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Choose your path: Divergent basolateral amygdala efferents differentially mediate incentive motivation, flexibility and decision-making

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ABSTRACT

To survive in a complex environment, individuals form associations between environmental stimuli and rewards to organize and optimize reward seeking behaviors. The basolateral amygdala (BLA) uses these learned associations to inform decision-making processes. In this review, we describe functional projections between BLA and its cortical and striatal targets that promote learning and motivational processes central to decision-making. Specifically, we compare and contrast divergent projections from the BLA to the orbitofrontal (OFC) and to the nucleus accumbens (NAc) and examine the roles of these pathways in associative learning, value-guided decision-making, choice behaviors, as well as cue and context-driven drug seeking. Finally, we consider how these projections are involved in disorders of motivation, with a focus on Substance Use Disorder.

1. Introduction

Motivation and decision-making processes depend on associations between salient, environmental cues and the natural rewards they predict, including food, water or drugs of abuse. The basolateral amygdala (BLA) is a critical brain region necessary for associative learning and decision-making processes, which depend on the learned incentive properties of cues and past and present reward value (for focused amygdala reviews, see [1–5]). The incentive motivational properties of reward-associated cues attract, reinforce and invigorate reward seeking, but are also pitted against changes in reward value. As such, individuals may respond based on learned incentive properties of the cues, or adjust their responding based on the current value of the reward. In this review, we discuss these competing psychological processes and how the tasks used to probe specific facets of motivated behaviors are mediated by distinct or overlapping BLA projections to cortical and striatal targets (see Fig. 1 and Table 1). We focus on the nucleus accumbens (NAc) and orbitofrontal (OFC; or anterior insular cortex, when specified) to describe the distinct and overlapping functions of these areas in several behavioral paradigms that probe associative learning, value-guided decision-making, choice behaviors and cue- and context-driven drug seeking. As a result, we aim to highlight how these psychological and neurobiological processes are implicated in disorders of motivation, with an emphasis on Substance Use Disorder (SUD).

The BLA is involved in appetitive associative learning, specifically for guiding higher-order conditioning after the initial acquisition of appetitive associations. However, the BLA is not necessary for the initial first-order conditioning (FOC), but BLA stimulation increases conditioned responding ([6,7,22,33,36,49–56; for reviews, see [5,48]]). Instead, the BLA is uniquely situated, anatomically and functionally, to represent previously acquired associations to facilitate higher order learning and motivational processes through interactions with downstream target regions. For the purpose of this review, we focus on the contribution of the BLA to what we broadly characterize as *incentive* and *flexibility processes*. Here, we operationally define an *incentive process* as one in which reinforcing properties of rewarding outcomes transfer to reward-predictive cues, such that the motivational properties of the conditioned cues facilitate new learning or support ongoing appetitive behaviors. We operationally define a *flexibility process* as one in which changes to, or differences between, outcome value(s) facilitate changes in conditioned responding to associated cues. Determining differences between outcome values may require tracking specific sensory features of outcomes, comparing expected and actual outcome values or choosing between high vs. low risk outcomes. We will review evidence that the BLA and its projections are necessary for incentive processes, including second-order conditioning, sign-tracking, general Pavlovian-to-instrumental transfer (PIT), conditioned reinforcement and cue- and context-induced drug relapse [4,6,7,22,51,52,57–59].

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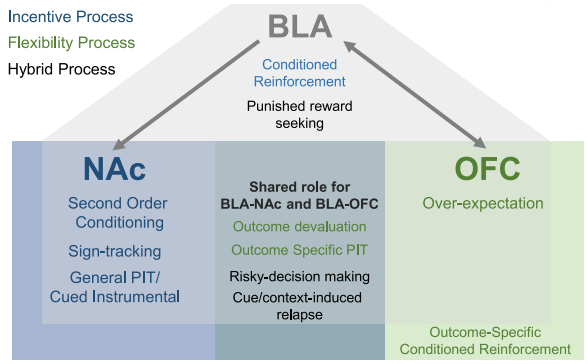


Fig. 1. Venn Schematic depicting circuitry contributions to learning and motivational processes categorized within our conceptual framework. See Table 1 for references. Areas of overlap indicate behavioral processes in which both the areas alone and the projections between areas are implicated. We operationally define
1) an incentive process as one in which reinforcing properties of rewarding outcomes transfer to reward-predictive cues, such that the motivational properties of the conditioned cues facilitate new learning or support ongoing appetitive behaviors,
2) a flexibility process as one in which changes to, or differences between, outcome value(s) facilitate changes in conditioned responding to associated cues and
3) a hybrid process as one in which both incentive and flexibility processes contribute to behavior at test. Notably, BLA alone plays a role in each of the behavioral paradigms listed (see Table 1), but for simplicity are not listed under BLA unless only BLA, and not its projections, has been implicated. Abbreviations: BLA = Basolateral Amygdala; OFC = Orbitofrontal Cortex; NAc = Nucleus Accumbens; PIT = Pavlovian to Instrumental Transfer.

Next, we will review evidence that BLA and its projections are necessary for flexibility and decision-making processes, including outcome devaluation, over-expectation, outcome-specific PIT, risky decision-making and punished reward seeking [6,22–24,26,30,36,49,53,59–62]. Overall, we aim to synthesize the literature to identify competing and complementary roles for amygdala-striatal and amygdala-cortical interactions to shape normal and dysregulated incentive learning and flexibility processes. The goal of the current review is to relate how these two general behavioral processes and associated circuitries are inherently involved in choice behaviors during decision-making for natural and drug rewards.

Table 1
Table listing references demonstrating circuitry contributions to learning and motivational processes categorized within our conceptual framework.

Psychological Process	Behavioral Paradigm	BLA	BLA → NAc	BLA ⇄ OFC
Incentive	Second Order Conditioning	[6,7,76]	[8]	
	Sign-tracking	[9]	[9,10]	
	General PIT/Cued Instrumental		[11,12]	
	Conditioned Reinforcement	[4,57]		
	Cue/Context-induced drug relapse	[13–16]	[16–19]	[15,20,21]
Flexibility	Outcome Devaluation	[6,22–26]	[10,27]	[28–31]
	Over-expectation			[32]
	Outcome-specific PIT	[22,33–36]	[27]	[29,36]
	Risky decision-making	[37–39]	[40–42]	[43]
	Punished reward seeking	[44–47]		

2. Amygdala-striatal and amygdala-cortical contributions to associative learning processes

Before reviewing the role of these circuitries in psychological processes, we first describe the anatomical connectivity patterns of the structures to be discussed and refer to these distinct pathways throughout the discussion where warranted. The BLA, specifically the anterior portion, is densely and reciprocally connected with OFC and neighboring anterior insular cortex (aIC) [63–67]. Likewise, the anterior BLA sends dense, unidirectional projections to the NAc core, while the posterior BLA projects more heavily to the medial portion of the NAc shell [64,65,67–72]. A small proportion of BLA neurons have collaterals that project to both the OFC and NAc core. A double retrograde study indicates that anterior BLA→aIC projections collateralize more with lateral portions of NAc core regions than with medial NAc shell [73], suggesting the anterior portion of the BLA is anatomically situated to simultaneously influence both NAc core and these cortical regions during associative learning and value updating.

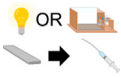
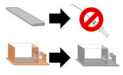
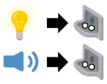
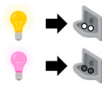
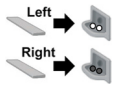
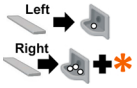
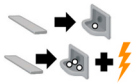
The BLA is critically involved in both Pavlovian incentive learning and flexibility processes, such as second order conditioning (SOC) and outcome devaluation, respectively [6,74,75]. These distinct behavioral processes are convenient to compare because both SOC and outcome devaluation have identical FOC (see Table 2). In both procedures rats initially learn to associate a neutral cue (e.g. light) with a rewarding food outcome. During this initial learning, the light cue acquires incentive motivational properties that promote conditioned approach to the reward location in anticipation of reward delivery. In the second phase of SOC, the light cue is paired with a separate, novel cue (e.g. auditory tone) in the absence of the reward. In so much as the light cue itself is reinforcing, the tone now elicits conditioned approach when it is presented alone at test. In contrast, in the second phase of outcome devaluation, no cues are presented. Instead, the value of the outcome is independently modified prior to testing, either through sating rats on the food reward or pairing the food reward with illness, and conditioned responding to the light cue is tested. SOC relies upon the positive incentive value of the conditioned stimulus to promote learning about a new stimulus (second order CS), while outcome devaluation relies upon the current value of the unconditioned stimulus (US) to suppress responding to the associated cue [74]. In the following sections, we review evidence for amygdala-striatal and amygdala-cortical contributions to incentive and flexible behavioral processes.

2.1. Role of BLA→NAc communication in incentive processes

As previously stated, the BLA is not necessary for the initial FOC phase, as pre-training lesions of BLA do not affect light-food conditioning, which is common to both procedures. However, BLA lesions impair both SOC and outcome devaluation [6,7,22,76]. Additionally, pre-training lesion studies also commonly implicate NAc in both SOC and outcome devaluation, suggesting some mechanistic overlap with BLA in mediating both forms of higher-order learning [77,78]. Given the dense, unilateral projections from the BLA to NAc, pre-training contralateral disconnection lesions do not impair FOC but do impair SOC, further indicating communication between BLA and NAc is critical for higher-order learning that depends on motivational properties of previously reward-associated cues [8]. Post-training lesion studies indicate the expression of SOC does not require BLA, but is instead mediated by downstream NAc. The unidirectional projections and temporally distinct involvement of the BLA and NAc in these studies indicate a transfer of information from the BLA to NAc to mediate higher-order learning (for reviews, see [1,79–82]).

Consistent with the role for BLA→NAc in driving incentive processes like SOC, the BLA→NAc pathway is necessary for the acquisition and expression of autoshaped lever pressing, a behavior termed "sign-

Table 2
Table depicting training and testing parameters often used in behavioral paradigms that probe learning and motivational processes. For simplicity, we do not show control cues or groups often included in these paradigms. Under Phase I for 'Risky decision-making', the orange asterisk indicates various forms of high-risk outcomes that accompany high reward delivery, such as low reward probability, increased delay to next trial, footshock punishment, high effort requirement, etc. Table uses images from Biorender.com.

Psychological Process	Behavioral Paradigm	Phase I	Phase II	Test
Incentive	Second Order Conditioning			
	Sign-tracking			
	General PIT/Cued Instrumental			
	Conditioned Reinforcement			
	Cue/Context-induced drug relapse			
	Outcome Devaluation			
	Over-expectation			
Flexibility	Outcome-specific PIT			
	Risky decision-making			
	Punished reward seeking			

tracking" that is conceptualized as an incentive salience process (see Table 2) [9,83–85]. To be considered an incentive salience process, cues acquire attracting, reinforcing and invigorating properties [86]. Accordingly, sign-tracking rats approach and vigorously engage with the lever cue during Pavlovian Lever Autoshaping and show greater conditioned reinforcement, but not greater SOC, effects than rats showing less sign-tracking behavior (intermediates and goal-trackers) [87,88]. The fullest expression of sign-tracking depends on intact BLA→NAc core communication. Contralateral inactivation of BLA→NAc core with either lesions or chemogenetic inhibition makes sign-trackers less sensitive to the incentive properties of the lever cue and more sensitive to changes in outcome value [9,10]. Furthermore, pathway specific tools have revealed that Pavlovian appetitive cue-reward presentations activate and result in synaptic potentiation of BLA→NAc pathway, which facilitates dopamine release in NAc [89–91] and inhibition of this pathway decreases consummatory responses during Pavlovian conditioning [92]. Disconnection of BLA and NAc shell reduces motivation to lever press for food when instrumental response requirements are high, suggesting this pathway is also necessary for enhanced motivation when reward is response contingent [93]. Altogether, there is considerable evidence that BLA→NAc communication facilitates incentive motivational processes, in particular, those driven by the reinforcing properties of conditioned cues.

2.2. Role of BLA-OFC communication in flexibility processes

In contrast, there is substantial evidence across Pavlovian and instrumental studies that the BLA, OFC and their interactions mediate flexibility processes, indicating a role for these regions in the updating and use of outcome information for adaptive behavior [6,22,24–26,29,30,57,59,61,62,94–97]. Post-training BLA lesions do not affect Pavlovian SOC or single reinforcer outcome devaluation; however, they do impair Pavlovian and instrumental outcome devaluation when specific outcome representations are needed to appropriately suppress responding [23,26,76,96,8,24,25]. The latter effect implicates BLA's known role for representing specific sensory properties of outcomes used by projection regions like OFC and aIC to update actions or responding to cues when outcome values are changed. As such, when the OFC (including neighboring aIC) is lesioned or inactivated either before FOC or immediately prior to outcome value updating, rats fail to suppress conditioned responding during the devaluation probe test [94,96–98]. These results indicate that both the BLA and OFC are involved in updating outcome value to guide appropriate responding to reward associated cues during probe tests.

Pathway specific studies provide additional insight into the interaction between BLA and OFC during flexibility processes including outcome devaluation. Contralateral inactivation of BLA-aIC in rats and BLA-OFC in primates disrupts outcome devaluation [28,30,31]. Unlike the unidirectional pathway from BLA→NAc, the BLA and OFC have dense reciprocal connections that warrant temporal- and

pathway-specific neural manipulations. The aforementioned contralateral disconnection studies are very informative in that they indicate the necessity of BLA and OFC communication for value updating and action selection, but do not elucidate the directionality or temporal specificity for each pathway in behavior. The use of a sequential cross-hemispheric temporal inactivation technique revealed that BLA is necessary for initial acquisition and value updating, while the aIC is needed for retrieval of the current outcome value during the devaluation test [30]. This is consistent with earlier lesion work indicating the BLA must be intact during the unconditioned stimulus value manipulation (i.e. satiation; conditioned taste aversion learning) but not during the value retrieval process necessary for devaluation expression, particularly when multiple outcomes must be discriminated [24–26]. In contrast, the aIC is necessary to retrieve the updated outcome value during test, similar to the role of anterior portions of OFC in non-human primates [30,98,99]. Tests for the role of direct, monosynaptic communication in these reciprocally connected pathways comes from a chemogenetic study that inhibits BLA or OFC terminals via designer receptors activated by designer drugs (DREADDs) [29]. When the BLA→OFC pathway is inactivated during value retrieval, rats displayed insensitivity to specific satiety-induced outcome devaluation, consistent involvement of not only BLA but the BLA→OFC communication when the current value of multiple reinforcers must be represented for appropriate responding. Importantly, this was only true for Pavlovian but not instrumental outcome devaluation, departing from BLA's common role in these processes [26,29].

Lesion and recording studies point towards information flow from OFC to BLA in facilitating flexible associative encoding during learning, value reversal and value expectation [32,100–102], with lateral and medial OFC inputs to BLA participating in encoding and retrieval of positive reward value, respectively [95]. Pavlovian over-expectation is a procedure that also requires outcome value inference when responding to cues, and OFC influences neural activity in the BLA during this task. First, two separately conditioned cues predict the same outcome (eg. 2 pellets; see Table 2). Next, the two cues are presented in compound, but instead of predicting double the reward, the amount of reward is consistent with what was associated with either cue alone (eg. 2 pellets). Violating rats' expectations during compound conditioning results in a spontaneous decrease in conditioned responding when the cues are again presented alone during a probe test. The BLA is not necessary for decreasing conditioned responding during the probe test, but the OFC is necessary for this over-expectation effect. The OFC is also necessary for driving BLA neural activity representing outcome estimates during compound conditioning and for spontaneous decrements in cue-evoked BLA neural activity during the expression of over-expectation during the probe test [32,103–105]. Together, devaluation and over-expectation studies indicate that reciprocal BLA-OFC communication is necessary for outcome value updating and reward expectations that drive adaptive behaviors.

2.3. Role of BLA→NAc in flexibility processes

The NAc is also necessary for outcome devaluation, but subregion specific. Bilateral lesions of the either NAc core or shell result in insensitivity to illness-induced outcome devaluation [78]. However other studies suggest NAc core and shell subregions are differentially involved in the devaluation process [106]. The greater proportion of cue-selective NAc core neurons during initial instrumental discrimination predicts better behavioral suppression during outcome devaluation. Conversely, NAc shell neuron activity better discriminates valued and devalued cues during test [106]. These results indicate the core is involved in behavioral acquisition and the shell in outcome value tracking. Despite these findings relating neural activity and behavior, disconnection of the BLA and NAc shell does not alter devaluation sensitivity, while BLA and NAc core disconnection abolished instrumental specific-satiety devaluation [27]. Chemogenetic contralateral inactivation of the BLA and NAc core also eliminates specific satiety-induced Pavlovian outcome devaluation, but only in goal-tracking rats [10]. In contrast, BLA and NAc core contralateral inactivation makes otherwise devaluation insensitive sign-tracking rats sensitive to outcome devaluation [10,87,107,108]. These findings suggest individual variability in BLA→NAc core communication for mediating incentive and reward value representations.

The aforementioned studies indicate that communication between BLA and NAc is necessary for flexibility processes such as outcome devaluation. However, these studies use contralateral disconnection techniques to inactivate one brain region in one hemisphere and the other brain region in the opposite hemisphere to examine BLA and NAc's involvement in outcome devaluation. To our knowledge, no study has yet investigated the involvement of direct projections from BLA→NAc with pathway-specific manipulation techniques in outcome devaluation. It remains likely that direct BLA→NAc pathway communication is involved in these behaviors, but there could be another intermediary brain region that receives input from BLA and projects to NAc that could explain these findings. Indeed, the BLA projects to OFC and OFC projects to NAc, leaving opportunity for the BLA to indirectly influence NAc through OFC [69,109]. Another contralateral disconnection study showed aIC-NAc communication is necessary for outcome devaluation [110]; however, due to reciprocal connections with the BLA, the aIC could be influencing NAc indirectly through BLA in this study. Nevertheless, future direct pathway manipulation studies are warranted to tease apart the contribution of these specific projections in outcome devaluation.

Taken together, the seminal work on BLA→NAc and BLA-OFC contributions to SOC, autoshaping, outcome devaluation and over-expectation point towards some overlapping, but also distinct roles for these amygdala pathways for incentive and flexible learning processes that rely on conditioned stimulus (CS) properties and/or current outcome (US) value. Notably, these associative representations between cues and outcomes are at the root of many learning and decision-making processes that are relevant for normal and dysregulated motivation.

3. Role of BLA projections in general and specific learning processes

Evidence for amygdala-striatal and amygdala-cortical contributions to incentive motivational processes are also further explored using Pavlovian to Instrumental Transfer (PIT) and conditioned reinforcement paradigms (see Table 2). We provide evidence for these circuitry contributions together, because both paradigms can be evaluated based on general and cue-specific representations. Similar to SOC and outcome devaluation, rats learn a first-order Pavlovian cue-outcome association. In PIT, rats next learn an operant (lever) association with the same outcome. During test, the lever cues are continuously available and presentation of the Pavlovian cue invigorates responding on the instrumental lever. PIT relies on retrieval from previously learned Pavlovian associations to invigorate instrumental responding. Studies have evaluated the neural underpinnings that are responsible for invigorated responding in two forms of PIT, general and specific. General PIT refers to the increased responding on multiple levers, independent of the associated outcome. Specific PIT refers to the increased responding on the lever specifically associated with the common Pavlovian and instrumental outcome but not another lever associated with a different outcome. Similarly, conditioned reinforcement studies examine the extent to which a Pavlovian cue acquires motivational significance such that it can serve as a reinforcer itself. After Pavlovian FOC, rats acquire a novel instrumental action that is reinforced with the Pavlovian reward-associated cue itself in the absence of the reward (e.g. lever press→light) to assess the incentive, motivational properties of the conditioned cue itself. Similar to PIT, conditioned reinforcement studies have also used sophisticated behavioral designs to tease apart general affective and outcome-specific representations that mediate the

reinforcing properties of conditioned cues.

Similar to the lack of BLA lesion effects on acquisition of Pavlovian associations, pre-training BLA lesions also do not affect the acquisition of instrumental responding. However, the BLA is necessary for the expression of outcome-specific, but not general, PIT [22,33–36]. Disconnection of BLA→NAc shell impairs outcome-specific PIT, while disconnection of BLA→NAc core does not, a set of findings that is consistent with reports that bilateral lesions or inactivation of NAc shell, but not core, also abolish outcome-specific PIT [27,111]. Conversely, bilateral lesions or inactivation of NAc core, but not shell, abolish general PIT [51,111]. Similar to the BLA and NAc shell, the OFC is necessary for outcome-specific PIT, and OFC neurons show Pavlovian CS-specific activity correlated with the strength of PIT behaviors [34,112]. Two recent chemogenetic studies demonstrate the involvement of BLA and OFC communication in stimulus-outcome associative learning that is necessary for the expression of outcome-specific PIT [29,36]. Using inhibitory opsins and chemogenetic inactivation to inhibit terminals in reciprocally connected BLA and OFC, these studies showed inactivation of the BLA and OFC→BLA during the initial cue-reward learning abolished outcome-specific PIT. While inactivation of OFC→BLA during PIT test had no effect on behavior, inactivation of BLA→OFC disrupted the expression of outcome-specific PIT. Consistent findings come from a recent sequential inactivation approach that inhibits OFC→BLA in one hemisphere during cue-reward learning and inhibits BLA→OFC in the other hemisphere during PIT test, which provides evidence for the direction of information flow - OFC→BLA for encoding of specific cue-reward associations and BLA→OFC for expression of cue-specific behavioral invigoration [29,36]. These results further clarify the critical role for BLA and its projections to OFC and NAc shell in representing specific cue-outcome associations for invigorating specific actions, whereas NAc core participates in general invigoration of instrumental responding.

Conditioned reinforcement studies also point towards overlapping roles of BLA and its striatal and cortical targets in incentive learning processes. In parallel with the aforementioned behavioral paradigms, the BLA is necessary for conditioned reinforcement effects in primates and rats [4,57]. Consistent with the outcome specific-PIT and devaluation work, the OFC is also necessary for outcome-specific conditioned reinforcement, but not for general affective contributions to conditioned reinforcement [113]. Lesion studies have not identified a role for NAc in conditioned reinforcement itself, but have identified opposite roles for NAc core and shell in amphetamine-potentiated conditioned reinforcement effects [78,114]. The BLA is necessary for mediating the potentiating effect of intra-NAc shell, but not NAc core, amphetamine on conditioned reinforcement, suggesting a synergistic role of BLA input to NAc in mediating dopamine-dependent behaviors. Optogenetic work has shown that both BLA→NAc pathway activation and VTA→NAc core dopamine neuron activation alone are reinforcing, supporting self-stimulation and conditioned reinforcement, respectively [92,115]. NAc dopamine receptor 1 signaling is necessary for optogenetic BLA→NAc self-stimulation, which is consistent with earlier work showing that BLA and dopaminergic convergence in NAc facilitates reward seeking in discriminative stimulus instrumental tasks [11,12]. Notably, VTA→NAc core, but not VTA→NAc shell, dopamine neuron optical stimulation alone is sufficient for conditioned reinforcement. These findings depart from the lesion work showing a necessary role for BLA to influence NAc shell amphetamine-induced potentiation of conditioned reinforcement [114,115]. These inconsistencies on the potential role of BLA and dopaminergic input to NAc may be due to limitations of dopamine agonist and optogenetic dopamine activation manipulations to approximate the endogenous mechanisms underlying conditioned reinforcement.

While such inconsistencies may be reconciled by causal role manipulations of BLA→NAc and VTA→NAc systems during conditioned reinforcement, we are not aware of such studies to date. Some hints may come from BLA→NAc cross lesion and NAc DA antagonist studies, both of which are sufficient to disrupt the acquisition and/or expression of sign-tracking responses during Pavlovian lever autoshaping [9,116]. Sign-tracking rats, that are strongly attracted to Pavlovian cues, also show strong conditioned reinforcement effects while intermediate and goal-tracking rats do not [88]. Thus sign-tracking, which depends on both BLA→NAc input and NAc core DA signaling, may provide a useful tool for determining the casual relationship between BLA inputs and DA in the nucleus accumbens for driving conditioned reinforcement effects [9,88,115,116].

Incentive and flexibility processes are higher order learning processes that are behaviorally distinct and often rely on discrete, but sometimes overlapping, neurobiological substrates. Usually, the learning processes discussed herein require initial learning of two or more cue-outcome associations. Whether it is discrimination of separate cues signaling distinct outcomes (i.e. discrimination learning), discrimination of a reinforced from a non-reinforced cue-outcome association (CS + vs CS-) or discrimination of an appetitive and aversive association (i.e. sucrose vs. quinine in go/no-go tasks), BLA and its projections support distinct associative representations for use in higher order learning and motivational processes. These include value discrimination, reversal learning, and extinction which have been previously and comprehensively reviewed [2,5,60,79,117–120] and while not detailed here, are important constructs for understanding the amygdala-cortico-striatal contributions to complex decision-making processes.

4. Role of BLA and its projections in choice behaviors

The contributions of amygdala-striatal and amygdala-cortical interactions to specific associative learning processes described thus far, rarely operate in isolation, particularly in the organization of human behavior. Adaptive and maladaptive decision-making in humans is highly complex and relies on the physiological processes described here, acting in synchrony with sensory, motor, and cognitive processes to mediate choices that benefit the individual. While some decisions may be adaptive in the short term, they may not be the most efficient strategy to maximize reward and avoid punishment in the long term. Such choices are based on learned associations and expectations about future events, and perhaps, not surprisingly, rely on similar underlying brain circuitry. While a distributed network of brain regions is involved in cost-benefit decision-making, rodent studies that aim to model more complex facets of human decision-making also implicate the BLA→NAc and BLA-OFC circuitries.

Various rodent tasks are used to examine the brain circuits driving risky decision-making, including the risky decision-making task (rDT), the rodent Iowa Gambling Task (rIGT), and probabilistic and effort discounting tasks, as well as the rat “Blackjack” task. The various tasks share some common features, namely pitting “low risk/low reward” options against “high risk/high reward” options. “Low risk/low reward” options are typically small immediate rewards delivered at high probabilities. Meanwhile, the high-risk option is associated with some form of negative consequences for choosing that option. The negative consequence of “high risk” option is typically what varies between tasks, and may include low probability of reward, delay to next trial, footshock punishment, and/or high effort requirement (e.g. many lever presses or overcoming physical obstacle). Depending on the task used, post-training BLA lesion and pharmacological inactivation studies indicate that BLA acts to either inhibit or promote responding for large risky rewards (footshock, delay to next trial, probabilistic reinforcement, high effort) [37–39,44]. When negative consequences of choosing the large reward option involves footshock or increasing delays to next trial, rats with inactivation of the BLA chose risky reward options more often than intact rats [39,44]. When large rewards are delivered with decreasing probabilities or increased physical effort, BLA inactivation results in choice of safer options [37]. Optogenetic work identifies a more temporally-specific role for BLA in the push and pull of cost-benefit

decision-making, such that BLA activity during the deliberation period promotes risky decision-making, while BLA activity during delivery of high-risk (large reward, probabilistic footshock punished) rewards promotes choice of the "low-risk/low reward", or "safe" option [45]. The communication of these temporally specific signals to downstream cortical and striatal targets mediates complex interactions between interconnected nuclei to orchestrate evaluative and decisive action in diverse environments.

The similarly contrasting findings for OFC suggest there may be analogous nuance in OFC's involvement in risky decision-making. Consistent with the role for the BLA in promoting low-risk choices, there is evidence that the OFC is also necessary to inhibit risky decision-making during learning. Lesions of the OFC, and its connections with BLA, result in riskier choices during learning, slowing the acquisition of optimal response strategies when large rewards are delivered with lower probabilities and are associated with increased delays to next trial [39,43]. However, BLA-OFC's role is time limited unless sensory-specific features or representations are needed for promoting optimal decision-making [43]. In contrast, footshock punished choices of large reward options are decreased by OFC lesions, suggesting OFC promotes choice of higher value rewards when probabilistic consequences are aversive [44]. Similarly, NAc core lesions bias choices towards smaller, more certain rewards, suggesting for probabilistic large rewards, both BLA and NAc promote "riskier" choices when intact [37,121,122,42]. However, one study identified NAc's role in promoting large uncertain reward choices only when the "risky" choices lead to greater payout over time, suggesting the NAc-driven 'win-stay' behavioral strategy biases rats towards optimal behavior over time [122]. Similarly, contralateral disconnection and inactivation of BLA terminals in NAc reduced large uncertain reward choice [40,42], particularly when odds were good (reinforced 50 % of the time); but the opposite was true when odds were poor (reinforced 12.5 % of the time), further lending support to the idea that BLA and NAc communication facilitates long term gains. Consistent with pharmacological disconnection, optogenetic work identifies temporally specific roles for BLA→NAc communication. Inhibition of this pathway during deliberation reduced preferred choice across good and poor odds blocks, whereas BLA→NAc terminal inhibition during reward omission increased large risky reward seeking on poor odds trials [41]. These results suggest the BLA→NAc pathway orchestrates optimal decision-making under reward uncertainty.

Navigating the complex choices in these rodent decision-making tasks requires evaluation of learned associations and expectations about future events, whether they have expected or unexpected outcome values. The extent to which there is individual variability in the psychological and neurobiological processes underlying incentive motivation and behavioral flexibility, suggests there may be paralleled individual variability in the engagement of amygdala-cortical and amygdala-striatal circuitry driving complex decision-making. While this remains to be determined, the implication may be that certain behavioral phenotypes are more prone to develop maladaptive behaviors that are characterized by aberrant decision-making, like SUD and gambling [123]. This inference is supported by behavioral evidence from separate rodent studies showing that both sign-tracking rats and risk-preferring rats show increased discrete cue-triggered cocaine relapse, increased incubation of cocaine-craving and increased choice of cocaine versus food reward [124–127]. In contrast, goal-tracking rats show greater vulnerability to drug associated discriminative and contextual stimuli [128,129]. Next, we review evidence from rodent studies for amygdala-cortical and amygdala-striatal contributions to drug-seeking, drug-relapse and drug choice.

5. Role of BLA and its projections in drug seeking, relapse and choice

The incentive properties of cues to attract, reinforce and invigorate responding are remarkably evident for drug associated stimuli [1,80,85,130,131]. In rodents, when discrete cues (e.g. light, tone, lever) or environmental contexts are repeatedly paired with delivery of self-administered drug reward, the incentive properties of drug-associated cues and context promote responding for the drug, even in the absence of drug reinforcement (see Table 2). In many cases, incentive properties of cues and contexts drive drug seeking despite drug non-availability, history of punishment or choice of alternative reinforcers. Thus, despite flexibility of drug seeking during extinction, punishment induced- or voluntary- abstinence, discrete and diffuse environmental stimuli remain powerful drivers of drug-seeking actions. In essence, incentive processes overcome flexibility processes to promote maladaptive behavior in addiction. In this section, we discuss how BLA and its projections described in this review serve to promote cue- and context-driven drug-seeking. We conclude with a discussion of drug choice procedures to evaluate the state of understanding for amygdala and its cortical and striatal targets in mediating adaptive and maladaptive decision associated with SUD.

In humans, neuroimaging studies indicate amygdala activation when presented with drug-associated cues (for reviews, see [132,133]). In rodents trained to self-administer cocaine, BLA neurons respond to cocaine-associated cues [14]. The BLA is necessary for drug-associated stimuli to control drug seeking following abstinence (for reviews, see [5,48]). BLA lesions, pharmacological and optogenetic inactivation decrease cue- and context-induced reinstatement of cocaine seeking after extinction [13,15,16,48,134]. In support of BLA's involvement in drug-stimuli associative learning, the BLA is also necessary for memory consolidation of drug-stimulus associations. Repeated pairings of drugs of abuse with drug-associated cues or contexts result in the formation, consolidation, reactivation and reconsolidation of drug-stimuli associative memories [135]. BLA pharmacological inactivation attenuates consolidation of cocaine-associated cue and context memories [136–138].

Both amygdala-cortical and amygdala-striatal interplay is vital in maintaining learned associations between cues and contexts paired with drug taking. In abstinent cocaine users, cocaine and exposure to cocaine-related stimuli increase neural activity in both the BLA and OFC. Enhanced BLA and OFC activation is associated with an increase in self-reported cocaine craving [139–142]. Further, BLA and OFC activation is attenuated in cocaine users treated with the $GABA_B$ agonist, baclofen, with concomitant reduced cocaine cue-induced craving, further implicating their similar roles and interaction in cue-induced relapse [143,144]. In rodent studies, BLA, OFC and their interactions are necessary to reinstate extinguished drug seeking in response to drug-paired cues and context. BLA or lateral OFC inactivation disrupt drug context-induced reinstatement of cocaine seeking behavior in rats [15,145]. Moreover, chemogenetic inactivation of OFC inhibits cue-induced reinstatement of ethanol and sucrose seeking [146]. An earlier study showed that contralateral or ipsilateral disconnection of BLA and lateral OFC attenuates context-induced cocaine-seeking behavior, suggesting functional interdependence between these structures in this behavior [20]. Since BLA and lateral OFC are reciprocally connected, the direction of information transfer during this behavior remained elusive. In a pathway-specific manipulation study, optogenetic inhibition of lateral OFC→BLA projections, but not BLA→lateral OFC projections, diminished cue-induced cocaine seeking behavior [21]. As discussed in previous sections, BLA→OFC, but not OFC→BLA, communication facilitates cue-induced outcome-specific reward expectations and promotes natural reward seeking in outcome-specific PIT [29]. These two studies are seemingly at odds [21,29]. There are obvious differences in drug and natural rewards as unconditioned stimuli, but one possibility for the divergent involvement of BLA-OFC communication in these studies is the use of single versus multiple reinforcers. There may be limited involvement of BLA→OFC circuitry when sensory specific features of rewards are not necessary to track for appropriate responding. Consistent with this, when a single instrumental reinforcer is used, lateral OFC to BLA inhibition was not necessary for cue-induced relapse to food

seeking [21]. Furthermore, the role for BLA→OFC in representing sensory-specific features is limited to Pavlovian and not instrumental associations [29]. However, OFC→BLA is necessary during stimulus-outcome encoding to later invigorate instrumental responding [36]. Perhaps, cue-induced relapse tests better reflect an invigorated reward seeking process that relies on OFC→BLA memories. From a plasticity perspective, it is also possible that drug exposure may strengthen OFC→BLA pathway to a greater degree than with natural reward experience and thus usurp behavioral control over cue-driven drug-seeking. Studies also indicate a role for OFC and BLA-OFC interactions in behavioral flexibility after drug experience. OFC-dependent outcome-guided behaviors and reversal learning are impaired after drug exposure [102,147–150]. Rigid associative encoding in the BLA is the culprit behind OFC-dependent reversal learning deficits after cocaine exposure [101,102,151,152].

BLA or NAc core lesions or direct chemogenetic inhibition of BLA→NAc core projections reduce cocaine seeking under second-order schedules of reinforcement in which drug-associated cues are the primary driver of drug-seeking [19,153,154]. These findings suggest a critical role for BLA→NAc projection in the conditioned reinforcing properties of cocaine-associated cues. A study using asymmetrical neuropharmacological disconnection of the BLA→NAc pathway by antagonizing BLA dopamine receptors and NAc core glutamate receptors also reduced cocaine seeking in a second order schedule of cocaine reinforcement [155]. Studies using ethanol as a Pavlovian reinforcer strongly implicate BLA, NAc and their projections in the attracting and reinforcing properties of alcohol-associated cues [156–158]. In addition, BLA and NAc core are active during the reconsolidation of a cocaine-induced conditioned place preference memory suggesting that these structures are also important for reconsolidation of a cue-drug memory [159]. Overall, these studies provide evidence for functional interaction between the BLA and NAc core in cocaine seeking maintained by cocaine-associated cues. Recent advances in circuit-specific techniques have provided direct evidence for the role of BLA→NAc projections in cue-driven reward seeking. In support of this, BLA→NAc core neurons are activated during cue-induced reinstatement of cocaine seeking as indicated by Fos (immediate early gene) analysis [17]. In addition, optogenetic inhibition of BLA→NAc core also reduced cue-induced reinstatement of cocaine-seeking [16]. Moreover, ablation of BLA→NAc projections and chemogenetic inhibition of BLA→NAc core glutamatergic projections reduced cue-induced reinstatement of alcohol seeking and cue-induced cocaine seeking under second order schedule of reinforcement, respectively [18,19]. BLA→NAc synapses have calcium permeable AMPA receptors inserted into the silent synapses during incubation of cocaine craving [160], suggesting synaptic plasticity in this amygdala-striatal pathway is a critical mechanism underlying incubation of cocaine craving (for review, see [161]). Incubation describes a time-dependent increase in responding for drug-associated cues that occurs in the absence of extinction. Thus, incubation isolates the incentive properties of drug-associated stimuli to drive behavior in the absence of a competing flexibility process, in contrast to in many other addiction models.

While we are unaware of studies examining the role of BLA and its projections in mediating choice between drugs and alternative reinforcers, such models are increasingly used in an effort to better model human decision-making in SUD [162–168]. Recent evidence indicates that NAc core, but not NAc shell, is critical for methamphetamine relapse in a procedure that gives rats choice between food and drug to promote voluntary abstinence [169]. In a cocaine versus food choice procedure, OFC, but not NAc, neuronal activation was associated with cocaine preference [170]. There is mounting evidence implicating OFC encoding of cocaine and heroin-associated choices [171–174].

Certain rodent models of addiction incorporate facets of the choice tasks described in the previous section, including delay to reward and punished reward seeking. There is evidence that cocaine exposure shifts delay discounting and BLA encoding of delayed rewards [175,176]. Evidence consistent with studies suggesting a role for BLA in suppressing risky choices comes from the punishment induced abstinence model, a procedure that gives rats a choice to seek or suppress drug seeking in the presence of probabilistic footshock of increasing intensity [44–47]. BLA neuronal activation is evident after cue-induced reward seeking after punishment, and BLA inactivation increases context-induced relapse to cocaine seeking after punishment-induced abstinence [46,47]. These studies suggest BLA is important for suppressing "risky" drug seeking behaviors. The conceptual and mechanistic bridge linking the BLA's role in natural and drug reward choice also requires careful consideration of the neurobiological mechanisms of punishment, probabilistic reinforcement and context [166,177–181].

While there are many unanswered questions regarding the role of amygdala-cortical and amygdala-striatal projections in choice between drugs vs non-drug alternatives, there is considerable evidence for the reviewed circuitry in driving incentive motivation and flexible decision-making processes. This review highlights the importance of probing the basolateral amygdala and its projections for understanding adaptive motivated behavior and dysregulated behaviors observed in addiction and other disorders of motivation.

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