcomes). The light prevents or blocks the tone from forming associations with any of these representations.

Transreinforcer blocking varies this procedure by using two different but equally preferred outcomes. The light is initially presented alone followed by one outcome. Subsequently the light is presented in compound with the tone, followed by the second outcome. Because both outcomes are equally preferred, they trigger comparable emotional responses. These general affective properties are already predicted by the light, thus the tone is blocked from forming associations with them. However, the light does not predict information that is specific to the second outcome, such as its particular sensory properties and the value the animal attaches to these, so the tone is able to form associations with these outcome-specific properties. As a result, the tone becomes able to preferentially evoke representations of the outcome and its specific value and not of general affective representations triggered by the outcome. This assertion is supported by the demonstration that responding to a cue trained in this manner will not support general PIT (Rescorla, 1999) but is sensitive to devaluation of the specific outcome it predicts (see below). We will use this cue to test whether conditioned reinforcement is mediated by outcome-specific information.

The training procedure is shown in Table 2.2. For this task, four unique visual and auditory cues (A, B, X, and Y) and two differently flavored food pellet outcomes (O1 and O2) were used. These pellets, termed O1 and O2 (i.e., banana- and grape/chocolate-flavored sucrose pellets; Research Diets, New Brunswick, NJ) are equally preferred but still possess distinct, devaluation-sensitive properties. This is illustrated by preference and devaluation testing results, shown in the bar graph inset in Table 2.2.

In initial training, neutral cues, A and B, were each paired with one of the two food outcomes (A-O1 and B-O2). After this training, compound stimuli—AX and BY—were presented. AX was paired with O1 in a standard blocking procedure, while BY was paired with O1 in a transreinforcer blocking procedure. Because A predicts all features of O1, no learning occurs for X. By contrast, B does not predict the specific properties of O1 (properties that allowed the selective devaluation of one outcome but not the other in Table 2.2). As a result, Y acquires an association with these unique devaluation-sensitive features of the O1 outcome, while it is blocked from acquiring

associations with the general affect shared between the two outcomes (properties that led to a similar preference between the two outcomes in Table 2.2).

At the end of testing, the effectiveness of this procedure was assessed in a single probe session, in which all four cues were presented alone, under extinction conditions. Consistent with predictions, rats responded most to the fully trained cue A/B, somewhat for the partially conditioned cue Y, and at levels comparable to the pre-CS period to the fully blocked cue X (data not shown; $p < 0.05$).

Subsequently, we tested the ability of the cues to support conditioned reinforcement. For some rats, pressing one lever resulted in presentation of the partially conditioned cue, Y, and another lever resulted in presentation of the blocked cue X. And for some rats, pressing one lever resulted in presentation of the fully conditioned cue A, while pressing on the other resulted in presentation of the blocked cue X. As illustrated in Figure 2.2, rats responded significantly more for either the fully or the partially conditioned cue when compared to the blocked cue, and there was no difference in responding for the fully or

Table 2.2 Outline of Events for the Transreinforcer Blocking Procedure Preceding Conditioned Reinforcement

<i>Blocking and Conditioned Reinforcement</i>		
Conditioning	Compound	Conditioned Reinforcement
A-O1, B-O2	AX-O1, BY-O1	Group 1: R1-A, R2-X Group 2: R1-Y, R2-X

Amount consumed (pellets)

Nondevalued
Baseline preference
Selective satiation

Cues A and B were two different light cues (house light and cue light) and cues X and Y were two distinct noise cues (76 dB tone and 76 dB white noise, 4 kHz). Food pellets O1 and O2 were banana and grape or chocolate flavored sucrose pellets. R1 and R2 were levers/chains inserted into the walls of the behavioral chamber. All cues and food pellets were counterbalanced. (A) Taste preference testing for banana (B) versus grape (G) or chocolate (C) flavored sucrose pellets. Food-deprived rats were tested in a series of three preference tests. Rats were given 50 pellets of each flavor in their home cage for five minutes. Following these tests, rats were tested in a satiation procedure (three tests) where they were given the pellet to be satiated for 20 minutes in an unlimited quantity and immediately following, rats were presented with 100 pellets of the satiated and nonsatiated pellet. Consumption over all three days is shown as an average. (*, $p < 0.05$) (Graph modified from Burke et al., 2007.)

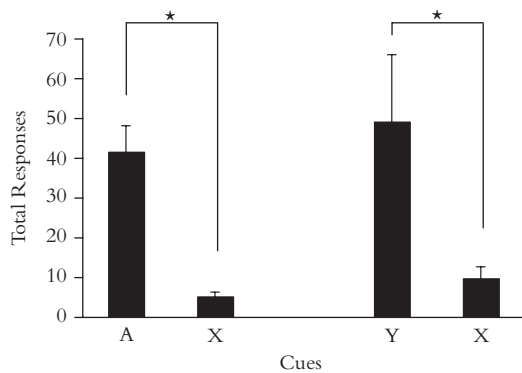


Figure 2.2 Acquisition of a new response mediated by a cue evoking an outcome representation. Figure shows the average total number of responses over two 30-min sessions on a VR2 schedule. Rats represented on the left side of the graph, had access to two levers/chains: one leading to the fully conditioned cue, A, and the other leading to the fully blocked cue, X. Rats, on the right side of the graph, had access to two levers/chains as well: one leading to the partially conditioned cue, Y, and the other to the fully blocked cue, X. Rats responded significantly more for the fully conditioned cue and the partially conditioned cue over the blocked cue ($*, p < 0.05$). (Graph modified from Burke et al., 2007.)

partially conditioned cues. These data show that representations of outcome-specific information evoked by Pavlovian cues are also sufficient to support conditioned reinforcement.

Roles of Basolateral Amygdala and Orbitofrontal Cortex in Conditioned Reinforcement Mediated by Affect and Outcome Representations

Data described earlier suggest that Pavlovian cues function as conditioned reinforcers due to their ability to evoke representations of the outcomes they predict and also due to their ability to signal the general affect normally evoked by those outcomes. The orbitofrontal cortex is known to play a role in signaling expected outcomes, thus the involvement of this brain region in conditioned reinforcement may reflect its role in outcome signaling. To test this hypothesis, we trained rats with lesions of orbitofrontal cortex in the trans-reinforcer and conditioned reinforcement task described earlier (Burke et al., 2008).

Neurotoxic lesions of orbitofrontal cortex were made prior to any training. After recovery from

surgery, lesioned rats and controls were trained as shown in Table 2.2. Orbitofrontal lesions had no effect on Pavlovian conditioning, either in the initial training or during the compound training. However, when these cues were used as conditioned reinforcers to support the acquisition of a novel instrumental response, orbitofrontal-lesioned rats exhibited selective impairments in their ability to use outcome representations. These results are shown in the upper panels of Figure 2.3. Controls exhibited greater responding for either A or Y versus X, replicating the effect described in Figure 2.2, showing that outcome representations will support conditioned reinforcement. By contrast, orbitofrontal-lesioned rats showed normal responding for A, but failed to respond for Y. This pattern of selective impairment is consistent with the hypothesis that orbitofrontal cortex is required for conditioned reinforcement mediated by outcome representations.

To confirm that responding for Y in controls was mediated by outcome-specific information, we next devalued the outcome predicted by Y, by pairing O1 with illness. After several O1-illness pairings, we tested whether devaluation had any effect on the previously established conditioned responding. The results are shown in the lower panels of Figure 2.3. As predicted, the controls no longer responded to Y, indicating that responding for Y had been completely driven by devaluation-sensitive information about the O1 outcome.

Interestingly, there was no effect of devaluation on responding for A when the responding was considered as a ratio versus X. This was true both in controls and also in lesioned rats. The lack of any effect of devaluation on conditioned reinforcement mediated by a fully conditioned cue is consistent with data in Figure 2.1, showing that rats will respond for conditioned reinforcers even after devaluation of the predicted outcome. Thus these data confirm that devaluation-insensitive representations of general affect will support conditioned reinforcement. Indeed, such information appears to be sufficient to support apparently normal levels of responding. In addition, the lack of any effect of orbitofrontal cortex lesions on responding to A is consistent with the proposal that orbitofrontal cortex is not involved in conditioned reinforcement mediated by general affect. As a whole, these results are consistent with the proposal that orbitofrontal cortex supports conditioned reinforcement due to its already appreciated role in signaling expected outcomes.

The selective effects of orbitofrontal lesions on a specific form of conditioned reinforcement contrasts sharply with more general effects of basolateral

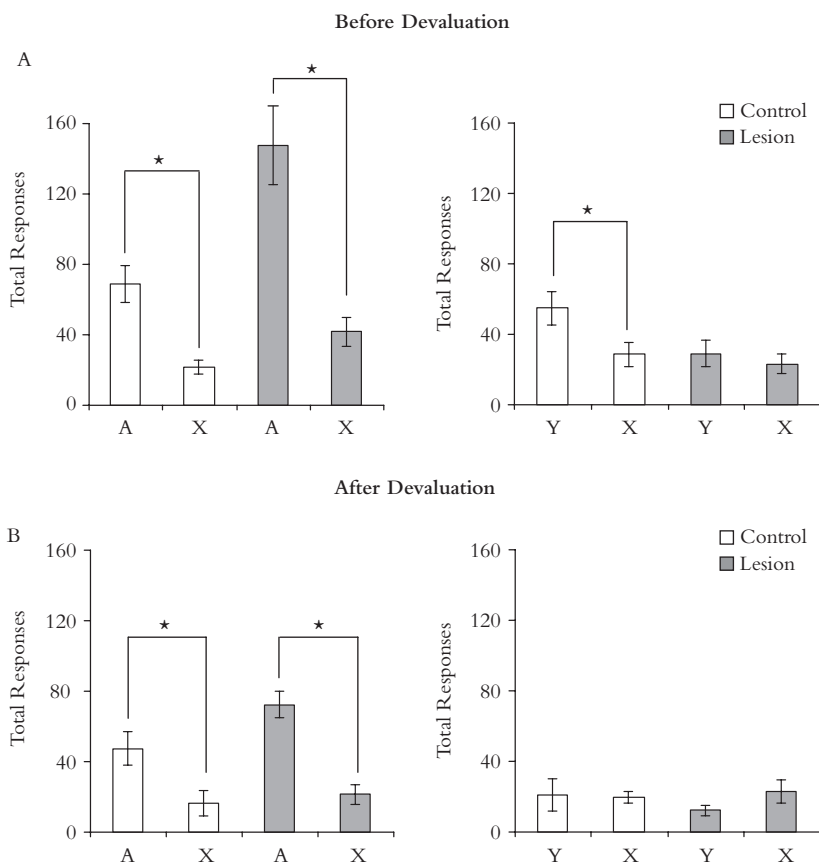


Figure 2.3 Effects of pretraining orbitofrontal cortex (OFC) lesions on conditioned reinforcement. Instrumental lever responding is shown before (3A) and after devaluation (3B) for cues A and X or Y and X. (A) Control rats responded significantly more for the fully conditioned cue, A, and partially conditioned cue, Y, over the fully blocked cue, X. On the other hand, as predicted, OFC lesioned rats showed conditioned reinforcement for the A cue but not for the Y cue. (B) Devaluation abolished responding for the Y cue in controls while having no effect on the A cue for either the controls or OFC lesioned rats (*, $p < 0.05$). (Modified from Burke et al., 2008.)

amygdala lesions on conditioned reinforcement (Burke et al., 2007, 2008). Rats with basolateral amygdala lesions were tested using the reinforcer devaluation and conditioned reinforcement task described in Table 2.1. Although basolateral amygdala lesions had no effect on Pavlovian conditioning, they completely abolished conditioned reinforcement. The results are shown in Figure 2.4. While responding for the cue that had been paired with food increased in controls across days of training, responding for these cues did not increase for the basolateral amygdala-lesioned rats. This effect was evident whether or not the food predicted by this cue had been devalued. These results are consistent with previously published reports that

amygdala damage causes general deficits in conditioned reinforcement.

Conclusions

Despite their apparent involvement in different forms of associative learning, basolateral amygdala and its various outflow pathways through orbitofrontal cortex, central nucleus, and nucleus accumbens are each critical for normal conditioned reinforcement. Thus, instrumental responding for cues previously paired with food reward is sensitive to damage to amygdala, particularly basolateral amygdala (Burns et al., 1993; Cador et al.,

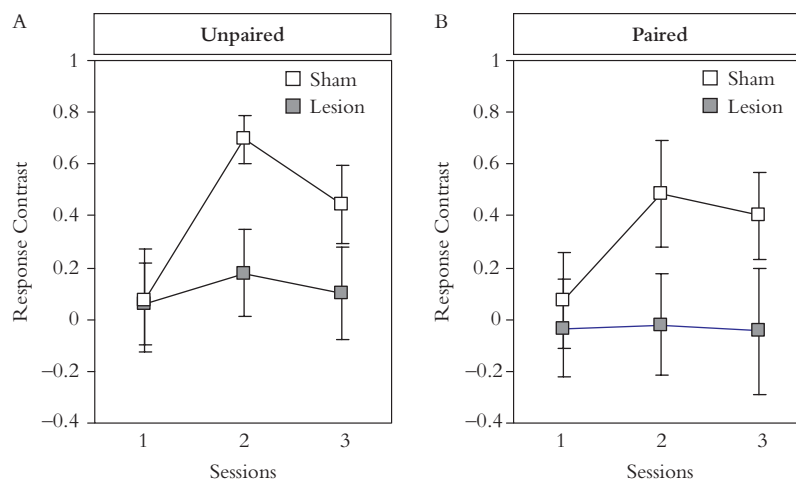


Figure 2.4 Effects of ABL lesions on conditioned reinforcement. For half of the rats, (A), the food outcome was not paired with LiCl. For the other half of the rats (B), the food outcome was paired with LiCl. The control unpaired and control paired rats (white boxes) showed an increase in their contrast after day 1, demonstrating conditioned reinforcement for the food-associated cue over the control cue with no effect of devaluation. ABL-lesioned rats (gray boxes), in both groups, did not show this increase of instrumental responding for these cues, compared to the controls, over the three sessions. (Graph modified from Burke et al., 2007.)

1989; Cousins and Otto, 2003; Hatfield et al., 1996; Parkinson et al., 2001; Setlow et al., 2002a), and also to the outflow pathways described earlier, including orbitofrontal cortex (but not other prefrontal areas) (Cousins and Otto, 2003; Pears et al., 2003), central nucleus of the amygdala, and regions of nucleus accumbens (Parkinson et al., 1999; Robledo et al., 1996; Setlow et al., 2002b; Taylor and Robbins, 1984). However, while damage to basolateral amygdala abolishes responding for these cues (Parkinson et al., 2001), manipulations elsewhere in these circuits have different effects. For example, in one report orbitofrontal-lesioned animals actually responded more for conditioned reinforcer cues compared to controls, as if their responding had become insensitive to some but not other aspects of the conditioned reinforcer (Pears et al., 2003). Similarly, central nucleus of the amygdala and nucleus accumbens seem to be important primarily for potentiating the control over behavior by conditioned reinforcers (Parkinson et al., 1999; Robledo et al., 1996; Taylor and Robbins, 1984). In addition, damage to basolateral amygdala is most effective when made before learning whereas damage to the outflow pathways—nucleus accumbens and orbitofrontal cortex—continues to be effective even when made after learning (Cousins and Otto, 2003; Pears et al., 2003; Setlow et al., 2002a,b).

One interpretation of these data is that conditioned reinforcement is not a unitary process but in fact reflects parallel activation of different types of associative information, mediated by these different circuits. Here, we have presented evidence in support of this proposal. Furthermore, at least for orbitofrontal cortex and basolateral amygdala, there appears to be some correspondence between the role these areas play in processing associative information evoked by Pavlovian cues and their roles in conditioned reinforcement. Thus basolateral amygdala is important in both settings for allowing cues to evoke representations of outcomes and also the affective information with which those outcomes are associated, potentially explaining why basolateral amygdala lesions cause a general deficit in conditioned reinforcement. By contrast, orbitofrontal cortex plays a more specific role in the process whereby cues evoke outcome representations in Pavlovian settings and orbitofrontal lesions cause a selective deficit in conditioned reinforcement when it is mediated by these representations. It will be of interest in the future to determine whether conditioned reinforcement mediated by other areas linked to basolateral amygdala, such as central nucleus or nucleus accumbens, is mediated primarily by affective information.

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